Newsletter
Ethics Committee Research UZ/KU Leuven
Number 19 – December 2022

Dear researchers and team

We wish you a Merry Christmas and a happy 2023.
With this newsletter we hope to support you in doing high-quality clinical and translational research with respect for the well-being and privacy of each patient and participant.

Ethics Committee Research UZ/KU Leuven

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1. Research with food products

From 31 January 2023 onwards, the European Clinical Trial Regulation will apply to all interventional clinical trials with medicines (CTR 536/2014).

Article 2(2) (1 and 2) of the Clinical Trials Regulation provides a definition of a "clinical study" as well as a "clinical trial":

'**Clinical study**' means any investigation in relation to humans intended:
(a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products;
(b) to identify any adverse reactions to one or more medicinal products; or
(c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products; with the objective of ascertaining the safety and/or efficacy of those medicinal products;

"**Clinical trial**" means a clinical study which fulfils any of the following conditions:
(a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned;
(b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or
(c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects.

On p. 117/142 of the Q&A about the CTR. It is mentioned that food products are not considered medicines.

This implies that research with food products will not fall under the definition of a Clinical study/trial described in the CTR.

In a study in which the safety and/or efficacy of food products will be investigated, the national Belgian law of 7 May 2004 does apply.

2. Winter clock stop

Please be informed there is a winter clock stop between 19/12/2022 and 01/01/2023. Submissions performed during this period, will have 02/01/2023 as a validation date.

3. Clinical trials: Development Safety Update Report replaces the Annual Safety Report

Since February 2021, it is required by FAMHP that the Development Safety Update Report (DSUR) must comply with the ICH E2F guideline. The previously accepted Annual Safety Report format is no longer acknowledged by FAMHP. The DSUR is submitted annually for the entire duration of the clinical trial to FAMHP and to the central Ethics Committee that has approved the clinical trial under the Clinical Trial Directive (CTD).
For clinical trials approved under the Clinical Trial Regulation (CTR) it is required to submit the DSUR through the EU portal CTIS. A trial is "ongoing" from the day of the first authorization, not as from its actual start date. Clinical trials lasting less than one year do not have to submit the DSUR. In such cases, a clinical study report at the end of the trial is sufficient. A new template for the DSUR is available on the CTC website. This can be found under "procedural documents".

4. Early Access Programs

The law on medicinal products of the 25th of March 1964 describes how medicinal products that are not authorized in Belgium (or only authorized in different indications), can be provided to patients under certain conditions.

The guidance describing, among others, the process to submit a compassionate use program and medical need program is available here.

Compassionate use program

For non-authorized medicinal products this can be done for compassionate reasons ("**compassionate use**") for a group of patients with a chronically or seriously debilitating disease or whose disease is considered to be life-threatening, and who cannot be treated satisfactorily by an authorized and reimbursed medicinal product. The medicinal product concerned must either be the subject of an application for a marketing authorization by the centralized procedure (cf. article 6 of Regulation 726/2004) or must be undergoing clinical trials for the related indication.

An applicant can apply for a compassionate use program as described in article 106 of the Royal Decree of 14/12/2006 as changed by the Royal Decree of 25/04/2014. A dossier needs to be submitted to the FAMHP.

Medical need program

For products authorized in Belgium, this can be done in cases where a patient has a chronic disease, a disease with a serious impact or a life threatening disease that cannot be treated satisfactorily by a product that is authorized and reimbursed for this indication in Belgium ("medical need programs"). Additional conditions are :

1. a demand to obtain authorization for the indication in question needs to be in process
2. or the indication has been authorized but the product is not yet commercially available
3. or clinical trials are ongoing in this indication or clinical trials have demonstrated the relevance of the use of the medicine in the envisaged indication

Only a single indication can be approved per program.

An applicant can apply for a medical need program as described in article 108 of the Royal Decree of 14/12/2006 as changed by the Royal Decree of 25/04/2014. A dossier needs to be submitted to the FAMHP.

In general

The main goal of a CUP or MNP is to provide early access to a new innovative medicinal product which addresses an unmet medical need or shows a major therapeutic advantage. From a methodological point of view, clinical trials are practically the only means of obtaining reliable and interpretable efficacy and safety data for a medicinal product. Although safety data may be collected during CUPs or MNPs, such programs cannot replace clinical trials for investigational purposes.

CUPs and MNPs are not a substitute for properly conducted trials and should therefore not slow down the implementation or continuation of clinical trials intended to provide essential information relative to the benefit/risk balance of a medicinal product. Patients should always be considered for inclusion in clinical trials before being offered inclusion into a CUP or MNP. Hence, if the objective is to continue the clinical data collection (e.g. extension of follow up), CUP/MNP shall not be possible. But if the objective is to continue access of the MP for patients included in the study pending the access through the normal distribution pathway, it is indeed possible to set up a CUP/MNP.

Responsible physician

The FAMHP guidelines and Q&A state that the responsible physician of the CUP cannot act as a treating physician in the CUP given that in this case this responsible physician would have to include his/her own patients to the program.
"The responsible physician" is understood as stipulated in the Royal Decree nr. 78. The task of the responsible physician falls within the practice of medicine (art. 2) and so art. 7 (license to practice) is applicable. This assures (because of the ethical oversight) the independency of the responsible physician with respect to the responsible of the program.

Urgent situations / patient named

Exceptionally, in urgent cases, a medicinal product which is not available on the market can be used without requesting a CUP. It has to be motivated by the fact that a patient is in immediate risk of dying or that the risk of non-treatment is higher than the inherent risks of the treatment.

Additionally the following conditions should be met:

1. The medicinal product in question is not a drug used in a CUP, in a clinical trial (or if the patient could not be enrolled within such clinical trial) or/and is not a drug for which a registration or a marketing authorization is not required;
2. The patient cannot be treated with a marketed medicinal product, a product under hospital exemption or with a magisterial preparation;
3. It is impossible to import a marketed medicinal product with the same qualitative and quantitative composition of active drug substance and the same pharmaceutical form (as stated in article 105 of the Royal Decree of 14/12/2006);
4. No submission can be made for a CUP, unless such an application has been made or if you have the intention to submit such a request. The FAGG stipulates in his guidance that, "if you have the intention to recruit several patients in this urgent program, the applicant should submit a CUP".

A **notification** to the FAMHP, the ethics committee of the site concerned and the medical director of the hospital is strongly recommended, but is not required for starting the treatment. We refer to article 107/1 of the Royal Decree of 14/12/2006 as changed by the Royal Decree of 25/04/2014.

This notification should consist of:

- the name of the sponsor
- the name of the treating physician
- a sworn statement from the physician that the informed consent was obtained in accordance with the law of 22 August 2002 on patient rights
- the indication
- the motivation that without appropriate treatment, it is expected that the patient's death occurs in a short delay or that the risk for the consequences of the absence of treatment is greater than the risk for the consequences of starting the treatment is included. Please discuss the indication of the patient as well as the previous treatments that the patient received, the unmet need and the benefit/risk balance of treatment along with the urgency for this treatment.

A template of an ICF, notification letter and sworn statement from the physician can be found on our website.

5. Off label use

When a medicine is used outside the authorized dosage, age/patient category, therapeutic indication and/or administration route, this is referred to as off-label use. Off-label use is done under the responsibility of the prescribing physician and fits in with his/her therapeutic choices. If not reimbursed, the patient should bear the costs for this him/herself and should be duly informed about the cost.

More information can be found here.

6. Good Clinical Practice (GCP)

In a collaborative effort, the CTC's of all 7 Belgian academic hospitals have developed a GCP-e-learning. The training is being offered through the UZ leercentrum. Completion of this e-learning via UZ leercentrum will result in an internationally recognized training certificate which remains valid for 3 years (or until the next GCP revision). Training in ICH GCP guidelines is mandatory for every principle investigator (PI) but also for each member of his/her study team. EC requests a copy of the ICH GCP certificate of the PI in the submission of a study file. We would like to emphasise that when the GCP training is completed through the UZ leercentrum, EC is automatically notified of this. In other words, when this GCP training is completed by the PI, for three years, a copy of the GCP certificate should not be submitted to EC.

7. Recommendation paper on decentralized elements in clinical trials

We mentioned in our previous newsletter, that an EU DCT project group has been launched to write a recommendation paper on the use of decentralised elements in clinical trials. We want to inform you that the recommendation paper is now published.

This recommendation paper aims to facilitate the conduct of decentralized clinical trials (DCTs) while safeguarding the rights and well-being of participants as well as the robustness and reliability of the data collected.

The recommendations include an overview of national provisions for specific decentralised clinical trial elements to be used in clinical trials. They are expected to evolve as knowledge increases and experience is gained. In particular, the overview of national provisions will be updated on a continuous basis.

We would like to highlight the importance of carefully looking at the decentral elements of any protocol you are confronted with as investigator, as numerous responsibilities may finally be yours.

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