Newsletter
Ethics Committee Research UZ/KU Leuven
Number 7 –November 2019

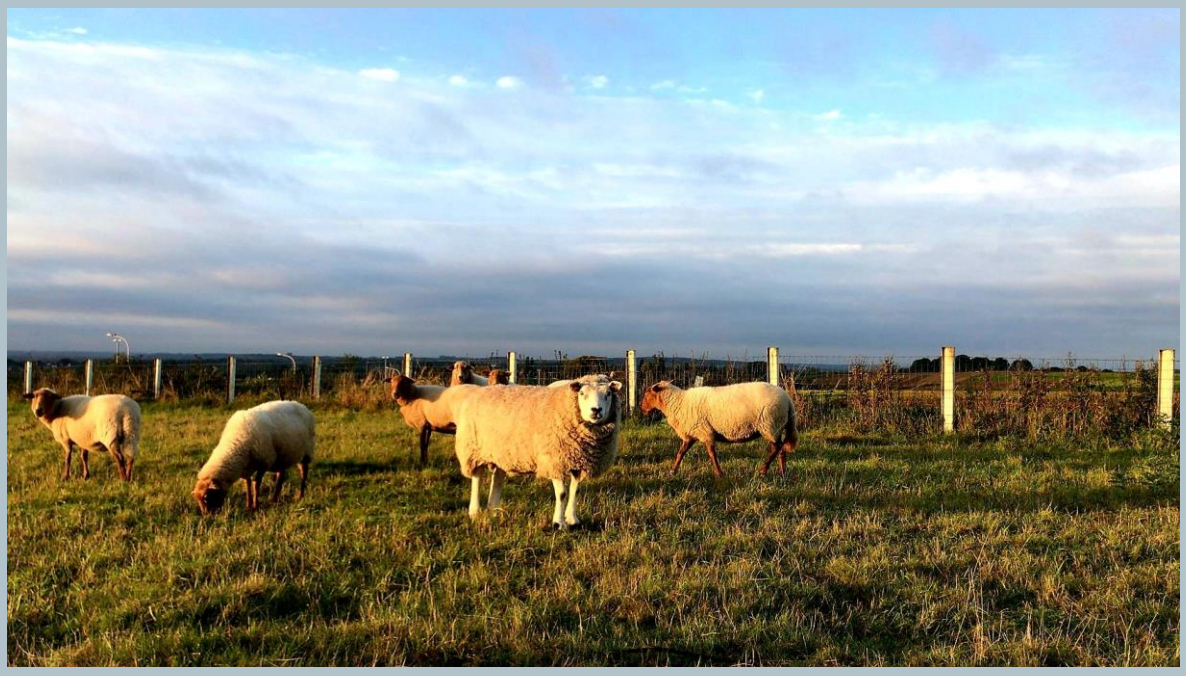
Dear researchers and teams

With this newsletter we would like to share some tips and tricks enabling and supporting high-quality clinical research with respect for the well-being and privacy of each patient and volunteer.

Ethics Committee Research UZ/KU Leuven

Members: Ariel Alonso Abad, Dominique Bullens, Simon Brumagne, Pascal Borry, Xavier Bossuyt, Lut De Groote, Jan de Hoon, Hélène De Somer, Jean-Jacques Derèze, Lieve Goossens, Stefanie Goris, André Loeckx, Kristof Muylaert, Ben Nemery, Marleen Renard, Katrin Roggeman, Miet Schetz, Karin Sipido, Anne Smits, Mathijs Swaak, Josse Thomas, José Thomas, Anne Uyttebroeck, Ben Van Calster, Jan Verhaegen, Gregor Verhoef, Minne Casteels

Staff: Valerie Alderweireldt, Eveline Claes, Britt Keyaert, Monique Leys, Lian Rijkers, Ruth Storme, Greet Verbeeck, Sofie Vervoort



## 1. Quality of academic studies

We would like to stress the importance of a scientifically valid protocol, a clear research question, and a statistical analysis plan when appropriate. If you describe a study as only exploratory, you are reminded that the exploratory nature should be duly reflected in the future publication/communication about the results.
We also invite you to review all documents carefully before submission to EC in order to provide sufficient consistency (e.g. between protocol and ICF) and to use appropriate language and spelling. EC is not able to review submissions where a proper protocol is missing.

## 2. Patient representatives as EC members

In 2021 or later, the European regulation will apply to all clinical trials with medicines (CTR 536/2014). This Regulation requires each Ethics Committee to appoint a patient representative as a member. This is a new requirement which is not applicable in the current legislation.

What is the role of a patient representative within EC Research?

- Reviewing and evaluating submitted clinical trial dossiers, which will be provided electronically;
- Preparing written comments as feedback which should be provided prior to the EC Research meeting;
- Participating in EC Research meetings on Monday morning (1 to 3 times/month);
- Presenting the patient's perspective: a "non-scientific" and humanistic vision together with the practical feasibility of the study from a participant's point of view;
- Ensuring that informed consent and information to patients is comprehensive;
- Ensuring that patients' rights are respected.

It is provided by law that the patient representative may not have a health care profession (such as a nurse, doctor, pharmacist, etc.).

We are currently looking for patient representatives to join EC Research.
If you know potential candidates who are interested, you may encourage them to contact Minne Casteels (minne.casteels@uzleuven.be) or Ruth Storme (ruth.storme@uzleuven.be).
After a meeting with the candidates a selection of complementary profiles is made.

### 3. Adverse events and "Patient-related incident reporting and management system" (PiMS)

EC already highlighted the importance of PiMS in its previous newsletter. More information about PiMS can be found in the Muzlidoc procedure (only accessible within UZ Leuven).

Some examples of PiMS in a study context are:

- Administration of the wrong medication (e.g. commercially available medication administered instead of study medication);
- Study participant develops anaphylactic shock;
- Administration of the incorrect dose of the supporting medication.

If an event is reported via this link for which it is indicated that EC review is necessary, it will automatically be forwarded to EC.

### 4. Ethical approval required when using "historical" cell lines

As several questions came up about this matter, we repeat this paragraph from a previous newsletter.

Cell lines (= cells that are manipulated in such a way that their characteristics differ from the original cell, such as industrial preparations) fall within the scope of the Human Body Material Law dd 19.12.2008. Article 21 of this Law describes that any secondary use of human body material (including cell lines, regardless of the degree of their manipulation) requires EC approval before the start of the research.
In the past, some uncertainty existed whether "immortalized"/"immortal" (i.e. "historical") cell lines (either commercially available or generated locally) fall under the scope of the above mentioned Law. This is clarified and confirmed at https://www.afmps.be/sites/default/files/content/compendium_20072018_0.pdf which clearly states that "historical" cell lines fall within the scope of the Human Body Material Law. The same applies for "transformed" material (material that has been manipulated in such a manner that the genetic code has been substantially modified).
Consequently, historical cell lines and transformed material used for scientific research fall within the scope of the Human Body Materials Law and therefore require an EC approval before the start of research.

Please be informed that human biological material must be registered in the UZ-KU Leuven Biobank before it can be used for scientific research. More information can be found on its website.

## 5. Good Clinical Practices (GCP)

Training in ICH GCP guidelines is mandatory for every PI, but also for each member of his/her study team. It is the responsibility of the PI to make sure that all members of the study team are properly trained and in addition, the PI should supervise that the study team is conducting the study according to ICH GCP.

The CV of the PI should explicitly state the date of the most recent ICH GCP certificate (**less than 3 years old**) and the certifying **organization**, or alternatively, a copy of the ICH GCP **certificate** should be included in the submission of the study file. EC currently accepts certificates

i) from the training at UZ/KU Leuven (cf. below), and
ii) from online training courses that have been approved by Transcelerate.

The Biomedical Sciences Group at KU Leuven regularly organizes ICH GCP trainings. The upcoming trainings are planned in UZ Leuven on 14 February 2020 and 8 May 2020. EC Research requests to follow at least once the complete GCP training. Subsequently, it is possible to take only the exam of this training at the end of the day without having to follow the whole training again.
For both options registration is requested and can be done via https://uzleuven.learn.taleo.net/ (Leercentrum).

A KU Leuven employee first needs to create an account by opening the following link: www.uzleuven.be/leercentrum. Then click on “Externen”.

## 6. Informed Consent Form (ICF)

EC understands that the research team often receives the IC forms for commercial studies at a late stage. However, we would like to ask you to carefully check these forms before submitting them to EC, in particular whether the ICF is written in a language that can be understood by lay people.

As described in our previous newsletter, a **new national ICF template** for adult **patients** participating in an interventional **clinical trial** is prepared. The template (in Dutch, French and English) is published on our website and is also available on the website of the CT-College.

Sponsors are highly recommended to use the template when preparing the ICF(s) for all **new** initial interventional clinical trials with an investigational medicinal product on adult patients. During the next months a transitional period will be in place during which both the old and the new template can be used. From 1st January 2020, the ethics committees will request that only the new template is used by all sponsors for new clinical trials with adult patients.

## 7. Harms from Uninformative Clinical Trials

This article (*Harms From Uninformative Clinical Trials)* criticizes uninformative clinical trials. An uninformative trial is one that provides results that are not of meaningful use for a patient, clinician, researcher, or policy maker. The article underlines the need for less research, better research and research for the right reasons.

The following are necessary conditions for a trial to be **informative**:

(1) the study hypothesis must address an important and unresolved scientific, medical, or policy question;
(2) the study must be designed to provide meaningful evidence related to this question;
(3) the study must be demonstrably feasible (e.g. it must have a realistic plan for recruiting sufficient participants);
(4) the study must be conducted and analyzed in a scientifically valid manner;
(5) the study must report methods and results accurately, completely, and promptly.

Trials that do not meet all of these conditions are very likely to be uninformative.

**Four broad recommendations** are described in this paper:

- Academic medical centers (AMCs) and other groups that sponsor research, should embrace their responsibilities as research sponsors by ensuring that each trial receives meaningful scientific review by a funder or another body identified by the AMC prior to its initiation. This review should ensure that each new trial is informed by the body of relevant completed and ongoing studies. The review should also include scrutiny of the study design to identify and remediate any serious design flaws. Such a process might focus on those trials that are not likely to get reviewed through other processes and those perceived to be at greatest risk for being uninformative (e.g. trials with no external funding, trials by less experienced investigators, or trials with design characteristics that carry high risk of bias).
- In the spirit of "*you can't improve it if you can't measure it*," priority should be given to the development of metrics that reflect the extent to which the 5 conditions (see above) of informative trials are being met.
- Incentives need to be developed that reward researchers, trial sponsors, or AMCs for conducting informative trials, and for strongly discouraging the conduct of uninformative trials.
- Funders similarly have a responsibility to ensure that the trials that they fund are likely to be informative. This would require a more detailed review of the trial protocol, in some cases, and a process for holding the researchers they are funding accountable for ensuring

that the conduct, analysis, and reporting are done in scientifically appropriate and timely manner.

## 8. Retrospective studies

In our newsletter of December 2018, we have already given some suggestions on how to set up a retrospective study and what to pay attention to. A retrospective study is a study based on data from the past, data which are already available in existing patient files, medical files or administrative files (cf. article 3, §2 of the Law of 7 May 2004).
We additionally advise you to always use the **protocol template** that is designed by the Clinical Trial Center (CTC).
You can find more information about retrospective studies on our website.

## 9. Response to comments of EC

For commercial trials where submissions are delegated to the sponsor or CRO, we often see that the local study team from UZ Leuven is not informed (in cc in e-mail) of a submission. We would like to ask you to communicate this to the sponsor and to always request to copy a dedicated person of your study team in UZ Leuven in the e-mail communication between sponsor and EC.

We observe this mainly in the submission of responses to EC's comments. In case we notice this, EC will ask the PI if he/she agrees with this resubmission. The Sponsor's/CRO's feedback to the EC comments will not be assessed until we have received the confirmation from the PI.

## 10. Submit separate documents

EC regularly notes (mainly in academic studies) that several documents are submitted as 1 document, for example questionnaires and ICF that are included in the same document as the protocol.

May we ask you to submit each document separately according to the folder structure available on our website.

## 11. Online registration CTC

From now on, the submission of a study to the Clinical Trial Center (CTC) can be done electronically via this registration form. Submission by email will still be accepted during a transitional period.

In order to facilitate contract review by the legal department and to allow a privacy check by the ethics committee you will also be requested (in the email in which the assigned S-number is mentioned)to complete the **GDPR questionnaire**.
The GDPR questionnaire needs to be filled in for each study or research project where UZ/KU Leuven acts as sponsor or as participating site and where personal data are used.
Please note that a completed GDPR questionnaire will be a condition for an acceptable submission to EC.
The GDPR questionnaire and the guidance document for completing such questionnaire can be found on the CTC's website: http://wiki/display/ctc/GDPR.

### 12. Confidential handling of patient data in communication to EC

We would like to stress the importance of confidential handling of patient data. When asking questions to EC Research or when submitting patient documents of deaths, SUSARs, Medical Need notifications… please make sure **never** to mention any patient names in the communication to EC.

### 13. Approval letter EC

EC would like to draw your attention to the fact that remarks and/or conditions can be listed in the approval letter. Therefore, it is important to carefully read the full content of our letter.
We also inform you that the approval letters of EC will soon only be sent in English.

### 14. Submitting amendments simultaneously to all participating sites

Please be aware that the EC of UZ Leuven, when acting as local EC, ratifies the approval of the central EC for a study.
We strongly advise to always submit a substantial amendment with an adapted ICF included, simultaneously to central and all local ECs involved in the study.
Currently, if UZ Leuven is acting as local EC in a study, our comments (if applicable) are sent to the central EC which will collect all local advices in one final advice that will be sent to the sponsor by the central EC.
Amendments are often only submitted to the central EC. As local EC, we receive afterwards the letter of approval as a notification. If EC UZ Leuven has comments on the submitted (and approved) documents, the sponsor will need to re-submit an amendment to the central EC in order to answer/implement our comments which causes delays. The flow proposed above will therefore be more efficient.

Within BAREC (Belgian Association of Research Ethics Committees), a working group, coordinated by EC UZ Leuven, will design a harmonized flow with regard to multicentric studies, also based on

the principle of simultaneous submission. We will keep you informed as soon as this flow will be established.

**15. Annual progress report**

We have already informed you via our previous newsletters that the submission of an annual progress report to EC according to ICH GCP is mandatory after ethical approval. We would like to add that this report must be submitted within 30 days of the anniversary date on which the favorable opinion was given, and annually until the study is declared ended.

**16. Reduced fee concept for National Scientific and Technical-Regulatory advice (STA) (communication from the Innovation office of FAMHP)**

The reduced fee concept comprises a reduced fee for small and medium enterprises (SME), universities, certified hospitals, foundations for the public good and statutory administrations for requests for national STA on research into and the development of a medicine with the intention of possible application for marketing authorisation or registration of a drug or a request for a change of such. The STA fee for those type of Applicants is reduced by 75% (i.e. compared to the standard fees for STA requests of type I, II and IIIa) to make this FAMHP service more accessible for SMEs and non-commercial organizations and thus support and accelerate the development and access to innovative medicines in Belgium.

In order to be eligible for the reduced fee as a university or certified hospital, they should be formally acknowledged by the FAMHP as sponsor of non-commercial studies as defined by art. 31 of the Law of 7 May 2004.

The exact fees for SMEs and universities, certified hospitals, foundations for the public good and statutory administrations can be found here:
o STA type I: €541.75
o STA type II: €3,250.49
o STA type III: €4,333.99

The differences between the three types are described in this document.

## 17. Contact EC Research UZ/KU Leuven

- EC Research is closed from 20 December 2019 to 27 December 2019.

Info

**Information**

ec@uzleuven.be
www.uzleuven.be/ethische-commissie/onderzoek
Telephone: 016 34 86 00 (between 10 am and 11 am)