BASIC RESEARCH: Guidance for researchers

This guiding document is intended for researchers who conduct basic research projects with persons according to chapter 2 HRO and for further use projects of human biological material with or without associated health-related personal data according to chapter 3 HRO.

The guiding document addresses the most common omissions made during the planning and writing of project research plans (study protocols) for basic research projects and addresses some of the questions raised by the researchers on the submission of those projects to the ethics committees.

What constitutes exactly «basic 'medico scientific' research» and does it fall within the scope of The Federal Act on Research involving Human Beings (HRA, HFG, LRH, LRUm)?

A broad general definition of **Basic Research** defines it as a synonym for fundamental research, which is the study of life processes. It includes for example cell studies, biochemical, genetic and physiological investigations, and studies on the properties of drugs and materials in contact with human biological material, i.e. cells or tissues.
Basic research also includes the development and improvement of analytical procedures such as analytical determination of enzymes, markers or genes
The development of biometric procedures such as statistical test procedures, modeling and statistical evaluation strategies also belongs here[1].

The **Federal Act on Research involving Human Beings** (Human Research Act, HRA) applies to research concerning **human diseases** and concerning the **structure and function** of the human body (HRA Art. 2 Abs 1). It does apply to uncoded or coded but not to anonymized[2] biological material and anonymously collected nor to anonymized health-related personal data[3] (HRA Art 2 Abs 2).

Basic research projects as mentioned above may fall within one of several different study categories subjected to prior ethics committee approval. When planning a basic research project, it is thus worth considering if the project can alternatively be conducted with anonymized human biological material and anonymized or anonymously collected health-related personal data, instead of using uncoded or coded[4] biological material and data. It is emphasized here that the anonymization of biological material and associated health-related personal data might not always be possible, practicable or even desirable. A research project conducted with anonymous biological material and associated anonymous health-related personal data does not fall within the scope of the HRA and thus it does not require an ethics committee approval.

[1] Modified from: Dtsch Arztebl Int. B. Röhrig et al. 2009 Apr; 106(15): 262–268.
[2] Anonymized biological material and anonymized health-related data means biological material and health-related data which cannot (without disproportionate effort) be traced to a specific person.
[3] Health-related personal data means information concerning the health or disease of a specific or identifiable person, including genetic data.
[4] Coded biological material and coded health-related personal data means biological material and data linked to a specific person via a code.

The researchers have to describe the procedure of anonymization in the project research plan and must inform the donors on the proposed anonymization of their biological material and related personal data for research purposes, especially on the consequences of anonymization with regard to results concerning their health, and on their right to dissent (HRO Art. 30).

In case of doubt on whether the research project requires ethics committee approval, the researchers should submit a clarification of responsibility[5] through the web-portal BASEC to the ethics committee for clarification, before starting the project. The procedure is given here.

What are the most common omissions made during the submission of a project of basic research to the ethics committee?

Quick links:

1. Missing information on the origin and storage of the biological material (e.g. missing biobank regulation, material transfer agreement)

The origin of the biological material used for the research must be given in detail in the research plan. If the biological material is obtained from different sources, all sources must be listed.
The material transfer agreement (MTA)[6] must be submitted to the ethics committee through the web-portal BASEC, as a standalone document. The MTA should not be integrated in or annexed to the project research plan.

Additionally, the researchers must indicate if the biological material and, if applicable, the associated health-related personal data will be received and used in uncoded or coded form. It also should be explained how the donors will consent or have consented to the use of their biological material for research (general consent, project specific consent, no consent for all – some of the samples[7]).

[5] The clarification of responsibility is called in German "Zuständigkeitsabklärung", in French "Clarification des compétences", and in Italian "Esame della competenza".
[6] The MTA is a legally binding agreement that governs the transfer of biological material and data between two parties, when the recipient intends to use them for research purpose. It defines the rights and obligations of the provider and recipient with respect to the use of the material and data and other related issues, such as confidentiality or intellectual property rights. A template to write the MTA can be downloaded from the webpage of the Swiss Biobanking Platform (swissbiobanking.ch).
[7] If no consent for all – some of the samples/data exist, HRA Art. 34 might apply.

If the biological material is obtained from a biobank, the biobank regulation[8] must be submitted to the ethics committee through the web-portal BASEC, as a standalone document. The biobank regulation should not be integrated in or annexed to the project research plan.

For biological material and/or data imported from abroad, proof of legality (e.g. an ethics committee positive decision from country of origin of the biological material, material transfer agreement or similar verification document) is needed.

The sample size (amount of blood or other biological material) used for the research project should always be given (see also below point 5. 'Missing / incomplete statistical analysis plan').

2. Use of «research-products»[9], including commercially available human cell-lines and use of non-commercially available human cell-lines

A basic research project with cell lines falls within the scope of the HRA if it is a method-driven search for generalizable knowledge (Art. 3, a, HRA) and if the biologic material used in the research project is coded (Art. 3, h, HRA) or uncoded (i.e. not anonymized, Art. 3, i, HRA).

Generally, research projects that use exclusively commercially available cell-lines (e.g. HeLa, HEK-293, Jurkat, etc.) or publicly available cell-lines do not fall within the scope of the HRA and as such do not require ethics committee approval. These cell-lines are so called «research-products» that have been produced or developed on the basis of human cell material. The processing steps have created a «research-product» from the donor's isolated biological material, which is no longer considered a «part of the human body»[10].

Human biological material becomes a «research-product» if it was substantially processed.[11]
S*ubstantially processed* means it underwent at least one of the following processing steps:

a) the multiplication of cells via cell culture;
b) the genetic modification of cells, or
c) the differentiation or activation of cells.

Thus, by analogy, human biological material is also considered a «research-product» if the substantial processing took place in animals (e.g. xenograft animal models, human cell-line derived xenograft (CDX), or patient derived xenograft (PDX)).

When should the researchers obtain a written informed consent, i.e. a study specific consent or a general consent for the further use of the donor's biological material, and when is an

[8] The biobank regulation is a document that defines the biobank purpose, activities, organization and reflects its daily practices. More detailed information on biobanks/biobank regulations can be found on the webpage of the Swiss Biobanking Platform (swissbiobanking.ch).
[9] This section 2 does not apply to products in scope of the Medical Devices Ordinance (MepV, SR 812.213) of 1 July 2020 and the Clinical Trials with Medical Devices Ordinance (KlinV-Mep, SR 810.306) of 1 July 2020.
[10] Dispatch on the Federal Human Research Act, of 21 October 2009, Chapter 2.1.2.6 Prohibition of commercialisation (Art. 9) (in German, in French, in Italian)
[11] In analogy to the regulations on definition of transplantation products (which are not considered part of the human body as well) described in the Transplantation Act of 8 October 2004 (SR 810.21) and Transplantation Ordinances of 16 March 2007 (SR 810.211), which are referenced in in chapter 2.1.2.6 of the Dispatch on the Federal Human Research Act of 21 October 2009.

informed consent not required? Here we distinguish between research projects with human biological materials that fall within the scope of the HRA and projects that are not in scope.

1. **Research projects that fall within the scope of the HRA.** The researcher must obtain the written informed consent of the donor before its biological material can be used in the research project. The origin of the biological material and confirmation that the informed consent of the donor was properly obtained must be submitted to the ethics committee with the application. The research project cannot begin previous approval by the ethics committee.

2. **Research projects that do not fall within the scope of the HRA.** There is no legal obligation for the researcher to obtain the donor's written informed consent for the use of the donor's biological material in the project. However, the trust of the participants in research projects and in the biomedical research in general, which is built on transparency and fair communication, is fundamental for the research involving human beings. It is therefore for ethical reasons that swissethics recommends that the researchers undertake the necessary efforts to obtain the written consent of the donors whenever possible.

3. Use of biological material (cells) from healthy volunteer for testing, controls, etc.

If biological material (cells) from healthy volunteers are used for example as negative control in an experiment, as feeder cells, for the establishment of cell-staining, for tests-runs made before an important experiment, etc., in the context of a research project to study human diseases or the structure and function of the human body (again method-driven search for generalizable knowledge) then the research project falls within the scope of the HRA and requires ethics committee approval.

If the biological material (cells) is not used in the context of a research project to study human disease or the structure and function of the human body, then its use does not fall within the scope of the HRA. However, a general consent or a specific written informed consent must be obtained from the volunteers (donors).

In case of doubt, before starting the research project, the researchers should submit a clarification of responsibility through the web-portal BASEC to the ethics committee to clarify whether the research project falls within the scope of the HRA. The procedure is given here.

4. Undefined / vague projects objectives and endpoints

Although it may not always be possible to give clear cut endpoints when conducting basic research projects, well-thought-out research objective(s) should be provided. The researchers should provide with the initial submission the raw road map, supported with hypotheses, pre-study observations, etc., on how the research objective(s) have been set.

The researchers are invited to discuss beforehand with the ethics committee if changes to the project objective(s) should be submitted to the ethics committee as a substantial amendment to the project research plan or as a standalone new research project (for more details, see below the chapter 6. 'Changes to the project research plan during the course of the project (amendments)).

5. Missing / incomplete statistical analysis plan

For some basic research projects, it may not be possible to write a detailed statistical plan, as instructed in the swissethics template for project research plan for HRO Chapter 2 research projects, i.e. with detailed statistical methods, level of significance, power, etc. Nonetheless, if different statistical methods (e.g. descriptive statistic) rather than hypothesis testing are used, those should be described in detail.

It is advised to consider the statistical aspects of the project (type of statistical analysis, sample size, etc.) very early in the stage of project planning/ research plan writing.
A justification of the sample size (expected total number of samples/quantities used, expected samples/quantity used per single donor, etc.) should always be given.

If the research does not foresee any statistical analysis at all, this must be justified in the study research plan.

6. Changes to the project research plan during the course of the project (amendments)

A guidance document for researcher on "notification of substantial amendments and other changes to the ethics committee" is published on the swissethics webpage (template/checklists/notifications). The document also includes a comprehensive list of changes and their classification in substantial and non-substantial amendments. For example:
Addition of research sites, change of the project leader, or changes to the patients' group without simultaneously changing the project's objectives, are substantial changes and must be submitted to the ethics committee and approval obtained before the changes are implemented. Changes to the research centre's SOPs, working instructions, etc. are not substantial changes and can be implemented immediately.

It should be noted here, that changes to the patients group combined with a change of the project's objectives must be submitted as a new research project. In some cases, the submission of a change as new standalone study protocol, might even be advantageous for the conduct of the project itself[12].

The researchers are invited to discuss beforehand with the ethics committee on how to submit changes that are not listed on the guidance document, if it is not immediately clear to what extend the changes listed on the guidance document also concern the projects of basic research, or if the submission of a new research project would be advantageous instead.

Depending on the classification, the ethics committee might also decide that the substantial change to the project research plan is submitted as a new standalone study protocol.

7. Missing information on the handling of incidental findings

The handling of incidental findings should not only be described in the patient information /informed consent form, but also in the project research plan.
To properly address this point in the project research plan, the researchers are advised to consult the document «guideline for handling incidental findings in medical search»[13] and the

[12] For example, fewer regulatory requirements if the study population is changed from minors to adults, while other changes to the study protocol might significantly simplify the statistical analyses, etc.
[13] swissethics, the document is available in German, French, Italian.

document «Ethical Framework for Responsible Data Processing in Personalized Health Research»[14], for guidance.
Only validated clinically actionable findings should be communicated to research participants through competent healthcare professionals, as agreed at the consent. This means that if a research participant does not want to be informed, her/his choice must be respected.

8. Incomplete information to the donors on genetic investigation

If genetic analysis is done in clinical routine, the Federal Act on Human Genetic Testing (HGTA[15]) applies, while genetic investigations (germline and non-germline) fall within the scope of the HRA (Art. 3, Abs c).
In case of genetic investigation, the donors must be informed that their genetic information (DNA sequences, etc.) may be deposited in national or international databases (e.g. SIB, NIH SNPdb), if this is the case. Some databases explicitly require confirmation and proof that the donors have given their written informed consent for the genetic investigations and for the storage of the genetic information (DNA sequences, sequence variants, genes, etc.). If cloud computing of storage is used for storage, this should be mentioned in the research study plan and the informed consent form.

Before providing the data, the researchers should check that the databases are compliant to the European General Data Protection Regulation (GDPR) or to the Swiss Federal Act on Data Protection (FADP[16]).

9. Missing or unprecise information on what happen to the biological material /health-related personal data at the end of the project

An expected end date of the project must always be submitted to the ethics committee with the initial submission. The researchers should describe in the project research plan what happens to the biological materials and health-related data at project end: e.g. "After analysis, the biological material will be destroyed at the research center, as per internal SOPs, and the coded data stored for *y* years at the hospital (address *x*)."

If the biological material is not immediately destroyed after use, the place and period of storage must be indicated in the project research plan: e.g. "After information to the participants/donors, as per HRO art. 30, the biological samples and the associated health-related personal data are anonymized after evaluation, i.e. the coding-key is destroyed, and stored at the research center (address *x*) for *y* years." or: e.g. "The remains of the unused samples are sent back to the hospital biobank (address *x*) and stored there for *y* years."

If it is planned to reuse the biological material and associated personal data for future, not yet defined, research projects in Switzerland or send them abroad, the donors must be informed accordingly and give their written consent (a template for writing an informed consent is available on the swissethics webpage).

[14] ELSI Advisory Group, published by SPHN in English.
[15] Bundesgesetz über genetische Untersuchungen beim Menschen (GUMG); Loi fédérale sur l'analyse génétique humaine (LAGH); Legge federale sugli esami genetici sull'essere umano (LEGU)
[16] Bundesgesetz über den Datenschutz (DSG); Loi fédérale sur la protection des données (LPD); Legge federale sulla protezione dei dati (LPD)