How to Create a Biological Sample Collection: Requirements and Tips from an Academic Research Example in France

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Abstract: This short paper examines the regulatory needs behind the creation of a biological sample collection in France. Many research projects, including for medical devices development and evaluation, need biological sample collections, this article's ambition is to provide a clear view of the requirements to create such collections. Numerous laws from the Public Health Code frame research in the health sector in France, starting with the definition of the research type, and going through the various documents needed, especially securing patient safety (in link with Good Clinical Practices –GCPs) and data protection. To have a better insight into the requirements to create a biological sample collection, the use of an on-going academic research will help illustrate our purpose. This research did not involve human subjects, and therefore had a "simplified" path regarding national competent authority approval, and what is called "reference methodologies". Even though the procedure was labelled "simplified", numerous interactions are required such as with clinicians, researchers, the clinical investigation center, the hospital research department, and different public administrations including the Hospital, the Minister of Higher Education, Research and Innovation, the National Commission for Data Processing and Liberty (CNIL), and the University of Franche-Comté.

1 INTRODUCTION

Collecting biological samples from patients is a key for investigating and researching diseases and treatments. A biological sample can refer to biopsies, fragments of surgical specimens (tumorous or not), blood, serum, umbilical cord blood, bone marrow, bone, stem cells, or microorganisms isolated from patients (https://www.chu-besancon.fr/la-recherche/faire-de-la-recherche-au-chu/declaration-des-collections-dechantillons-biologiques.html). It is important to note that the extraction of samples of tissues and cells from the human body may only be carried out in authorised health establishments.

A collection of human biological samples is taken from a specific group of people identified and selected according to their clinical or biological characteristics. This collection must have a scientific

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purpose (Légifrance, 2021).

Eventually, a sample collection will help to understand the changes in tissues and cells related to a disease, and thus help to develop better treatments, diagnosis or medical devices specifically designed for that illness. For exemple PrediMAP an in-vitro diagnostic medical device in development that uses collections of vaginal secretions, placenta and membranes (Assistance Publique - Hôpitaux de Paris, 2022).

The law provides a framework for the collection and conservation of these samples. However, the creation of the procedure will involve many interactions with different partners.

In France, the creation of a biological sample collection requires a clear understanding of the scientific and regulatory procedures. Therefore, the French laws regarding the definition of a study and the different categories of research are the starting point. Then, to help illustrate the different interactions the example of a French academic study that intends to create a tissue and cell collection to further study a skin disease will be used.

2 DEFINITION OF RESEARCH IN FRANCE

As mentioned before, the creation of a collection must have a scientific purpose, and must be part of a research program, defined as a set of research activities organized with a goal to facilitate and accelerate discoveries in a specific scientific field, defined by an organization carrying out or promoting research activities (Légifrance, 2021).

In France, research in the health field can be schematically divided into:

- Research "under Jardé law" or Research projects Involving Human Subjects (RIPH *Recherche Impliquant la Personne Humaine*);
- Research "outside Jardé law" or Research projects not Involving Human Subjects.

It is to note that for medical devices, research falls under the European Union Medical Device Regulation (MDR) (European Parliament, Council of the European Union, 2017). These categories will lead to different procedures regarding the authorisations required to start a biological sample collection.

2.1 Research Projects Involving Human Subjects

The research under Jardé law can be divided into three different categories, each with their own specifications according to the article L1121-1 from the public health code (Légifrance, 2022a) :

- *" 1° Interventional research which includes an intervention on the subject not justified by their usual treatment;*
- *2° Interventional research involving only minimal risks and constraints, the list of which is specified by [...] the Minister of health [...];*
- *3° Non-interventional research that does not involve any risks or constraints in which all the medical acts are performed and the products are used in the usual way."*

These different studies will later need different authorisations.

For example, a study falling under 1° (or RIPH 1) can only be conducted after a favourable opinion from the Ethical Committee "Committee for the Protection of Persons" (in France *Comités de Protection des Personnes* or CPP) and after authorisation from the national competent authority (in France the *Agence Nationale de Sécurité du Médicament et des Produits de Santé* or ANSM). On the other hand, the studies falling under 2° (or RIPH 2) and 3° (or RIPH 3) only need a favourable opinion from the CPP. Here, the national competent authority only needs to be informed of the opinion of the CPP and sent a summary of the research (Légifrance, 2016).

On the same note, to follow the General Data Protection Regulation (GDPR or RGPD from French *Règlement Général sur la Protection des Données*) different approaches will be required. To help the implementation of these regulations the National Commission for Data Processing and Liberty (CNIL from French *Commission Nationale de l'Informatique et des Libertés*) created reference methodologies (MR from French *Méthodologies de Reference*) which offer a framework for the implementation of research treatments in the field of health. If the research complies with these reference methodologies, a referral to the ethic and scientific committee for research, studies and evaluations in the field of health (CESREES from French *Comité éthique et scientifique pour les recherches, les études et les évaluations dans le domaine de la santé*) is not required. For RIPH the reference methodologies are MR001 or MR003 (Section 3.3) (https:// www.cnil.fr/).

2.2 Research Projects not Involving Human Subjects

Research projects not involving human subjects are studies that do not meet the definition of research involving human subjects (section 2.1), in particular studies relating to the reuse of data. The research must also be in the public interest or a legitimate interest (GDPR Info, 2016a).

This collection must also be submitted to the CNIL and comply with the reference methodology MR004 (Section 3.3) (Commission Nationale de l'Informatique et des Libertés, 2018a).

3 TISSUES AND CELL COLLECTION IN FRANCE

To illustrate the establishment of a biological sample collection the example of a tissue and cell collection in an academic research project will be used.

This study aimed to better understand the biological processes that interfere with the effectiveness of the local treatment of a skin disease. The project uses tissue samples from a surgery performed in the normal treatment of the patients in the hospital in Besançon and a private clinic in Lyon. In addition, these tissues, after pathological examination, are considered as biological operative waste, meaning that if they were not collected for this research they would be discarded. It must be noted that these samples can only be used after approval from the patient.

Once the tissue samples have been gathered, multiple *in vitro* and *ex vivo* tests will be performed. Afterwards, a tissue (microscope slides) and cell (primary cell culture) collection will be stored in the university research laboratory. This research will allow making numerous analyses for this disease (Figure 1) from data gathered from the initial testing but also after the collection has been created. It is important to note that the objective of this collection it is not to be distributed to other organizations but only to be used in the research programs of the institution (if the aim is to distribute the samples to other organizations other documents are needed).

3.1 French Laws

Tissues, cells and human products removed during a medical intervention when stored for later use, are subject to the public health code (CSP from French *Code de la Santé Publique*), and more precisely to

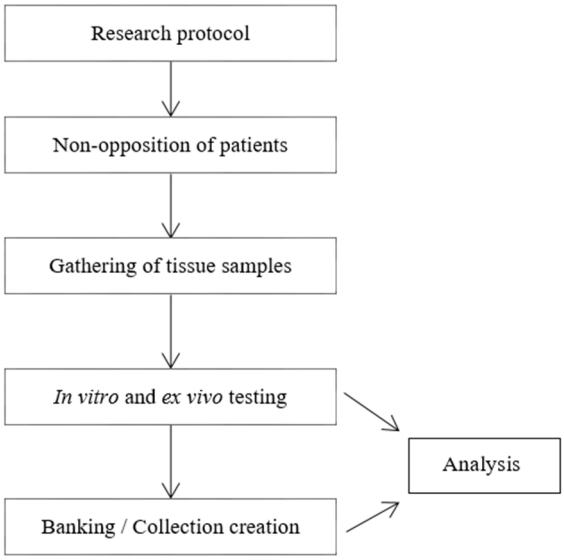

Figure 1: Schematic structure of the proposed academic research and use of tissue samples.

Articles L1241-1 to L1245-8 about "Tissues, cells, products of the human body and their derivatives". (Légifrance, 2022b).

During the establishment of a biological sample collection within the context of an RIPH, the collection no longer must be declared to the Ministry of Higher Education, Research and Innovation (Figure 2). However, the declaration of these samples is necessary if they are stored following the study and if this is the case, a requalification of the collection before a CPP will be needed (Lemaire, 2019).

If the collection is formed during research "outside Jardé law", the collection must be declared to the Ministry of Higher Education, Research and Innovation but does not require the opinion of a CPP (although it is recommended to have an opinion from a local ethics committee for research).

This academic research project is listed as a study "outside Jardé law". It will then need (Figure 2):

- The approval of the Ministry of Higher Education, Research and Innovation ;
- Compliance with the CNIL Reference Methodology MR004 (Section 3.3);
- A favourable opinion from a local ethics committee (not mandatory but recommended).

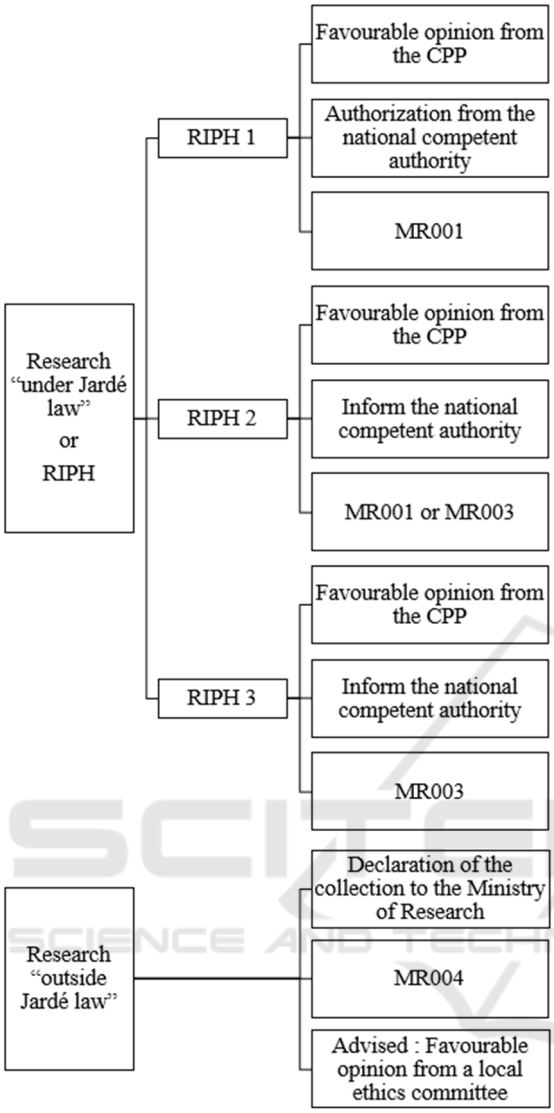

Figure 2: Non-exhaustive diagram about the requirements for the creation of a biological sample collection with research "under Jardé law" and "outside Jardé law".

3.2 Ministry of Higher Education, Research and Innovation

To have the approval of the Ministry of Higher Education, Research and Innovation for the conservation of elements of the human body a declaration must be made. This declaration consists of a letter signed by the legal representative of the applicant organization and a supporting document. These two documents must be transmitted to the Ministry of Higher Education, Research and Innovation using the online webpage to submit the files: "CODECOH" (from French *COnservation d'Eléments du COrps Humain*) (https://appliweb.dgri.education.fr/appli_web/codecoh/IdentCodec.jsp).

The supportive document as explained by the CODECOH has three essential parts: administrative, methodologic, and scientific. The administrative part will provide the basic information of the organization. The methodologic part however needs the expertise of field investigators familiar with the structure and procedures of the laboratory where the samples will be stored. Lastly, the scientific part guarantees the compliance with the law; for example justifying the importance of the envisioned research, data protection procedures, or patient consent. Overall, the procedure and information needed for the document is documented by the Ministry of Higher Education, Research and Innovation.

After the submission of a complete file, the Ministry of Higher Education, Research and Innovation has two months to notify its disagreement. If there is no feedback during those months, the project is allowed to start. (Ministère de l'Enseignement supérieur, recherche et innovation, 2018).

3.3 CNIL

The CNIL is an administrative authority that helps organizations comply with the RGPD (section 2.1). This study "outside Jardé law" will need to act in accordance with the CNIL reference method 004 (Commission Nationale de l'Informatique et des Libertés, 2018a). To fulfil the MR004, multiple procedures will have to be considered (Table 1).

This study will only collect the needed information from the patient, more specifically information about the progression of the disease and the drugs the patient administered to treat it. Additionally, this information will only be used by the laboratory of the University to create a correlation between the tissue structures and the progression of the disease.

Concerning the reference method MR004, the study must justify in the protocol why this information about the patient must be collected. Additionally, a procedure must be put together in order to protect the privacy and data of the patients: the information must be anonymised, the correspondence table (patient-code) must be kept secure and whoever has access to the information must be identified from the beginning and be bound to professional secrecy.

Table 1: Non-exhaustive comparison of the different reference methodologies by the CNIL. (Commission Nationale de l'Informatique et des Libertés, 2018b).

	MR001	MR003	MR004
Data controller	Study sponsor		
Health Data Hub registration	No		Yes
Patient information	Only necessary information may be collected and a scientific justification in the protocol is needed.		
Duration of data storage	Until the market launch of the studied product or the same duration as MR003 and MR004.	Two years after the last publication of the research results or until the release of the final research report.	
Access to the data	Clear distinction between accesses to directly and indirectly identifying data. Whoever has access to the information must be identified and be bound to professional secrecy.		
Informing people and respecting their rights	Written, free and informed consent from the patient.	Patient does not object to participating after having been individually informed.	
Security and Privacy	Data protection impact assessment carried out by the data controller. Implement and monitor the application of a security and confidentiality policy.		

Also, for this study, in order to comply with the provisions of Article 13 of the GDPR (GDPR Info, 2016b), the patient must be notified of the information that will be collected and its purposes. Furthermore, the patient must be "not opposed" to the collection of the biological sample or of data concerning the disease in order to be included in the study. For this, a patient information notice and non-opposition will be written and handed in to the doctor for the patient.

If information regarding the patient or doctors is shared in the European Union, the reasons must also be justified (Commission Nationale de l'Informatique et des Libertés, 2018a).

3.4 University

The University of Franche-Comté (UFC) not only has various research laboratories but also an ethical committee for research.

This research project will take place in the university laboratories with the required material for *ex vivo* and *in vitro* sample testing and storage of samples.

Even though is not legally needed to have an ethics committee's approval to perform the study, having one will allow the publication of the study in American journals too (Lemaire, 2006). The local ethical committee for research will make sure the patients included in the study are protected. For example, they will assess the potential effect on patients, evaluate the information given to participants, the treatment of personal data and the potential threat of identification (https://www.ubfc.fr/en/research/ethical-committee-for-research/).

3.5 Hospital

The sponsor of this study is the University Hospital of Besançon. Additionally, the tissue samples used in this project will be acquired in the hospital and clinic.

The hospital department of Clinical Research and Innovation (DRCI from French *Délégation à la recherche clinique et à l'innovation*) and the Clinical Investigation Centre (Inserm CIC 1431) have an undeniable role in the regulatory aspect of the study. The legally defined purposes of the DRCI are (Légifrance, 2011) :

- *"Promotion (organization, administration, management, control, technical regulatory support for clinical trials);*
- *Methodological assistance, data management; and biostatistics (editorial help, clinical trial design, database management)".*

According to the same legal document (Légifrance, 2011), the CIC is a research structure of the hospital that helps to develop studies by relying on one side on an efficient research environment with multiple parties and on the other side on the recruitment of patients.

Thus, the multiple files needed will be handled by the DRCI and the CIC: protocol, resume, budget, patient notice, CODECOH, local ethics committee document and partnership document between hospital and university but also with the private clinic. It must be noted that having more than one research location (in this case hospital, university and private clinic) will need more procedures regarding storage and transport of the biological samples but also legal documents confirming the agreements and partnerships with the different sites.

On the same note, it must not be forgotten to classify the biological sample especially if it could be an infectious substance and if it might go across country borders. The rules on storage, packaging and transportation (Genève : Organisation mondiale de la Santé, 2019) are to be taken into account for the protocol, partnership and CODECOH documents.

Overall, writing the protocol needed not only information exchange with the DRCI and the CIC but also with the hospital and the clinic doctors, as well as with the university researchers, in order to provide a strong clinical and scientific justification (the "rational" of the study).

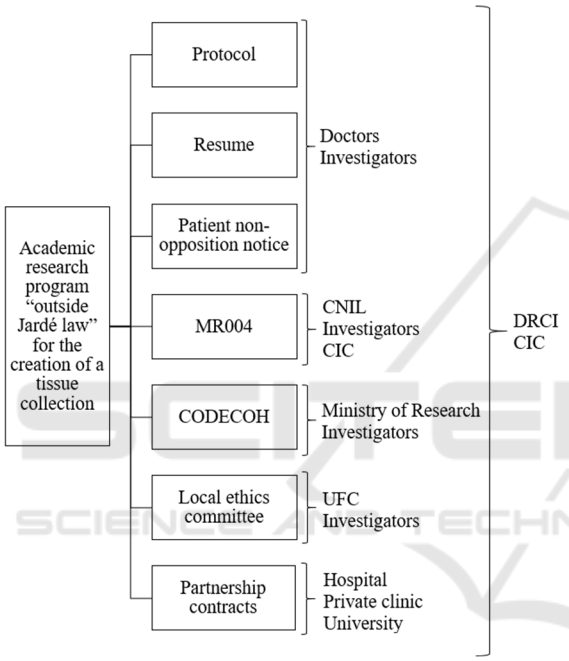

Figure 3: List summarizing the documents needed and the exchanges of information: example from our proposed academic research.

4 CONCLUSIONS

Biological sample collections are important to help increase the understanding of a disease and eventually improve patient care. The process needs to be part of a clinical study, and as such various procedures and documents are required to collect biological samples from patients, posing an entry barrier.

In France, the procedure is regulated in a very specific way that requires multiple contributors with different skills in order to complete the project. There is no "simple" way to obtain approvals, but this work hopes to facilitate the approach.

It must be noted that this is only an example for a French study, many of these procedures are not yet harmonised in the European Union.

Even if there are tools to help identify the applicable laws (http://campus.ecrin.org/) or to identify the administrative authorities in the European countries (such as the national competent authority (https://www.ema.europa.eu/en/partners-networks/eu-partners/eu-member-states), the ethics committee (http://www.eurecnet.org/) or the data protection authority (https://edpb.europa.eu/about-edpb/about-edpb/members_en)), the research project's specific regulatory requirements need to be evaluated case by case. Therefore, it is not surprising that the regulatory needs of a study are dependent on the nature of the research, the countries involved and the timing of application of new regulations (the laws regarding European clinical trials and clinical investigations are constantly changing and databases might not be up-to-date yet). Some examples of these complex procedures can be seen in retrospective studies in Europe (Houg, Lihoreau, Hennessy, Mouyabi, et al., 2022), non-interventional studies in the European Union (Ramirez, 2015) or multinational clinical investigations for medical devices (Houg, Lihoreau, Hennessy, Esperou, et al., 2022).

Consequently, for a multicentre and international study aiming to create a biological sample collection from different countries, the procedure will have a tendency to become more complex. The study will need to comply with multiple competent authorities and possibly adapt to local requirements too (center dependant).

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