Follow-up - Annual report submission procedure

N° de référence :	CEHF-SOP-126
Commission d'éthique hospitalo-facultaire	**Version :** 1.0
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1. OBJET DE LA PROCÉDURE

This procedure describes the submission of an annual report to the Ethics Committee (CEHF) by an investigator and a sponsor of an INTERVENTIONAL PROSPECTIVE EXPERIMENTATION.

2. DOMAINE D'APPLICATION

This procedure is applicable to investigators et sponsors of an INTERVENTIONAL PROSPECTIVE EXPERIMENTATION and to the members of the CEHF[1].

3. DESCRIPTION

3.1. Responsibilities and authorities

3.1.1. Responsibilities of the commercial or non-commercial sponsor of a clinical drug trial

- Submission within the set deadlines, of a Development Safety Update Report (DSUR[2]) (106-AAHRPP-FORM-018) for each clinical drug trial to the competent national authorities and to the main Ethics Committee. This requirement is also specified in the Clinical Trial Agreement.
- Continuously assessment of the benefit / risk ratio of the experiment.
- Inform the investigator of any new element that may influence the safety of participants during or after the end of the experiment.

3.1.2. Responsibilities of the investigator of any prospective interventional experimentation

- Send the annual report form of the experiment to the CEHF (whether local or principal committee) before the annual evaluation date of the protocol determined by the CEHF. This form is prepared, signed and submitted by the investigator to the CEHF
- Provide explanations to the CEHF as required.
- Stop all research-related activities if the CEHF requires so.
- Inform the promoter of the decision issued by the CEHF.
- Inform the participant of any new element that may influence his safety during or after the end of the experiment.

[1] CEHF : Comité d'éthique hospitalo-facultaire
[2] DSUR = DEVELOPMENT SAFETY UPDATE REPORT

3.1.3. Responsibilities of the CEHF[3]

- Receive and evaluate DSURs (if CEHF is PEC/CEP[4]) and annual reports (whether CEHF is PEC/CEP or LEC/CEL[5]).
- Have the authority to stop an experiment carried out at the CUSLs when the evaluation of the benefit / risk balance becomes unfavourable.
- Have the authority to temporarily stop an experiment carried out at the CUSLs when the annual report is not provided within the time limits.
- Provide a renewal of the favourable opinion to the investigator to allow him to continue the clinical research.

3.2.Preamble

3.2.1. Duration of the Ethics Committee agreement

The agreement of the principal ethics committee is valid for the entire duration of the experiment. The date of approval corresponds to the date on which all the conditions for granting the agreement were fulfilled.

- However, with regard to prospective interventional experiments, the sustainability of the agreement depends on the evaluation of the annual report provided by the investigator to the CEHF.
- The CEHF may request that the investigator sends a monitoring report at a higher frequency. The types of research projects subject to such a requirement are those which present an increased risk to the participants (i.e., certain phase 1 protocols, innovative therapies or certain specific medical devices). This more frequent request for review is made by the CEHF on a case-by-case basis after discussion during the initial evaluation of the protocol. This will be clearly notified to the investigator in the initial opinion letter.
- The CEHF agreement is valid for the entire study without any conditions whatsoever for retrospective or prospective non-interventional studies (involving no more than the minimum risk).

3.2.2. Annual report submission date

The annual evaluation date corresponds to one year (365 calendar days) after the approval of the protocol by the **Ethics Committee or by the Ethics Committee responsible for issuing the single opinion in the case of multicentre studies**.

Eleven and twelve months after the CEP agreement date, an email will be automatically generated and sent to the principal investigator and to the principal CRCM[6] to remind them of the sending of this annual report.

The review of the annual report by the CEHF **MUST** be carried out within 365+ maximum 60 days (= 14 months) following the initial or previous agreement. The extension of the agreement therefore begins the day after that date. The annual report must therefore reach the CEHF a maximum of 15 days before the end of this 365 + 60 day period (= 14 months) in order to allow the CEHF to assess the information received within the set deadlines.

[3] CEHF : Comité d'éthique hospitalo-facultaire
[4] PEC/CEP = Principal ethics committee / COMITE D'ETHIQUE PRINCIPAL
[5] LEC/CEL = Local ethics Committee / COMITE D'ETHIQUE LOCAL
[6] CRCM = COORDINATEUR DE RECHERCHE CLINIQUE MEDICALE

Example :

- The initial agreement of the PEC/CEP[7] (whether CEHF[8] or an external ethics committee) is provided on January 20, 2014.
- The annual evaluation date will be January 19, 2015 (agreement date + 365 days)
- An email will be generated automatically on December 19, 2014 and sent to the principal investigator and to the principal CRCM[9].
- A reminder email will also be generated on January 19, 2015.
- The deadline for submitting the annual report will be March 5, 2015 (January 20 + 45 days)
- The deadline for CEHF analysis of the report is March 20, 2015 (January 20 + 60 days).

This period of 365 days + maximum 60 calendar days corresponds to the periods prescribed for the submission of the DSUR to the regulatory authorities (ref: ICH guideline E2F on development safety update report: 2.2 Periodicity and DSUR[10] data lock point)

3.3. Documents to be submitted by the investigator to the ethics committee of the CUSL

3.3.1. *Clinical Drug trial (commercial or non-commercial)*

3.3.1.1. *DSUR : for al clinical trial*

The sponsor provides the DEVELOPMENT SAFETY UPDATE REPORT (106-AAHRPP-FORM-018[I]) containing the list of SAE[11] and SUSARS[12] as well as the safety assessment of participants to

- The competent authorities
- The CEHF or the ethics committee responsible for issuing the single opinion (PEC/CEP) in multicentric studies taking place on the territory of member states and as long as the treatment of participants is in progress in the member state concerned, i.e. until the last visit of the last patient (LPLV[13])) or until the end of the experiment as defined in the protocol

➔ The deadlines for transmitting annual reports begin on the date of the first authorization of the clinical trial by a competent authority in a member state. The annual report must be submitted within 60 days of this deadline. In the case of short-term trials (less than 6 months), the safety report must be sent within 90 days of the end of the trial (as an end-of-study report)

➔ The DSUR must be issued even if no patient was included in the trial.

➔ The sponsor can delegate the realization of the DSUR to a third party.

[7] CEP : COMITE D'ETHIQUE PRINCIPAL
[8] CEHF : Comité d'éthique hospitalo-facultaire
[9] CRCM : COORDINATEUR DE RECHERCHE CLINIQUE MEDICALE
[10] DSUR : DEVELOPMENT SAFETY UPDATE REPORT
[11] SAE : serious adverse event
[12] SUSARS : Suspected Unexpected Serious Adverse Reactions
[13] LPLV : last patient, last visit - dernière visite du dernier patient

3.3.1.2. THE ANNUAL REPORT TEMPLATE

The principal investigator will complete and sign the annual report template (CEHF-FORM-110[II]) in all cases even if another document is provided by the sponsor.

3.3.2. Other prospective interventional experiments

3.3.2.1. ANNUAL REPORT TEMPLATE

The principal investigator will complete and sign the annual report template (CEHF-FORM-110) and send it to the CEHF[14] whether PEC/CEP[15] or LEC/CEL[16] in all cases even if another document is provided by the sponsor.

DOCUMENTS TO BE PROVIDED TO CEHF FOR THE ANNUAL EVALUATION

	Paper Version	Electronic Version	Provided by the sponsor	Provided and signed by the investigatpr
Annual Report		X		X
TO BE ADDED FOR CLINICAL DRUG TRIALS				
DSUR		X	X	

3.4. Evaluation by the Ethics Committee

3.4.1. Annual report received before the annual evaluation date (within the prescribed deadline: 365 + 45 days))

3.4.1.1. After *receipt by the CEHF* and analysis of the annual report during the protocol analysis meeting, if no objection is made regarding the continuation of the study, the investigator will be informed by mail that he can continue the experiment. The investigator will forward this notice to the sponsor.

3.4.1.2. Otherwise, the CEHF will send a letter to the principal investigator asking him to provide the necessary details. The investigator is required to answer these questions.

3.4.1.3. If the CEHF considers that the conditions of the agreement are no longer fulfilled, a temporary cessation of recruitment or an early termination of the study may be required.

- The investigator will notified by letter and will immediately inform the sponsor. The investigator always has the opportunity to respond in person or by mail.
- The CEHF informs the Medical Director and CEO of the CTC[17], he Belgian authorities, the PEC/CEP and the FDA if applicable. In addition, the letters are also available (depending on authorized access) in the Claire database.

[14] CEHF : Ethics Commmittee / Comité d'éthique hospitalo-facultaire
[15] PEC / CEP : Principal ethics committee / COMITE D'ETHIQUE PRINCIPAL
[16] CEP / CEL : local ethics committee / COMITE D'ETHIQUE LOCAL
[17] CTC : Clinical Trial Centre

3.4.2. Annual report not received within 365 + 45 days

- If the CEHF does not receive the annual report within the required deadlines:
  - an email will be sent by the CEHF to the principal investigator informing him that the study will be placed on the agenda of the CEHF meeting held 14 days later.

3.4.3. Annual report received after the annual evaluation date (365 + 60 days)

- If the annual evaluation date is reached before the CEHF agreement is reviewed and approved:
  - No further inclusion of participants can be made at the CUSLs until the extension of the agreement has been obtained.
  - All research activities related to this protocol must be stopped.
  - All interventions on participants during the study must be stopped, unless the CEHF considers that ethical or safety considerations imply that it is in the interest of the participants to continue their participation in the study. In this case, the investigator will also justify the ethical and safety reasons to the CEHF. Therefore, participants during the study will be guaranteed to be kept in the experiment until they withdraw from the study.
- The investigator will be informed by mail and will inform the sponsor immediately.
- The CEHF informs the Medical Director and CEO of the CTC[18], he Belgian authorities, the PEC/CEP and the FDA if applicable. In addition, the letters are also available (depending on authorized access) in the Claire database.

[18] CTC : Clinical Trial Centre

4. DISTRIBUTION

Cette procédure est à diffusion

Publique ☒

Restreinte à l'unité/entité/département ☐

5. RÉFÉRENCES

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...

ICH GCP 1996 –Directives 2001/20/CE et 2001/83/CE – Loi relative aux expérimentations sur la personne humaine 7/5/2004

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500097061.pdf

http://ec.europa.eu/health/files/eudralex/vol-10/2011_c172_01/2011_c172_01_en.pdf

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM294558.pdf

http://www.fagg-afmps.be/fr/humain/medicaments/medicaments_a_base_de_plantes/recherche_developpement/essais_cliniques/ : Circular 586

http://www.fagg-afmps.be/fr/binaries/Circulaire-593-2012-12_tcm291-208387.pdf

[I] 106-AAHRPP-FORM-018_ Modèle Development Safety Update Report (DSUR)

[II] CEHF-FORM-110_Suivi - Template rapport annuel