COMITÉ NATIONAL D'ÉTHIQUE DE RECHERCHE

Recommendations for the secondary use of samples and data, collected in a primary research project

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This document will be reviewed by the CNER every two years.

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Background

What is meant by primary use and secondary use / further processing of samples and data collected in the framework of a research project?

Primary use = the use for which the samples/data were collected, i.e. to meet the purpose of a research project. Here the data collected is clearly linked to the objectives of the study.

Secondary use (or further processing) = other use, for a different purpose, not immediately related to the purpose of the primary research project.

A research project and a collection project are two different types of projects

Collection project = project aiming at collecting tissue and/or fluid samples and some associated data from sick or healthy participants without a defined research purpose.

A distinction should be made between submissions for opinion to the CNER which concern research projects on the one hand, and collection projects dedicated to supplying/serving one or more research projects (samples and associated data = biobanking) whose purposes are not yet clearly defined.

In a collection project, the use of samples and associated data to feed third party research projects is the primary use of these samples and data, as this is the purpose of the collection. Some of these research projects may already be defined when the collection project is envisaged, and others may not. But the implementation of a biobank cannot be an end in itself, as the objective of data valorisation would necessarily be too vague.

It is therefore logical that the collection project should be submitted to the CNER first, and that the research projects that will use the collected samples and data should be submitted for opinion separately, after the CNER has issued a favourable opinion for the collection. Therefore, a research project "with an open collection design" behind it cannot be presented and submitted to the CNER for opinion.

For these two types of projects, which are conceptually very different, the CNER publishes separate ICF recommendations and templates.

Note: The abbreviation "ICF" is often used in our field to refer indistinctly to the subject information sheet (SIS) and the informed consent form (ICF) all in one, even though the ICF is strictly speaking only the consent form.

Legal basis for secondary use of samples and data

As we were well reminded in our survey of other EU countries, the legal bases for secondary use of samples and data are not the same.

Regarding secondary use of samples for health research purposes:

In Luxembourg there is unfortunately no other, more precise legal basis than the 2018 Hospital Law, and its Article 27 (1) in particular.

The absence of specific legislation on secondary use in Luxembourg means that the general - European - legal framework for data protection must be used. Indeed, the only existing regulation that clearly addresses the subject of secondary uses is the RGPD, which the CNER applies. The most relevant criteria of the GDPR to be respected are:

- legal precision (of the purpose of the data processing),
- consent of the fundamental rights holder, and
- proportionality, of which the data minimisation principle is an important element.

Regarding secondary uses of data (also called "further processing") for health research purposes:

At European level: GDPR (Regulation (EU) 2016/679)

At Luxembourg level: Law of 1 August 2018 on the organization of the National Commission for Data Protection and implementation of Regulation (EU) 2016/679

Extracts from the relevant articles of the RGPD:

"RGPD Article 9 Processing of special categories of personal data

1. Processing of personal data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, or trade union membership, and the processing of genetic data, biometric data for the purpose of uniquely identifying a natural person, data concerning health or data concerning a natural person's sex life or sexual orientation shall be prohibited.

2. Paragraph 1 shall not apply if one of the following applies:

a) the data subject has given explicit consent to the processing of those personal data for one or more specified purposes, except where Union or Member State law provide that the prohibition referred to in paragraph 1 may not be lifted by the data subject;

(j) processing is necessary for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes in accordance with Article 89(1) based on Union or Member State law which shall be proportionate to the aim pursued, respect the essence of the right to data protection and provide for suitable and specific measures to safeguard the fundamental rights and the interests of the data subject.

4. Member States may maintain or introduce further conditions, including limitations, with regard to the processing of genetic data, biometric data or data concerning health."

"Article 89 Safeguards and derogations relating to processing for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes

1. Processing for archiving purposes in the public interest, scientific or historical research purposes or statistical purposes, shall be subject to appropriate safeguards, in accordance with this Regulation, for the rights and freedoms of the data subject. Those safeguards shall ensure that technical and organisational measures are in place in particular in order to ensure respect for the principle of data minimisation. Those measures may include pseudonymisation provided that those purposes can be fulfilled in that manner. Where those purposes can be fulfilled by further processing which does not permit or no longer permits the identification of data subjects, those purposes shall be fulfilled in that manner.

2. Where personal data are processed for scientific or historical research purposes or statistical purposes, Union or Member State law may provide for derogations from the rights referred to in Articles 15, 16, 18 and 21 subject to the conditions and safeguards referred to in paragraph 1 of this Article in so far as such rights are likely to render impossible or seriously impair the achievement of the specific purposes, and such derogations are necessary for the fulfilment of those purposes."

In the Luxembourg data protection law of 8 August 2018, the organisational aspects for the implementation of Article 9 RGPD are further specified in Chapter 2, articles 63, 64 and 65.

Recommendations for the secondary use for a new research project of samples and/or data that have been collected in a first research project

Summary of recommendations

Recommendation No 1: Systematic submission for opinion to the CNER of projects for secondary use of samples and/or data for subsequent research projects

Recommendation No 2: Provide a separate consent form to accept secondary uses of data and/or samples collected as part of the primary research project

Recommendation No 3: Refusal of secondary uses does not preclude participation in the primary research project and this must be clearly stated in the primary research project's information sheet and consent form.

Recommendation No 4: In projects where secondary uses are planned, obligation to inform participants (who have agreed to secondary uses) of what has been done with the samples and data. This information can be communicated via newsletters, information campaigns, or the primary project website.

Recommendation No 5: Favour the anonymisation of samples and/or data before transmission to the principal investigator (PI) of the secondary study (if PI is not the same), and in case of transfer outside the EU

Recommendation No 6: In the consent form for secondary uses, provide a basic introduction and limit the consent options as described below

General comment on these recommendations:

In order to issue its recommendations, the CNER first conducted a dedicated survey within the European Network of Research Ethics Committees (EUREC).

Further explanation of each recommendation:

Recommendation No 1: Systematic submission for opinion to the CNER of projects for secondary use of samples and/or data for subsequent research projects

Note: As in Germany, Switzerland, Belgium, Cyprus, Italy and Portugal, projects for secondary use of samples and/or data for further research projects are systematically submitted to the competent ethics committee for opinion.

Recommendation No 2: Provide a separate consent form to accept secondary uses of data and/or samples collected as part of the primary research project

Notes:

In Luxembourg, the CNER recommends in all cases a consent form dedicated to secondary uses, well separated from the ICF of the primary study.

In case the secondary use project is a project in the same field as the primary study, and the CNER issues a favourable opinion for this secondary project, the patient/participant should not be contacted again to ask for a new consent.

For secondary use projects outside the scope of the primary study, not only is a positive opinion from the CNER required, but the patient/participant must also be contacted again and sign a new consent form for the new study. This implies that he/she has accepted, in the ICF of the primary study in which the samples/data were collected, the option to be recontacted to participate in other research projects.

Recommendation No 3: Refusal of secondary uses does not preclude participation in the primary research project and this must be clearly stated in the primary research project's information sheet and consent form.

Recommendation No 4: In projects where secondary uses are planned, obligation to inform participants (who have agreed to secondary uses) of what has been done with the samples and data. This information can be communicated via newsletters, information campaigns, or the primary project website.

Note:

If the "website" option is chosen, this implies that the participant should be informed of the existence of the website in the primary study information sheet. The newsletters/information campaign/websites also serve as a reminder that withdrawal of consent is possible at any time.

Recommendation No 5: Favour the anonymisation of samples and/or data before transmission to the PI of the secondary study (if PI is not the same) and in case of transfer outside the EU

Note:

Applying Article 89 of the GDPR to the issue of secondary uses of research data for secondary research projects, it follows that, whenever the secondary research project can be carried out on anonymised rather than pseudonymised data, the data to be transmitted by the primary study PI to the secondary study PI should be anonymised before transmission.

Of course, this recommendation requires consideration if the primary research (with pseudonymised data) involves the possibility of incidental findings and that there is also the possibility of incidental findings in the project making secondary use of the data. Anonymisation when transferring the data to the secondary study PI would mean that the patient could no longer be traced in the event of incidental findings. Hence the choice of the word "favour" in the recommendation, as anonymisation should not have negative consequences for the patient.

Recommendation No 6: In the consent form for secondary uses, provide a basic introduction and limit the consent options as described below:

Basic introduction content:

- describe the primary use foreseen by the primary study and explain what a secondary use is, i.e. a re-use of samples and/or data, for another research project, in this case limited to the same research area as the primary study;
- remind that consent to secondary uses of one's samples and/or data for other studies is voluntary, and that refusal of such secondary uses does not lead to exclusion from the primary study;
- specify how long the samples and data will be stored and may be subject to secondary uses if the person has consented;
- explain that withdrawal of consent for secondary uses is only possible for samples and data that have not yet been re-used, while also explaining why (e.g. because it would compromise the study, or is no longer possible if the data have already been anonymised/aggregated);
- remind that if they consent to secondary analyses of their samples, incidental findings are possible and that their expressed choice about sharing these with them or their relatives in the primary ICF will be respected. If the primary study ICF did not address this issue because there was no possibility of incidental findings in the primary study, a checkbox for this purpose should be added in this ICF dedicated to secondary uses (see checkbox for proposal No 4. in the tables that follow);
- specify that secondary uses may involve public or commercial/private partners but never include the sale of samples or data;
- specify where the participant can be informed of the secondary use projects (e.g. primary study website, ...);
- explain that the consent options presented in the document differentiate secondary uses according to:
    - whether the investigator remains the same or not,
    - whether data or samples are involved,
    - whether or not the planned analyses of the samples include genetic analyses.
- remind what is meant by pseudonymisation and anonymisation, as should normally have been done in the primary study information sheet;
- explain that in case of transfer of pseudonymised samples / data outside the European Union, the applicable data protection legislation may be less strict, and, if applicable, explain to the participant that they must give their explicit consent for this transfer. Also explain that agreements between the different partners will however be put in place to ensure a data protection level that is at least equivalent. Note: the transfer of data/samples in an anonymised form is to be encouraged;
- certify to the participant that their data will be protected in accordance with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of individuals with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (hereinafter: "General Data Protection Regulation"), respectively the law of 1 August 2018 on the organisation of the National Commission for Data Protection and the general data protection regime (if the project is exclusively Luxembourgish) and more particularly articles 63 to 65 of this law;
- mention the contact details of the DPO of the primary study;

- We also suggest that you mention all the rights of the persons concerned with regard to the protection of personal data, for example in this way:
- "You have the right to request from the controller access to, rectification or erasure of personal data, or a restriction of processing; you have the right to object to processing and the right to data portability under the conditions set out in Articles 15 to 21 of the General Data Protection Regulation. If you consider that the processing of your data constitutes a breach of the General Data Protection Regulation, you may lodge a complaint with the National Commission for Data Protection (CNPD)."

In the ICF for secondary uses, the following two tables with the different consent options must be included:

SECONDARY USES OF SAMPLES AND/OR DATA BY <u>THE SAME INVESTIGATOR / RESEARCH TEAM / INSTITUTION:</u>

For other subsequent projects in the same field of research (to be clearly named here and which must be seizable for the individual) that are conducted **by THE SAME INVESTIGATOR / RESEARCH TEAM / INSTITUTION**:

1. I agree to the re-use of my pseudonymised or anonymised **data**	**No**	☐			
	Yes	☐			
2. I agree to the re-use of my pseudonymised or anonymised **samples**	**No**	☐			
	Yes	☐	➔ I also agree to **genetic analysis** being carried out on my pseudonymised or anonymised **samples**	**No**	☐
				Yes	☐
3. my choices expressed above remain valid if the proposed secondary use project involves a transfer outside the European Union of my samples and/or data	**No**	☐			
	Yes	☐			

4. <u>Please note that this proposal only applies if I have agreed to the re-use of my **samples**</u>:

In the event of an incidental finding (some of which, in particular germline mutations, could not only affect my future health, but also that of my children, brothers/sisters, parents...),
I agree to receive such information through my treating physician / the study responsible physician / a geneticist (CHOOSE APPLICABLE MENTION)**, to discuss the possible implications and to be referred to a local geneticist if needed.**

[__] yes [__] no

In making my decision, I confirm that I have been well informed and that I understand that the researcher has no obligation to actively search for such “findings”, which are incidental by definition, in my sample(s), and that in the case of the incidental finding of a germline mutation, this does not in any way constitute a diagnostic.
I have also been informed that if such a finding occurs, it will occur at the time of data analysis for this current project, or for future projects if I have consented to the secondary use of my samples/data in the separate informed consent form. This is also when I will be contacted again if I have ticked "yes" above. Finally, I confirm having been well informed that I can change my decision at any time.

→ Consequences of my decision:

If I answer “no”, I will not receive any information about these incidental findings, nor will my relatives be informed.
If I answer “yes”, I will be informed of the incidental finding(s) through my treating physician / the study responsible physician / a geneticist. I will then be invited to discuss the possible implications and to be referred to a local geneticist if needed.

If the answer to the question above is “yes”, and in case of an incidental finding that may be relevant for the health of a relative, and if I am not able to receive this information myself (including if I am deceased at the time this information is identified), I wish to designate a member of my family (representative) to whom these results could be communicated, who could discuss the implications with my treating physician or the study responsible physician, and be referred to a local geneticist if necessary.

[__] yes [__] no

Name of my representative: _____

If I answer "yes", this means that I agree that my representative may receive such information, discuss the implications with my treating physician, and be referred to a local geneticist.

SECONDARY USES OF SAMPLES AND/OR DATA BY <u>OTHER RESEARCHERS:</u>

For other subsequent projects in the same field of research (to be clearly named here and which must be seizable for the individual) that are conducted **by other researchers**:

1. I agree to the re-use of my pseudonymised or anonymised **data**	**No**	☐			
	Yes	☐			
2. I agree to the re-use of my pseudonymised or anonymised **samples**	**No**	☐			
	Yes	☐	➔ I also agree to **genetic analysis** being carried out on my pseudonymised or anonymised **samples**	**No**	☐
				Yes	☐
3. my choices expressed above remain valid if the proposed secondary use project involves a transfer outside the European Union of my samples and/or data	**No**	☐			
	Yes	☐			

4. <u>Please note that this proposal only applies if I have agreed to the re-use of my **samples**:</u>

In the event of an incidental finding (some of which, in particular germline mutations, could not only affect my future health, but also that of my children, brothers/sisters, parents...),
I agree to receive such information through my treating physician / the study responsible physician / a geneticist (CHOOSE APPLICABLE MENTION)**, to discuss the possible implications and to be referred to a local geneticist if needed.**

[__] yes [__] no

In making my decision, I confirm that I have been well informed and that I understand that the researcher has no obligation to actively search for such “findings”, which are incidental by definition, in my sample(s), and that in the case of the incidental finding of a germline mutation, this does not in any way constitute a diagnostic.
I have also been informed that if such a finding occurs, it will occur at the time of data analysis for this current project, or for future projects if I have consented to the secondary use of my samples/data in the separate informed consent

form. This is also when I will be contacted again if I have ticked "yes" above. Finally, I confirm having been well informed that I can change my decision at any time.

→ Consequences of my decision:

If I answer “no”, I will not receive any information about these incidental findings, nor will my relatives be informed.
If I answer “yes”, I will be informed of the incidental finding(s) through my treating physician / the study responsible physician / a geneticist. I will then be invited to discuss the possible implications and to be referred to a local geneticist if needed.

If the answer to the question above is “yes”, and in case of an incidental finding that may be relevant for the health of a relative, and if I am not able to receive this information myself (including if I am deceased at the time this information is identified), I wish to designate a member of my family (representative) to whom these results could be communicated, who could discuss the implications with my treating physician or the study responsible physician, and be referred to a local geneticist if necessary.

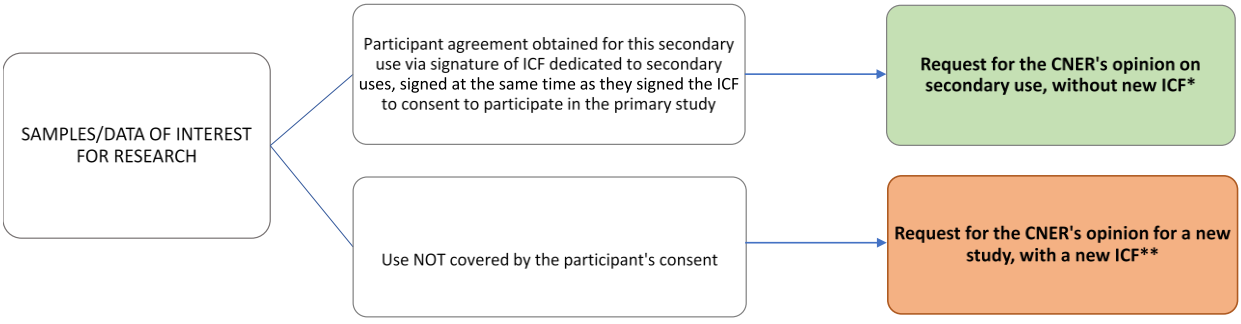
[__] yes [__] no

Name of my representative: _____

If I answer "yes", this means that I agree that my representative may receive such information, discuss the implications with my treating physician, and be referred to a local geneticist.

ANNEXE 1 CNER secondary use procedure scheme

SECONDARY USE OF SAMPLES AND DATA COLLECTED IN A RESEARCH PROJECT



*** the participant must not be recontacted to ask for their agreement for this secondary use**
**** participants in the primary study can be contacted again to offer them the secondary study on their existing samples/data, but only if they have ticked the relevant box in the primary study's ICF.**