Decision tree 06.10.2023

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Purpose: To establish clear guidelines for researchers/Master's students on the process flow they need to follow.

Abbreviations

CTC	Clinical Trial Center
ECD	Ethics Committee for Animal Experimentation
EC Research	Research Ethics Committee
EC Health Care	Health Care Ethics Committee
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
OBC	Teaching Advisory Committee
SMEC	Social & Societal Ethics Committee

Definitions

- Anonymous data: data that can no longer be associated with an identified or identifiable person and are therefore no longer personal data. Researchers who receive an anonymized dataset from fellow researchers, but where the fellow researcher holds the key, are not working with anonymous data, as this remains an encrypted dataset.

- Incidental findings: findings/results unrelated to the original purpose of the study and discovered by chance.

- Clinical Trial (hereinafter referred to as "trial"*) (Clinical Trial Regulation (CTR), regulation (EU) 536/2014)*: any investigation in the human subject intended to establish or confirm the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse effects of one or more investigational medicinal product(s), and/or to study the resorption, distribution, metabolism and excretion of one or more investigational medicinal product(s), in order to determine the safety and/or efficacy of these medicinal products.

- Non-interventional clinical trial: study in which the medicinal products are prescribed in the usual way, in accordance with the conditions laid down in the marketing authorization. The assignment of the patient to a particular therapeutic strategy is not determined in advance by a study protocol, but is part of common medical practice, and the decision to prescribe the medicinal product is entirely separate from the decision to include a patient in the study. The patient in question does not have to go through an additional diagnostic or monitoring procedure, and epidemiological methods are used to analyse the results obtained.

- Medical device *(Medical Device Regulation (MDR), regulation (EU) 2017/745, Article 2)*: an instrument, device or apparatus, software, implant, reagent, material or other article intended by the manufacturer to be used alone or in combination in humans for one or more of the following specific medical purposes:
    - diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,
    - diagnosis, monitoring, treatment, alleviation or compensation of an injury or impairment,
    - investigation of or replacement or modification of the anatomy or of a physiological or pathological process or condition,
    - provision of information through in vitro examination of specimens derived from the human body, including organ, blood and tissue donations,
    - where the principal intended action in or on the human body is not achieved by pharmacological, immunological or metabolic means, but may be assisted by such means.

  The following products are also considered medical devices:

    - devices for the control or support of fertilization;
    - products specifically intended for cleaning, disinfecting or sterilizing devices referred to in Article 1(4) and those referred to in the first paragraph of this section;

- Clinical investigation *(Medical Device Regulation (MDR), regulation (EU) 2017/745, Article 2):* systematic investigation in one or more human subjects conducted to assess the safety or performance of a device;

- Human body material *(19 DECEMBER 2008. - Act on the Acquisition and Use of Human Bodily Material for the Purpose of Medical Application to Man or Scientific Research, Article 2):* any biological bodily material, including human tissues and cells, gametes, embryos, foetuses, as well as the substances extracted from them, whatever their degree of processing, with the exception of substances of non-human origin.

- Excluded from the scope of the Law 19 December 2008 are: hair and body hair (except follicles), nails, urine, breast milk, tears and sweat, except if intended for scientific research without application to humans (Law 19 December 2008, article 3).

- Primary use of human body material *(Law 19 December 2008, Article 2)*: any use of the human body material for which the donor has specifically given his/her consent in the context of the removal.

- Secondary use of human body material (Law 19 December 2008, Article 2): any use of human body material other than that for which the donor has given his consent in the context of removal.

- Residual human bodily material *(Law 19 December 2008, Article 2)*: the part of the bodily material removed for the purpose of diagnosis or treatment of the donor that, after a sufficient and relevant part is kept for the purpose of making, refining or completing the diagnosis or treatment of the donor on the basis of new scientific data, is superfluous with regard to these purposes and could therefore be destroyed.

1. Background

There are three government-approved Ethics Committees (ECs) active within KU Leuven: the Animal Research Ethics Committee (ECD), the EC Care (which advises on the ethical aspects of hospital care and provides support and guidance on ethical issues) and the Research Ethics Committee. There is also a Social Ethics Committee within the University (SMEC), which advises on projects that are not governed by the Belgian law of 7 May 2004 on experiments on human beings (the 'Human Experiments Act').

The Teaching Advisory Committee is a unique and obligatory portal for Master's experiments applying specifically for the Biomedical Sciences Group (BMW); it operates via the SCONE platform.

Protecting vulnerable human and animal trial subjects is a key focus area for all ECs.

Websites of the ECs at UZ/KU Leuven	
EC Animal Experimentation	https://admin.kuleuven.be/raden/ethische_com_dierproeven.html
EC Care	http://www.uzleuven.be/ethische-commissie/zorg
EC Research	https://www.uzleuven.be/nl/ethische-commissie/onderzoek
Social & Societal Ethics Committee	https://ppw.kuleuven.be/home/onderzoek/SMEC
Teaching Advisory Committee	https://med.kuleuven.be/nl/obc/index_en.html
UZ/KU Leuven Biobank	http://wiki/display/biobanking/Scientific+Biobank
EC DMM	https://set.kuleuven.be/ethicsatarenberg/expertise-center-ethics-arenberg-1/copy_of_dual-use/dual-use

This document is intended to provide researchers at KU Leuven with guidance on submitting research projects to the appropriate Ethics Committee (EC) using a decision tree (see section 2). It makes a number of recommendations to help researchers in their choice and provide them with an insight into how the regulatory framework for the ECs operates (see sections 1.1 – 1.4). Submission of research projects to the right Committee first time is the preferred route. Referral from one Committee to another takes up additional time and is therefore best avoided as far as possible.

Each EC meets at regular intervals, though applicants should be aware that every advisory or approval procedure takes a certain amount of time to complete (each with its own templates), and that applicants should therefore allow sufficient time in the application process. For example, extra time is needed for the Clinical Trial Center (CTC; ctc@uzleuven.be) or KU Leuven Research &

Development (LRD; LRD.Legal@kuleuven.be), for example to allow for negotiation of contracts with external partners and to examine the financial aspects where support services are involved.

1.1 The law of 7 May 2004 on experiments on human beings ('Human Experiments Act')

The Human Experiments Act defines an experiment as "a*ny test, study or research carried out on a human person, for the development of the knowledge specific to the exercise of the health care professions*".

The Human Experiments Act was established in order to protect trial subjects, partly by introducing a mandatory ethical test to be performed by a legally (fully) recognised ethics committee and the compulsory requirement to take out insurance to cover no-fault liability on the part of the party commissioning the research.[1] As further explained below, the Experiments Act has a broad scope and, for example, observational studies can also fall within its scope. In addition to the Experiments Act, there is the Clinical Trials Act of 7 May 2017 (Dutch) and the Medical Devices Act of 22 December 2022 (Dutch) with similar principles (faultless liability, insurance obligation, ICF and ethical review).

The following **always** fall under the Human Experiments Act (sections 2-3), **or** under any of the above-mentioned legislation:

- Research using medical devices which are themselves the subject of the research.
- Research involving surgical techniques.
- (Prospective) epidemiological research
- Clinical trials
- Research involving the removal/collection of human bodily material.

  For example, a study investigating mental effort in daily life by determining cortisol levels in saliva samples is considered under the Experiments Act.

Purely non-interventional use of a diagnostic tool does not automatically mean that a study falls within the Human Experiments Act (e.g. performing an EEG as part of a theoretical research project on the functioning of sensory stimuli in typically developing participants), as long as this is not intended for the development of knowledge specific to the exercise of the health care professions.

Under the Human Experiments Act, no experiments may be started without obtaining the advice of the appropriate Committee. Advice is not given retrospectively.

The following do **not** fall under the Human Experiments Act:

- If the purpose of the research is purely to improve practice and **not** intended for the development of knowledge specific to the exercise of the health care professions (see definition

[1] If a study does not qualify as an experiment on a human being, a patient who suffers harm cannot claim against the no-fault liability cover provided in the policy on experiments on human beings, but will need to demonstrate an error by KU Leuven in order to receive compensation based on the public liability cover.

of ‘experiment’), it does not fall under the Human Experiments Act. An example of such research would be a survey of doctors about the use of evidence-based guidelines in their day-to-day practice.

Other examples:

- Research with the aim of better understanding how recently developed advanced running shoes affect the human-shoe interaction during walking.

- Retrospective studies are also not governed by the Human Experiments Act. Retrospective studies are defined as follows (Section 3 of the Human Experiments Act): **“retrospective studies based on past data which is located in existing patient case notes, medical notes or administrative files or databases, and in so far as no new data whatsoever has been obtained in relation to those patients for these studies”.** According to UZ Leuven policy, retrospective studies at UZ Leuven always require an opinion from EC Research in order to perform a "privacy check" in accordance with the GDPR.

- Fundamental research projects with no immediate intervention goal, conducted primarily (but not necessarily exclusively) in participants from the general population of adults or children, especially (but not necessarily exclusively) when not involving clinically sensitive topics (such as reference to traumatic experiences).

- Research that uses only **anonymous** data also falls outside the scope of the Human Experiments Act. An accurate definition of anonymous data must however be used here.[2] However, a privacy test by an ethics committee will be necessary where appropriate, for example when the data are anonymised by the researchers themselves (after all, in this case the data are not initially anonymous yet). Also note that patient data (including images) are rarely anonymous (or can be anonymised) in practice because the data in the patient file can still be linked to a specific person. If truly anonymous data is used in a study, the Experiments Act does not apply. Also, the General Data Protection Regulation (GDPR) or General Data Protection Regulation (AVG) then does not apply.

1.2 Health care profession

For experiments falling within the scope of the Human Experiments Act, the lead researcher must be qualified in and exercise a **health care profession** (Law of 10 May 2015). If the experiment falls within the scope of the Human Experiments Act and the researcher does not themselves practise a health care profession, the researcher must engage at least one qualified fellow researcher in the research project who practises a health care profession that is relevant for the research.

A researcher who practises a health care profession should also involve other researchers with the requisite qualifications if this is deemed necessary for the specific type of research concerned. If not all requisite qualifications are present, the EC may request that additional researchers with the necessary qualifications be brought into the research project. For example:

[2] For a definition of anonymous data see: https://admin.kuleuven.be/privacy/intranet/AVG-gegevens#section-4

- A clinical psychologist/remedial educationalist wishing to set up a psychophysiological research project to study the effect of a rewards system in ADHD using neuro-imaging is asked to involve a physician with the necessary qualifications (e.g. a radiologist);
- A gynaecologist who is planning an outcome study of cognitive development in children born after a foetal of operation will bring in a clinical psychologist with the appropriate qualifications (and specifically for young children).

The qualified fellow researcher:

- is fully aware of and agrees with the research design and process;
- takes responsibility for the health-related aspects of the research project (and is among other things recorded as the designated contact for this on the Informed Consent Form (ICF));
- signs and submits the application to EC/SMEC together with the researcher.

This does not automatically imply co-authorship or co-supervisorship: specific rules of co-authorship and co-supervisorship apply for this (https://www.kuleuven.be/english/research/integrity/practices).

The need to engage a qualified co-researcher does not change the researcher's overall responsibility or publication opportunities.

For a **clinical trial (CTR)**, the principal investigator must be a doctor or dentist (if it concerns clinical trials related to dentistry) (cf. Article 36 of the Law of 7 May 2017).

For a **clinical trial (MDR)**, the principal investigator must be a healthcare professional according to the law of 10 May 2015 (cf. article 28 of the law of 22 December 2020).

1.3. Good Clinical Practice (GCP) training

Researchers seeking ethical approval for their study from EC Research must submit a certificate of Good Clinical Practice (from their own or another institution, valid for three years). The Clinical Trial Centers (CTC) of the 7 Belgian teaching hospitals have jointly developed a GCP e-learning. The training is offered through the UZ learning centre & KU Leuven Toledo. The training has been fully validated by TransCelerate and consequently successful completion of this e-learning will result in an internationally recognised training certificate that remains valid for 3 years (or until the next GCP revision).

Certificates obtained after attending another online training course approved by Transcelerate, for example at https://globalhealthtrainingcentre.tghn.org/ich-good-clinical-practice/, can also be accepted by EC Research.

For more background information on the GDP training, please refer to the following document: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf

1.4. The place of CTC and LRD in the research application

Please refer to the following websites:

https://www.uzleuven.be/clinical-trial-center/ (in Dutch)

https://lrd.kuleuven.be/

2. Decision tree

As a researcher, where can you seek advice about your research?

A. You have already received ethical approval for your research:

If the research is an amendment of a study that has already been approved within UZ/KU Leuven by (1) EC Research UZ/KU Leuven; (2) Social & Societal Ethics Committee (SMEC); (3) Ethics Committee for Animal Experimentation (ECD), (4) EC Health Care, this amendment should be submitted to the Committee which originally evaluated the research project. That Committee will evaluate the amendment and where necessary forward it to the appropriate Ethics Committee (e.g. if the amendment constitutes an extension that falls under the Human Experiments Act, SMEC will forward the application to EC Research). The amended study cannot begin until it has been approved.

NB: if the question statement of the initially approved study fundamentally changes, we do not ask for an amendment but a new study to be submitted to the appropriate Commission.

B. You are seeking advice on a new research project:

1. If you are the supervisor of a Master's project of a student in the Biomedical Sciences Group (BMW), the first and only entry portal for these experiments is OBC (via the SCONE platform); When following the process through the OBC decision tree, depending on the answers to the questions you will receive advice from OBC, a referral to EC Care, ECD or EC Research, or amendments to projects already approved will be referred to the ethics committee which gave the original advice. If, based on the answers to the questions in the decision tree (SCONE) tool, you are advised to submit the project to EC Research, that is then the only option if you wish to carry out this project. It remains your responsibility as supervisor/researcher, together with the student, to take the appropriate steps after receiving the OBC advice to submit your project to the correct body.

   An initial approval from EC Research can also be obtained after which the S number is entered in the decision tree.

2. Ethical screening is not required for research which consists exclusively of a literature review.

3. Where the research involves experiments with experimental animals and/or animal material obtained specifically for the purpose of the research, you must submit an application to the government-approved Ethics Committee for Animal Experimentation (ECD).

4. Research is done on bodies donated to science via will. In this case, you will have to submit an application to EC Care, after consultation with those responsible at the Skilled Anatomy Centre (Vesalius Institute). More information can be found at: https://med.kuleuven.be/nl/samenwerken/anatomie

5. For research projects falling under the Human Experiments Act and *in vitro* research on embryos, you submit an application to EC Research following the procedure described on its website: https://www.uzleuven.be/nl/ethische-commissie-onderzoek. Where necessary, you will also seek advice from the Biobank (http://www.uzleuven.be/nl/biobank).

6. Research projects involving the use of human bodily material that is already available (commercially or otherwise), including cell lines (= secondary use), must be submitted to EC Research (pursuant to Section 21 of the Law of 19 December 2008). You will also seek advice from the Biobank.

7. For artificialized and extracted material, if not used for genetic research, it is sufficient to submit the research project and its purpose to EC Research and registration with the biobank is no longer necessary. The researcher is responsible for compliance with all conditions (including not being used for genetic research...) and confirms this in a template provided by EC Research.

8. Research projects which do not involve intervention and in which prospective data is gathered from living persons, which do not fall under the Human Experiments Act, which do not involve patients or employees of UZ Leuven or their data and which are not carried out at UZ Leuven, may be submitted to SMEC. Examples of this type of survey are:
    - Questionnaires around general cognitive, emotional or social factors (e.g. association between psychological factors or personality traits and job or life satisfaction)
    - Qualitative research such as interviews, focus groups
    - Experimental manipulations of psychological variables (such as memory, learning, arousal, mood) in the general population (e.g. impact of leadership dimensions on social interactions)
    - Research in pedagogical settings or on cognitive/psychological training in the general population

If it is unclear whether or not your research project falls under the Human Experiments Act, you can contact SMEC (smec@kuleuven.be) or EC Research (via ecstaf@uzleuven.be). SMEC and EC may liaise with each other if there is uncertainty, and may issue advice on where the project should be submitted. Members of SMEC/EC will ultimately take a final decision. This means it is possible that, notwithstanding mutual liaison, after being submitted to SMEC your project is referred to EC Research, or that after submission to EC Research the judgement is that the project

does not fall under the Human Experiments Act, in which case a 'letter of no objection' will be drawn up.

Important points to note:

1. The research uses only existing data/data that has already been collected (**retrospective** research, of which the end date (in the past) is explicitly stated), where the data is initially not anonymous, but is coded or anonymized during further processing after collection.

   For purely retrospective research, you will need to submit an application to SMEC or EC Research. If the research is clearly retrospective (both anonymous and coded), it does not fall under the Human Experiments Act (though may be covered by GDPR), and SMEC or EC Research will be able to evaluate the submission; the only potential issues here are privacy and the method of recruitment. If the retrospective study involves use of patient data, EC Research will need to perform a privacy test. Master's research projects within the BMW group must be submitted to OBC for evaluation.

   Approval should be sought from the head/staff of the clinical department or care programme responsible for the study and consequently for the use of data obtained by the treatment team; this is the responsibility of the PI principal investigator.

2. The research involves the collection of **prospective** (or a combination of retrospective and prospective) data from living persons (patients and/or healthy volunteers); this implies a need for GDPR compliance.

   → If the health care-related intervention or action falls under the Human Experiments Act (i.e. "any test, study or research carried out on a human person, for the development of the knowledge specific to the exercise of the health care professions"), only EC Research may give advice.

   → There is a standing arrangement that all research carried out within UZ Leuven is always assessed by EC Research, even if it does not fall under the Human Experiments Act.

   → Research involving individuals (or their data/body material) primarily from their role as UZ Leuven staff members and/or as UZ Leuven patients is always assessed by EC Research, even if it does not fall under the Experiments Act. When any association to UZ Leuven is incidental or coincidental, the research can also be assessed by SMEC as long as it does not fall under the Experiments Act. For example: individuals with ADHD are recruited through an interest group and one or a few of them happen to be patients at UZ Leuven.

3. Research which takes place (at least partially) **within UZ Leuven**

   If a researcher carries out a research project which takes place (at least partially) within the UZ Leuven hospital setting or which involves the use of data from UZ Leuven, EC Research may advise the researcher to seek the agreement of the lead physician. UZ Leuven has responsibility for what is organised within its walls and what is included in patient files via the KWS electronic patient record system. The advice of EC Research is also required for research apparatus

purchased by UZ Leuven and used for patient flows. Where apparatus is used which could give rise to *incidental findings*, it must be clearly stated on the ICF whether any such findings will be fed back to the trial subjects. The following is an example of a statement on the ICF: *"You are not a patient of UZ Leuven for the purpose of your participation in this study, and any results of tests/investigations will not appear in your medical files and will not be fed back to you"*. It must be clear where responsibility lies.

4. Research carried out on the **Health Sciences Campus**, but outside UZ Leuven

   If a research project is carried out outside the UZ Leuven hospital setting but still on the GHB Health Sciences Campus in a broad sense, it is made clear to the trial subjects that the research is taking place outside the UZ Leuven hospital setting. This must be stated specifically on the Informed Consent Form (ICF).

5. Where projects involve surveying staff of KU Leuven, UZ Leuven or an external company/organisation/institution, the EC will ask the researcher to obtain the consent of GEBU, the lead physician and the management of the external company/organisation/institution, respectively.

6. The specific policy guidelines relating to the protection of personal data in the context of research must be respected at all times (for example the UZ Leuven ("Health data and research") policy, which is can be accessed on Muzlidoc).

Amendment to already approved research

This amendment should be submitted to the Commission that initially evaluated the research project.

New research

ECD

- In research, experiments take place with laboratory animals and/or animal material taken specifically for that purpose

EC Care

- Research is done on bodies donated via will for science

OBC

- Possible after completing the decision tree in SCONE for master's thesis of a student within the Biomedical Sciences group

EC Research

- Research under the Experiments Act
- Research with medical devices, which are themselves the subject of the research
- Research involving surgical techniques
- Clinical trials
- Research involving the prospective removal/collection of human bodily material for research purposes
- Research conducted within UZ Leuven
- Research involving individuals (or their data/body material) primarily from their role as UZ Leuven staff members and/or as UZ Leuven patients
- Research projects using human body material that is already available (secondary use)
- Retrospective research with UZ Leuven patient data

SMEC

- Research projects that do not fall under the Experiments Act and involve prospectively collecting data from living individuals and also do not involve UZ Leuven patients (data) and/or staff and do not continue at UZ Leuven
- Retrospective study (no use of UZ Leuven data)