Newsletter
Ethics Committee Research UZ/KU Leuven
Number 25 – May 2024

Dear all,

As EC Research we have the task to protect study participants and to guide you (and ourselves) through an increasingly complex regulatory landscape which does not (always) facilitate research or innovation, and can be demotivating to all of us.
We are aware of the challenges you encounter, and try to find the best way forward, aiming for an optimal benefit/risk balance for participants, your research and our institution.
Our comments and suggestions are intended as an auxiliary means towards a study which is acceptable in the present regulatory framework, and which is methodologically sound.

Our ongoing mission is to contribute to safeguarding the general well-being, safety, dignity, rights, and privacy of patients/healthy volunteers participating in clinical research. EC ensures independent advisory services, always prioritizing the welfare of the participants. EC Research is obliged to adhere to strict time lines, which only start at the moment a study submitted to EC is eligible.
On the other hand, the Clinical Trial Center (CTC) is a separate entity and supports financial and legal handling of clinical studies and data management.

Wishing you all the best in your endeavours,

Ethics Committee Research UZ/KU Leuven

Members: Dominique Bullens, Ariel Alonso Abad, Pascal Borry, Guy Bosmans, Xavier Bossuyt, Simon Brumagne, Michèle Dekervel, Jean-Jacques Derèze, Erwin Dreesen, Lut De Groote, Theresia De Fraye, Jan de Hoon, Aernout De Raemaeker, Lia De Wilde, Dorien Fierens, Rik Gosselink, Walter Janssens, André Loeckx, Koen Luyckx, Marleen Renard, Angélique Rézer, Miet Schetz, Peter Sinnaeve, Karin Sipido, Anne Smits, Mathijs Swaak, Anne Uyttebroeck, Annick Vanclooster, Marilien Vandeputte, Veerle Vanparys, Frank van Calenbergh, Ben Van Calster, Bart Van der Schueren, Laura Van Gerven, Kristel Van Landuyt, Katelijne Van Overwalle, Jan Verhaegen, Gregor Verhoef, Minne Casteels

Staff: Irene Borginon, Britt Keyaert, Monique Leys, Lian Rijkers, Ruth Storme, Kaat Van huyck, Indra Verhaeghe, Sofie Vervoort

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1. New members

We welcome Catherine Cassiman, Kristin Verbeke, Heleen Delbeke, Francesca Bosisio, Kamiel Verbeke, Ellen Deleus, Valerie Christens, Marie Gilliot and Frederik Nevens in EC Research.

2. Statistical Analysis Plan

In its October 2021 newsletter, EC already referred to L-BioStat for statistical advice. To all researchers of the Group Biomedical Sciences, L-BioStat offers consultation to provide statistical advice on various methodological and statistical aspects of the research project. Free advice is provided through scheduled one hour consulting appointments. Furthermore, it also offers in-depth collaborative consulting, including analysis of data, writing of a statistical report and incorporation of the results in (an) article(s). You can also discuss/collaborate with colleagues with extensive biostatistical expertise, from several departments in KU Leuven both in Biomedical Sciences as in the other groups.

EC Research invites you to mention in the cover letter accompanying the initial submission of a retrospective study whether the statistical aspects of the protocol (design, rationale of sample size, SAP) have been discussed with a stats expert. In that case EC may waive stats review of your study.

Please be aware that approval by EC does not guarantee the absence of issues within the protocol, nor does it ensure that all advice provided will be adhered to during data analysis or the preparation of scientific publications. Reviewing the quality of publications is primarily the responsibility of the journals themselves, but as a researcher, you also have the necessary responsibility in this matter. It is fortunate that the most reputable journals generally maintain relatively high standards, and these are the publications that have the most significant impact on the scientific community. We encourage researchers to include the EC-approved protocol alongside their submissions as supplementary material. This step not only enriches the transparency of your research but also sets a commendable example of Open Science principles in action.

3. Secondary use of patient data

As stated in our previous newsletter, there is an opt-out mechanism providing patients with the option to oppose data reuse in cases where scientific studies are conducted outside the public interest. For these studies, participants are only informed about the study by Mynexuzhealth. The sections under 'Research' in the GDPR questionnaire will automatically be included in Mynexuzhealth. The description of the study that must be filled out in the GDPR questionnaire needs to be completed in Dutch and in layman's terms. This is crucial as it will serve to properly inform the data subjects in accordance with the information and transparency obligations under GDPR.
This ensures that patients understand how their data have been utilized, and it guarantees the comprehension of the research's significance by individuals without medical training.
You can find an informative video here which explains data reuse: https://wiki.uz.kuleuven.ac.be/pages/viewpage.action?pageId=761456327

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4. Deviation from an approved protocol is only possible after a prior approval of an amendment by EC/competent authority (CA)

For studies sponsored by UZ/KU Leuven, the CTC monitoring unit continues to observe an alarming amount of 'waivers' with regards to inclusion and/or exclusion criteria, without prior EC/CA approval. Adherence to the protocol is a fundamental part of the conduct of a clinical study. Any significant change to the protocol should be submitted as an amendment/modification to the competent regulatory authority and ethics committee. Significant changes to the protocol include any change in inclusion and exclusion criteria, addition or deletion of tests, dosing, duration of treatment etc.
Deviations from the inclusion/exclusion criteria of the protocol might erode the scientific and ethical value of the protocol and its authorisation and might have an impact on the processes put in place for the care and safety of the study subjects.
Sponsors and investigators should not downplay or systematically approve protocol deviations, in order to effectively widen the scope of a protocol.
The protocol design should be appropriate to the populations required and if the protocol design is defective, the protocol should be amended and submitted for approval as soon as possible.
GCP does permit deviations from the approved protocol when necessary to eliminate immediate hazards to the subjects, but this should not normally arise in the context of inclusion/exclusion criteria, since the subject is not yet fully included in the trial at that point in the process.
EMA GCP inspectors have observed a number of these situations and have published a Q&A on this topic. See Question B1 https://www.ema.europa.eu/en/human-regulatory-overview/research-development/compliance-research-development/good-clinical-practice/qa-good-clinical-practice-gcp#b-gcp-matters-7075

The use of waivers with regards to inclusion and/or exclusion criteria, without prior EC/CA approval is not considered to be appropriate nor compliant with GCP. Additionally, the insurance policy for the study may not cover any claims if the approved protocol was not followed, and grant providers may recall (part of) the research funding based on breach of contract.
Instead of deviating from an approved protocol, the sponsor should submit a protocol amendment without delay, and await approval from EC and/or CA prior to implementation.

5. Intranet UZ Leuven for study announcements and participant recruitment

Intranet might be used for announcing your study and recruiting participants. Please ensure that the utilization of Intranet as well as any other means used to announce a study are explicitly stated in your study protocol; they need approval by the Ethics Committee. These include both "traditional" channels (posters, leaflets, etc.) and various forms of advertising via the internet (website, social media, etc.). Any specific text, flyer, or poster intended for dissemination via Intranet must receive approval from the Ethics Committee (EC) before distribution. Any announcement should mention the S number and the approval by an EC.

6. Retrospective study

For the definition of a retrospective study, we refer to the Law of 7 May 2004: *a retrospective study is a study based on data from the past already available in existing patient files, medical files or administrative files and to the extent no new data will in any way be collected for the purpose of such study (cf. article 3, §2 of the Law of 7 May 2004).*

Any research project involving the processing of personal data should be submitted to EC Research to enable a "privacy check", among other things; this applies also to retrospective studies. A GDPR questionnaire was developed to facilitate such a privacy check and is an integral part of the registration process at EC Research.

In addition to facilitating the privacy check, this GDPR questionnaire serves another purpose: fulfilling the information obligation towards research participants (transparency), i.e. to provide a description of the purpose of the research. The sections under "Research" in the GDPR questionnaire are automatically included in Mynexuzhealth for UZ Leuven patients (or patients in other Nexuz hospitals). Research participants are informed about the studies in which their data are processed after being flagged with the corresponding S number in KWS. In Mynexuzhealth, the description of the study can consequently be found, and this under "Projects".

Below is a paragraph containing the definition of a retrospective study that can be included in this patient-friendly summary to inform patients about the use of their data in a retrospective study:

"Retrospectieve studies maken alleen gebruik van gegevens die reeds beschikbaar zijn in het medisch dossier of in een database en bekomen op geen enkele wijze nieuwe gegevens met betrekking tot een patiënt of studiedeelnemer. Dit type onderzoek kijkt terug in de tijd om patronen of resultaten te onderzoeken die verband houden met specifieke aandoeningen of behandelingen. Uw medische informatie zal gebruikt worden in deze retrospectieve studie."

7. Fee commercial retrospective studies

We want to inform you about a recent update regarding the submission fee for commercial retrospective studies. Please note that a fee of €1000 is requested for the evaluation of commercial retrospective studies by EC Research. Therefore, please provide the following data to EC research on submission of a commercial retrospective study:

- Invoicing address (preferably an address in Belgium)
- Name of contact
- PO number (Purchase Order), if applicable
- VAT number

You will receive an invoice from the Financial department of UZ Leuven (with payment reference).
Payment is only possible upon receipt of an invoice of the Financial department.

8. Patient Referrals

All referrals of UZ Leuven patients to external centers for studies or research-related examinations, which do not take place within UZ Leuven, necessitate approval from the Medical Director, and preferably, the Medical staff council in your clinical department. This procedure also applies to the distribution of flyers for non-UZ Leuven studies within our institution. Submission to the Ethics Committee Research of UZ/KU Leuven is not required.

9. How to make proper audio recordings?

It is essential to ensure secure methods for audio recording in clinical studies. Here are some best practices to follow:

- **Use Secure Devices**: Avoid using personal devices like mobile phones for recording due to security risks. Instead, utilize institution-provided or dedicated recording equipment. The risk of data breaches with mobile phones is too high (failure to delete recordings promptly, others accessing the phone, etc.). Better alternatives are available, such as making recordings using laptops or dedicated recording devices that offer better security and control over data.
- **Access Control**: Limit access to recorded data to authorized personnel only, and implement measures to prevent unauthorized access.
- **Deletion**: Delete recordings promptly after transcribing them, when they are no longer needed for analysis or documentation purposes to minimize the risk of data breaches.

By adhering to these practices, we can safeguard the integrity and confidentiality of data collected through audio recordings in clinical studies.

10. Necessity of respectful interaction among colleagues and good communication within research projects

Recently, EC experienced some issues with the involvement and communication between researchers. Specifically, it pertains to situations where Human Biological Material (HBM) from previous studies is utilized for further research, with ambiguity regarding the involvement and consent of all relevant parties.

It concerns new requests for research studies utilizing HBM obtained from patients, originally collected as part of an earlier study. In this initial study, which received approval under a specific S-number, one of the PI's was affiliated with one department and the co-investigator was the treating physician (from another clinical department). However, in the submission of the new study with a different S-number, there is no reference to the involvement or consent of the treating physician in the protocol. It remains unclear whether this colleague has been informed of the new study, let alone if they agreed with it.

This situation emphasizes the necessity of respectful interaction among colleagues and effective communication within research projects, regardless of whether they are prospective or retrospective in nature. It is crucial that all relevant parties are fully briefed and consent to the progression of research endeavors, especially when these involve valuable bodily materials from patients. The inclusion of treating physicians in such follow-up studies is of great importance. Merely informing them about the outcomes *post facto* is insufficient.

Hence, we call for mutual respect, alignment and communication among all parties involved in future research undertakings.

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11. Use of medical devices in the study

When a medical device is used as part of a study to assess its effectiveness or safety, the study may fall under the Medical Device Regulation (MDR). There is a distinction when a device is utilized during the study solely for data capture purposes but is not the focus of the study itself. However, even in such cases, we ask to inform us about the device being used. This information must be included in the study application. The use of devices that capture and potentially further process data may entail privacy or other risks. As such, the EC has formulated a paragraph to be included in the Informed Consent Form (ICF) when, for instance, a Fitbit is used in the study.
It is crucial to ensure transparency and mitigate any associated risks by adequately addressing the use of such devices in the study protocol and consent documentation. Additionally, researchers should provide detailed information on how data, collected from these devices, will be handled, stored, and protected to safeguard participants' privacy and confidentiality.

Hereby the proposed paragraph in the ICF:

> *"Bij het gebruik van Fitbit (of vul naam in van een ander consumentenproduct waarbij een gelijkaardige datacollectie gebeurt (m.n. verzamelen gezondheidsdata)) als onderdeel van deze studie dient u zich bewust te zijn van en akkoord te gaan met de volgende voorwaarden:*
>
> - [optioneel: schrappen indien niet van toepassing] *U begrijpt dat het gebruik van Fitbit noodzakelijk is om deel te nemen aan deze studie.*
> - *U begrijpt dat UZ Leuven geen invloed kan uitoefenen op de gebruiksvoorwaarden van Fitbit.*
> - *U begrijpt dat uw gegevens worden verzameld en verwerkt volgens de voorwaarden van Fitbit.*
> - *U begrijpt dat uw gegevens mogelijk door Fitbit kunnen worden gebruikt voor andere doeleinden (zoals beschreven in de gebruiksvoorwaarden van Fitbit)en dat anonimiteit niet volledig kan worden gegarandeerd.*
>
> *U heeft het recht om op elk moment uw deelname aan het Fitbit-gebruik in deze studie te beëindigen* [optioneel: zie hoger, schrappen indien niet van toepassing]*maar weet dan dat uw gehele deelname aan de studie stopt. Het gebruik van Fitbit is namelijk noodzakelijk om deel te nemen aan deze studie.*
>
> *Door akkoord te gaan met deze voorwaarden, verklaart u dat u geïnformeerd bent over de risico's die gepaard gaan met het gebruik van Fitbit en stemt u in met het gebruik als onderdeel van deze studie."*

The use of Fitbit (and similar devices) will always be evaluated on an *ad hoc* basis by the EC in terms of risks/benefits for the participant. Compliance with GCP and GDPR must also be ensured in all cases.

The study team must first assess whether it is feasible to create study-specific "anonymous" accounts on Fitbit, i.e. accounts that could be created with "fake" data (birthdate, weight, gender, etc.) and/or with pseudonymized data (e.g., study-specific patient codes, study-specific email addresses): this can only be done if it is suitable for the study. After the study, these accounts would then be deleted/cancelled.

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