"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 SharePoint PaCo 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 the different steps of a clinical drug trial sponsored by Cliniques Universitaires Saint-Luc (CUSL), from the preparation of the trial to the notification of the end of the clinical trial and the encoding of the results in the European database.
This procedure also describes the responsibilities and rules to be followed in terms of eudravigilance for clinical drug trials.

2 PROCEDURE'S SCOPE

Cliniques Universitaires Saint-Luc member of the health professions staff acting as the non-commercial sponsor of the clinical drug trial on behalf of CUSL, referred to as "the sponsor".
Cliniques Universitaires Saint-Luc physician acting as the principal investigator of the clinical drug trial, referred to as "the investigator".
Cliniques Universitaires Saint-Luc's academic central office providing administrative support to the Sponsor.

3 RESPONSIBILITIES AND AUTHORITIES

3.1 Sponsor's responsibilities

The sponsor's responsibilities include, but are not limited to:

- Initial submission of the clinical trial and submission of amendments
- Registration of adverse events
- Reporting SUSARS to the national competent authority and the ethics committee
- Informing investigators about the procedures for reporting adverse events. These are also described in the protocol.
- Providing investigators with SAE form documents.
- The establishment of an annual safety report (AAHRPP-FORM-018) for the competent authority and the ethics committee
- Continuous evaluation of the benefit/risk ratio of the trial
- Assurance of compliance with quality standards through the establishment of standard operating procedures
- Follow-up of the SAE collected at the center level, as well as their closure
- Informing the investigators of any new element that could influence the safety of the participants during or after the end of the study.
- Registration of trial results in the EMA database

If the sponsor of a clinical trial is Cliniques Universitaires Saint-Luc, the physican in charge (principal investigator) is responsible for the study. He manages the clinical trial for the institution of which he is an employee.

3.2 Investigator's responsibilities

The investigator's responsibilities include:

- Reporting adverse events and/or abnormal test results to the sponsor.
- Reporting suspected adverse events (SUSARs) to the sponsor.
- Informing participants of any new safety issues that arise during or after the completion of the clinical trial.

3.3 Responsibilities of the academic central office

The responsibilities of the academic central office include:

- The initial submission of drug studies to the appropriate authorities and the CEHF.
- Submission of SUSARs to the relevant authorities.
- Notification of the end of a clinical drug trial via the European portal.
- Encoding the results of a clinical drug trial in the European registry.

4 PROCEDURE'S REVISION

Merger and update of the following procedures:

- AAHRPP-SOP-004 (Non-commercial Non-interventional Clinical Trial Submission)
- AAHRPP-SOP-006 (Non-Commercial Interventional Clinical Trial Submission)
- AAHRPP-SOP-007 (Non-Commercial Drug Trial Submission)
- AAHRPP-SOP-015 (Pharmacovigilance)

5 PROCEDURE'S DESCRIPTION

All clinical drug trials and amendments must be submitted to the FAMHP and the ethics committee responsible for the single opinion. It is essential to obtain the agreement of the FAMHP and the ethics committee in charge of the single opinion before starting a clinical drug trial.

For any new drug trial with a CUSL sponsor, the physician in charge of the study must complete the document AAHRPP-FORM-006 IMP-DEVICE CUSL AVIS DIR MED which will be submitted to the medical director for validation in order to assess the physician's ability to assume the regulatory and logistical responsibility of his project as sponsor.

5.1 Submission of a clinical drug trial

In case of doubt about the type of clinical trial (drug study or non-drug study), refer to the table "Is it a clinical trial or a medicinal product?" in Appendix 1 of this document.

The different cases of clinical drug trials and submission to the competent authorities are

- Single-center clinical trial with a CUSL sponsor: submission through the CUSL central academic office (CEHF + FAMHP)
- Multicenter and/or multinational clinical trial with sponsor :
    - CUSL: submission through the CUSL academic central office, if the CUSL is the Belgian coordinator of the drug trial (FAMHP + CEHF + EC of each country involved simultaneously)
    - External: submission through the CUSL academic central office but only to the CEHF. The external sponsor is responsible for the submission to the FAMHP.

The submission of a clinical drug trial with a CUSL sponsor is done by the academic office at the CEHF and the FAMHP simultaneously.

Documents to be submitted to the competent authorities and the CEHF

Documents submitted electronically must be in PDF format ONLY, except for the Clinical Trial Application Form which, in addition to PDF, must also be in XML format:

- CTA :
    - PDF version
    - Scan of the signature page
    - xml version
- Protocol:
    - pdf version (must allow copy and paste)
    - Scan of the signature page

Files must be named as follows: **Eudract number-Name of file.pdf**

- To name the scanned signed pages: **Eudract Number-File Name-Signature.pdf**
- To name a document referring to a specific drug (investigational or authorized): **Eudract Number-Manufacturing Authorization- Drug Name.pdf**
- Sample file names: Covering-Letter.pdf, Application-Form.pdf, Application-Form.xml, Application-Form-Signature.pdf, Protocol.pdf, Simplified-Impd.pdf, Smpc.pdf, Labels.pdf

The document templates are sent by the academic office after the clinical trial has been taken over.

The following is a list of documents to be submitted to the appropriate authorities and the CEHF:

- Document Checklist (AAHRPP-DSQ-111)
- Cover Letter (AAHRPP-FORM-073)
- Clinical Trial Application Form
- Protocol
- Summary: 1 page in French
- Informed Consent Form (CEHF-DOE-092_v2_DIC_ICF)
- Certificate of Insurance (AAHRPP-FORM-003)
- Conflict of Interest Form (AAHRPP-FORM-035)
- IMP Record (Drug):
- IMPORTANT: if the drug under investigation has a marketing authorization (used for the same indication, in the same form and dosage) and if it is a non-commercial study, you do not have to provide a chemical-pharmaceutical dossier or an investigator's brochure, but you must nevertheless enclose the complete qualitative and quantitative composition of the drug, with indication of the active ingredients, in usual terms and, if such a denomination exists, with the international non-proprietary name recommended by the World Health Organization (cfr: Summary of Product Characteristics).
- If not, please attach an investigator's brochure and a complete or simplified chemical-pharmaceutical dossier, as the case may be. The investigator's brochure must be updated every year.
- Labeling of the IMP
- The content of the IMP labeling must be provided (a concrete example is no longer mandatory).
- General rule: in case of a trial, the investigational medicinal products and, if applicable, the devices to administer them are provided free of charge by the sponsor. Specific labelling in the 3 national languages is required on the primary and secondary packaging.
- Language exemptions:
    - Phase 1 units: if IMPs are administered on the unit, staff understand the language used, and participants do not handle the product: labeling in only one language (including English) is accepted.

    - if IMP is administered on site, if subjects do not handle the product, if the clinical team understands the national language used, if the reasons for not applying the general rule are explained, a waiver may be granted.
- Exception: the sponsor is not required to provide the drug free of charge if he can demonstrate at any time, in the case of a trial with a registered drug, that this drug would have been prescribed in any case by the treating physician if the patient had not been included in the trial. In this case only, specific labelling is not required.
- In the case of a randomized study, if the comparator is the registered treatment that would have been provided to the patient anyway, it does not have to be provided free of charge by the sponsor. The trial treatment must be provided free of charge by the sponsor. The trial treatment and the comparator must be labelled for clinical trials (cfr Belgian Law on experiments on the human person of 7 May 2004: Art.31-§2. MB18/05/04 Article 24 § 7. page 39532)
- Any scientific opinion
- The decision of the European Medicines Agency and the opinion of the Pediatric Committee if the trial is part of a PIP.
- The opinion of the Hospital-Faculty Ethics Committee of the Cliniques universitaires Saint- Luc.

5.2 Submission of a non-interventional clinical drug trial[1]

In the context of a non-interventional clinical trial, the sponsor is not required to provide the drug free of charge. The sponsor who uses this option must, however, inform the INAMI (Law of 7 May 2004 on experiments on the human person; art. 31§2).

As this is a non-interventional clinical trial (see definition), no submission to the competent authorities is required.

Here is the list of documents to be submitted to the CEHF:
- Protocol
- Certificate of insurance
- One-page summary in French
- Drug File
- Informed Consent Form

5.3 Deadlines

Tacit authorization is acquired 28 days from the date of validation of the files (T0) (or 15 days for monocentric phase 1)
A confirmation email is sent to the Sponsor upon receipt of the file.
- If the submission file to the competent authorities is complete, it is validated by the FAMHP within 3 calendar days of receipt. A new email is sent to the Sponsor. The date on which the processing period for the application starts is the date of the email confirming receipt of the file. So starting date T0 = date of the email of reception
- If the submission file to the competent authorities contains minor deficiencies, the Sponsor receives an email with the list of these deficiencies and the deadline to correct them. The date on which the deadline for processing the application will be the date on which the file is validated. So T0 start date = date of the reception email + max 3 days

[1] A non-interventional clinical trial is a prospective study in which the drug(s) is (are) prescribed in the usual way in accordance with the conditions set out in the marketing authorization. The assignment of the patient to a particular treatment strategy is not predetermined by a trial protocol, it is routine, and the decision to prescribe the drug is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures should be applied to patients and epidemiological methods are used to analyze the data collected. (Examples: no additional blood sampling, no additional visits to the physician, no additional radiological examinations). Having patients keep diaries or fill out questionnaires does not make a trial interventional. However, if this procedure is done outside of routine, the trial becomes interventional.

- If the submission file to the competent authorities contains major deficiencies, the Sponsor receives an email with the list of these deficiencies and the deadline to correct them. The date on which the deadline for processing the application will be the date on which the file is complete. So T0 start date = date of the email confirming that the file is complete

5.4 Submission of a Substantial Amendment

The responsibility for submitting an amendment lies with the Sponsor.

To make changes to the CTA Form, the responsible physician must go to the EudraCT website: https://eudract.ema.europa.eu/

- Click on the 4th line, left side (highlighted in blue on the picture).
- Click on "load", then "clinical trial protocol", then on "EEA CTA" and download the CTA Form xml version to modify it.

It is important to frequently save the modifications made to the document on your server.

The submission of amendments is done via the European Portal: https://cespportal.hma.eu/
A CESP account is required and obtained after completing the podcast training:

- AAHRPP-SOP-061 - Procedure for access to podcasted training
- Podicampus : PODIFORM : Clinical Research Training (CRCM) : CESP Common European Submission Portal

Upon successful completion of the training, the training certificate must be sent to the academic office (guichetacademique-saintluc@uclouvain.be) to obtain access.

Documents to be submitted :

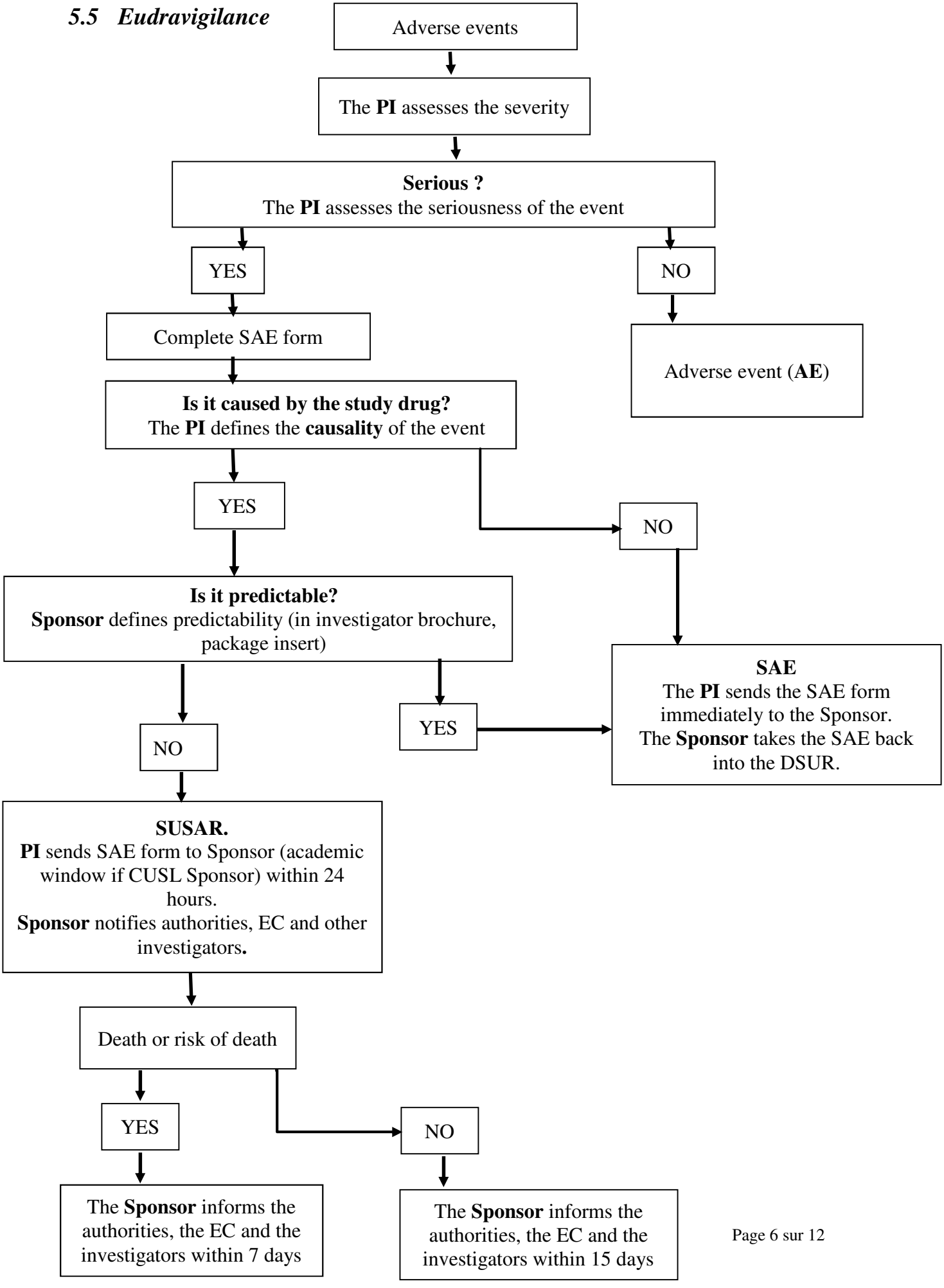
- Modified CTA
- Protocol and other modified documents: with tracking of modifications
- Other useful information to justify the changes made
- Sample letter for the FAMHP (AAHRPP-FORM-073 to be adapted)
- Acknowledgement of receipt (CEHF-FORM-104) for the CEHF

For FAMHP:

- Names of individual documents: Eudract number-Name of file.pdf
- Prepare a zip file containing all the documents to be submitted.
- Create a new delivery file: https://cespportal.hma.eu/delivery/create#

- Submit the zip file containing the documents and the new delivery file via the European portal cesp

5.5 Eudravigilance



5.5.1 Adverse events (AES)

- The investigator :

1. Continuously identifies, records and reports adverse events and reactions.
2. Evaluates adverse reactions and events as soon as they occur with respect to
   - seriousness
   - causality
   - degree of intensity (severity)
3. Follows adverse reactions and events until they are resolved.

The seriousness and unexpectedness of a reaction is used as a guide to define the type of report to be made to regulatory authorities and the ethics committee. It is the responsibility of the Sponsor to determine whether the reported adverse event is unexpected or not.

- The Sponsor (physician in charge of the trial):

1. Defines the predictability of adverse events according to the Safety Reference Information (SRI). The SRI is included in the package insert or investigator brochure for the drug. If predictability information has been made available by the reporting investigator, it should be considered by the sponsor.
2. Maintains a record of all adverse events reported by investigators.
3. Assess the safety of the drug on an ongoing basis and decide if necessary to unblind the treatment applied (only if necessary for the safety of the participant).
4. Is responsible for promptly notifying all investigators, the principal ethics committee and the competent authorities of findings that could adversely affect the health of the subjects, impact the conduct of the study or alter the authorization given by the competent authorities to continue the study.

As a reminder, in certain cases predefined in the protocol and/or the contract with the supplier of the study drug, some of these tasks may be assumed by the MA holder (or patent holder when the drug is not yet registered) if he is not the sponsor of the study.

5.5.2 Serious adverse events (SAE)

The investigator assesses:

- Seriousness
- Causality (the degree of causality determined by the investigator cannot in any case be downgraded by the sponsor)
- Degree of intensity (severity)

The Sponsor defines predictability and determines whether the SAE becomes a SUSAR.

The investigator/co-investigator immediately notifies (within a very short period of time, which in no case should exceed 24 hours after knowledge of the event) the sponsor of the serious adverse event except those identified in the protocol or investigator brochure as not requiring immediate notification. Immediate notification is followed by detailed written reports allowing the sponsor to reassess the benefit/risk ratio. In this notification and in subsequent reports, participants are identified by a code number.

The investigator uses the standard CIOMS SAE FORM (AAHRPP-FORM-019) for the transmission (within the timeframe of the protocol) of SAEs to the sponsor.

If the event is not closed, the same form is used for follow-up and should include the following information:

- full description of reactions
- outcome
- in case of death: cause and relationship to trial treatment + autopsy report
- other relevant etiological factors
- date and time of treatment discontinuation or duration

- additional tests and/or treatments required and their results

The investigator conducts follow-up until resolution of the SAE or stabilization if resolution cannot be achieved.

The investigator is responsible for reporting any serious adverse events that involve participants he/she treats in the context of the clinical trial. The investigator is not required to actively monitor participants for SAEs after the trial has ended, unless otherwise specified in the protocol. SAE experienced by a participant after completion of treatment should be reported to the sponsor if the investigator is aware of them.

Serious and expected adverse events should be reported by the MA holder within 15 days.

In case of death, whatever the cause, the investigator informs simultaneously the sponsor and the Hospital-Faculty Ethics Committee.

Note:
If the clinical trial is double-blind, the investigator assesses the seriousness, causality, and expectation of the event as if the patient were receiving the active drug. If it is a potential SUSAR, the blind is lifted and a report is sent by the sponsor to the authorities only if the patient was receiving the active ingredient. In any case where the blind is lifted, the center must notify the sponsor as soon as possible. The modalities of unblinding should be systematically foreseen in the protocol and documented by the investigator.

5.5.3 SUSAR

A SUSAR is primarily an SAE but is also unexpected and possibly related to the clinical trial drug. Therefore, the requirements for an SAE apply to a SUSAR.
The investigator must also report to the sponsor (similar to SUSARs):

- individual reports of expected adverse events with unexpected outcomes (unexpected severity)
- a clinically significant increase in the frequency of occurrence of expected adverse events
- SUSARs that occur after the patient's participation in the trial has ended (e.g., development of cancers, fetal malformations, etc.)
- any clinical or non-clinical information that could negatively influence patient safety (e.g. lack of efficacy)
- SUSARs associated with the comparator follow the same requirements as if they were associated with the investigational drug.
- a SUSAR associated with a placebo (e.g. reaction to an excipient or impurity) should also be reported.

SUSARs must be notified to EudraVigilance by the sponsor within 7 days (followed by information with details within a further 8 days).

In the case of a CUSL sponsor, the responsible physician must therefore complete the SUSAR reporting form (AAHRPP-FORM-019) and send it to the CTC. The CTC is responsible for reporting SUSARs to EudraVigilance (responsible person for EudraVigilance) via the EV Web site: https://eudravigilance-human.ema.europa.eu

Remarks: there is no obligation to inform the MA holder. The competent authorities inform the MA holder in an anonymous way if he is not the sponsor.

5.6 Annual reports

5.6.1 Annual Report

Annual reports (CEHF-FORM-110) are the responsibility of the investigator and must be sent annually to the CEHF.

5.6.2 DSUR

Purpose: annual evaluation of the safety of participants in a clinical trial.

It consists of 3 parts:

1) Safety analysis of study participants.
2) List of serious adverse events (SARs) and SUSARs
3) Summary table of serious adverse events (SARs) and SUSARs.

DSURs are the responsibility of the sponsor. The physician in charge of the clinical trial must send the DSURs annually to the FAMHP, to the CEHF and to each country where the clinical trial takes place:

- CEHF: the template (AAHRPP-FORM-018) must be completed by the sponsor and sent to the CEHF via email: commission.ethique-saintluc@uclouvain.be
- FAMHP: submission of the following documents via the cesp portal
    - Template (AAHRPP-FORM-018) must be completed, signed by the responsible physician (or the responsible person designated by him/her) and sent in word format (in order to allow copy and paste)
    - Signed cover letter (AAHRPP-FORM-028)

The DSUR must be sent annually no later than the last day of the month preceding the month of acceptance of the first trial by a competent authority of a member state of the European Union or, for short-term trials (< 6 months), 90 days after the end of the trial. The DSUR should be performed even if there are no patients yet included in the study.

5.7 Notification of the end of a clinical trial to the FAMHP

To notify the end of a clinical drug trial, the Sponsor completes and signs the FAMHP end of clinical trial notification document (clinical drug trials).
The academic central office is responsible for submitting this document via the CESP portal.

5.8 Encoding the results of the clinical trial

The encoding of the results is done via EudraCT: https://eudract.ema.europa.eu/results-web/
The investigator completes the document (AAHRPP-FORM-015) and sends it to the CTC academic office (primary user).
To become the primary user, the authorization document to manage the encoding of results, available on the EudraCT website, must be completed and submitted via EudraCT. The authorization to encode the results is given via EudraCT by email within 5 working days.
An EMA account is required.
To create an EMA account: https://register.ema.europa.eu/identityiq/login.jsf?prompt=true - "Create a new EMA account".
To assign a back-up user (result user) to the encoding of a clinical trial:

- Primary user must assign a person to the clinical trial
- The user must approve the role in order to make changes

6 DEFINITIONS AND ABBREVIATIONS

6.1 Abbreviation

AE = ADVERSE EVENT

AFMPS = AGENCE FEDERALE DES M2DICAMENTS ET PRODUITS DE SANTE

AMM = AUTORISATION DE MISE SUR LE MARCHE

CEHF = COMITÉ D'ETHIQUE HOSPITALO-FACULTAIRE

CTA = CLINICAL TRIAL APPLICATION

CTC = CLINICAL TRIAL CENTER

DSUR = DEVELOPMENT SAFETY UPDATE REPORTS

IMP = INVESTIGATIONAL MEDICINE PRODUCT

IRS = INFORMATIONS DE REFERNCE SUR LA SECURITE

PI = INVESTIGATEUR PRINCIPAL

SAE = SERIOUS AE

SAR = SUSPECTED SERIOUS ADVERSE REACTION

6.2 Definitions

IMP = INVESTIGATIONAL MEDICINAL PRODUCT : active ingredient in pharmaceutical or placebo form tested or used as a reference in a clinical trial, including products already benefiting from a marketing authorization, but used or formulated (presentation or packaging) differently from the authorized form, or used for an unauthorized indication or in order to obtain further information on the authorized form

AE = ADVERSE EVENT: any noxious occurrence in a patient or treatment group in an experiment that is not necessarily related to treatment.

SAE = SERIOUS ADVERSE EVENT = Serious adverse event:

- that results in death or,
- endangers the life of the participant or,
- requires hospitalization or prolongation of hospitalization or,
- results in significant and prolonged disability or incapacity or,
- results in a congenital anomaly or malformation, regardless of dose in a trial.

SUSAR = SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION:
3 CONDITIONS ARE NECESSARY IN RELATION TO THE DEFINITION OF SUSAR:

- serious (intensity defined by the investigator)
- unexpected: the nature or severity of which is not consistent with the product information provided by the sponsor
- suspected drug-related causality as defined by the investigator

SUSAR CAN ALSO BE EXPECTED ADVERSE EVENTS BUT WITH AN UNEXPECTED OUTCOME (E.G., DEATH):

- AN UNEXPECTED OUTCOME (E.G. DEATH) OR
- A CLINICALLY IMPORTANT INCREASE IN THE FREQUENCY OF EXPECTED ADVERSE EVENTS OR
- UNUSUAL SEVERITY OR
- INSUFFICIENT EFFICACY IN LIFE-THREATENING DISEASES.

ASSESSMENT OF CAUSALITY
IMPUTABILITY ALGORITHM USED BY THE WORLD HEALTH ORGANIZATION COLLABORATING CENTER FOR PHARMACOVIGILANCE - UPPSALA-SUEDE (HTTP://WWW.WHO-UMC.ORG/DYNPAGE.ASPX?ID=22682)

- **Certain (certain):** a clinical event, including an abnormality in a laboratory test, that occurs within a plausible time frame following the administration of a drug and cannot be explained by a concomitant disease or other drugs or chemicals. The response to drug withdrawal (cessation of treatment) must be clinically plausible. The event must be definitively pharmacologically or clinically related to the product. A satisfactory method of re-treatment must be employed to determine if the same effect recurs.
- **Probable (probable/likely):** a clinical event, including an abnormality in a laboratory test, which occurs within a reasonable period of time following administration of the drug and is unlikely to be attributable to concomitant disease or other drugs or chemicals. The response to drug withdrawal (cessation of treatment) should be clinically reasonable. Information on resumption of treatment is not required for the event to meet this definition.
- **Possible (possible):** a clinical event, including an abnormality in a laboratory test, that occurs within a reasonable period of time following administration of the drug, but which could also be explained by a concomitant disease or other drug or chemical. Information on drug withdrawal may be absent or unclear.
- **Unlikely:** A clinical event, including a laboratory test abnormality, which occurs within a time frame after drug administration that makes a causal link unlikely. Other drugs, chemicals, or underlying diseases may be plausible explanations.
- **Conditional/unclassified (conditional/unclassified):** a clinical event, including an abnormality in a laboratory test, that is reported as an adverse reaction and for which more information is essential to make a proper assessment or for which further data are under investigation.
- **Unassessable/unclassifiable:** a report suggesting an adverse reaction that cannot be adjudicated because there is insufficient or conflicting information that cannot be completed or verified.

ASSESSMENT OF SEVERITY: The severity of an effect may be classified as mild, moderate, or severe, according to criteria usually specified in the protocol. However, the medical significance of the effect itself may be minor, and the effect may not require immediate reporting to the sponsor and applicable regulatory agencies.
The terms serious and severe are therefore not synonymous.

ASSESSMENT OF SERIOUSNESS: The effect is classified as "serious" if it is associated with effects that threaten the life or physiological functions of the subject, or requires hospitalization or prolongation of hospitalization, or causes significant and long-lasting disability or incapacity, or results in a congenital anomaly or malformation.
The seriousness of an effect is used as a guide to define whether it should be reported.

ASSESSMENT OF EXPECTED OR UNEXPECTED: The adverse reaction is classified as unexpected if, based on its nature or severity, it is not reported in the Investigator's Brochure (for an unapproved investigational product) or the Summary Information Sheet (for an approved product).

7 REFERENCE DOCUMENTS

AAHRPP-FORM-003

AAHRPP-FORM-006

AAHRPP-FORM-015

AAHRPP-FORM-018

AAHRPP-FORM-019

AAHRPP-FORM-028

AAHRPP-FORM-035

AAHRPP-FORM-073

AAHRPP-DSQ-111

AAHRPP-SOP-061

CEHF-DOE-092

CEHF-FORM-104

CEHF-FORM-110

CEHF-DOE-118

Communication from the European Commission - Detailed guidance on the preparation, verification and presentation of adverse event/reaction reports based on clinical trials of medicinal products for human use ('CT-3') (2011/C 172/01)

8 AAHRPP ACCREDITATION STANDARDS

AAHRPP\DOMAIN 1\Standard I-3

AAHRPP\DOMAIN 1\Standard I-7\Element I.7.A

AAHRPP\DOMAIN 1\Standard I-8\Elements I.8.A

AAHRPP\DOMAIN 1\Standard I-8\Element I.8.B

AAHRPP\DOMAIN 1\Standard I-8\Element I.8.C

AAHRPP\DOMAIN 1\Standard I-8\Element I.8.E

AAHRPP\DOMAIN 3\Standard III-2\Element III.2.A

AAHRPP\DOMAIN 3\Standard III-2\Element III.2.C

AAHRPP\DOMAIN 3\Standard III-2\Element III.2.D