



Special article

Biobanks and use of samples of human origin for surgical research. Current regulatory framework

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In recent years, there has been a growing interest in the development of biological samples and biobanks that make it easier for investigators to have access to quality samples and their associated clinical and epidemiological data. Thus, biobanks have become indispensable technological platforms for the development of both basic and clinical research.

The properties of the biological sample as a support medium of personal and family information require that they are treated in accordance with new ethical standards. For this reason, the Law on Biomedical Research, provides a new regulatory framework in the process of obtaining samples and their storage for research purposes, where the consent of the source subject, data protection, the favourable opinion of a Research Ethics Committee, the prior taking out of an insurance policy against possible adverse effects, and the quality and safety requirements in the handling and management of these materials are key elements.

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Biobancos y utilización de muestras de origen humano en investigación quirúrgica. Marco normativo actual

R E S U M E N

En los últimos años se ha despertado un interés creciente por el desarrollo de colecciones de muestras biológicas y biobancos que faciliten a los investigadores el acceso a muestras de calidad y a sus datos clínico-epidemiológicos asociados. Así, los biobancos se han convertido en plataformas tecnológicas indispensables para el desarrollo de la investigación tanto básica como clínica.

Las propiedades de la muestra biológica como soporte de información personal y familiar requieren que sean tratadas de acuerdo a nuevos estándares éticos. Por ello, la Ley de Investigación Biomédica dota de un novedoso marco normativo al proceso de obtención de

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las muestras y a su almacenamiento con fines de investigación, donde el consentimiento del sujeto fuente, la protección de datos, el informe favorable de un comité de ética de la investigación, la contratación de un seguro previo ante posibles efectos adversos, y los requisitos de calidad y seguridad en el tratamiento y gestión de estos materiales son elementos clave.

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Introduction

There is unanimous agreement that for biomedical investigation to reach standards of excellence it needs samples and data of human origin. This research area's purpose is becoming more centred towards approving hypotheses through *in vitro* studies performed on human samples.¹ As such, several clinical pathological entities have been discovered through analysing clinical samples stored in anatomical disease departments. This has had a direct impact on the health and survival of thousands of patients. Therefore, facilitating access to high-quality samples and related clinical and socio-demographic data constitutes one of the key aspects for developing translational research.^{2,3}

Although this has helped generate interest in developing sample collections and biobanks during the past 15 years, if human samples for research purposes are used incorrectly it could lead to pertinent ethical problems. The advances in molecular biology and new technology developments have made it much easier to access genetic information. Furthermore, biological samples are today considered as a biological data support which determines the state of health or predisposition to certain diseases, not only for the source subject, but also for his or her close relatives. Therefore, the general principles for personal data protection must be applied when using and exchanging samples.⁴

In Spain there are plenty of regulations on biomedical research, although they mainly concern drug clinical trials. The publication of the Spanish royal decree which regulates the clinical trials for pharmaceutical products and medicinal preparations dates back to 1978.⁵ However, legislation on obtaining, storing and using human samples in research was comparably scant until 2007, when the Spanish Law 14/2007 on biomedical research (LBR)⁶ came into force, which partly aimed to cover the previously indicated deficiency.

Pre-existing regulatory framework

The main regulations in force in Spain, concerning the use of human biological samples and associated data are: the Convention for the Protection of Human Rights and Dignity of the Human Beings with regard to the Application of Biology and Medicine,⁷ the Spanish Organic Law 15/99,

on the protection of personal data⁸; and Law 41/2002, regulating patient autonomy, rights and obligations regarding information and clinical documentation.⁹

There are also international, non-binding guidelines which make reference to research in humans, mainly being the 6th Helsinki Declaration,¹⁰ the CIOMS 2002 Guidelines,¹¹ and the UNESCO Declaration, which recognises in its preamble that to progress we need to research humans and use biological material of human origin.¹²

Although storing biological samples for research purposes is an old practice, the concept of biobanks in laboratories and hospitals is, however, very recent. The first European biobanking regulation was adopted in 2000, with the Act on Biobanks being approved in Iceland, and from this date onwards several other European countries have adopted similar regulations.^{13,14} Furthermore, numerous national bioethics committees and some international organisations have produced recommendations or consensus guidelines regarding biological sample collections and biobanks.¹⁵⁻¹⁸

Most of the Spanish regulations were developed after European Parliament and Council approved the relevant European directives.¹⁹ Until the LBR was approved, there was no specific regulation applicable to obtaining and using biological samples for scientific research, although banks with samples of human origin (i.e. *Banco Nacional de ADN* [Spanish DNA bank] or the *Banco Nacional de Líneas Celulares* [Spanish cell lines bank]) were covered by laws.^{20,21}

The Law 14/2007 on biomedical research

The LBR introduced important new measures concerning the storage and use of samples. Firstly, it establishes that the subject must provide consent before any sample is extracted for research use or for it to be stored and used at a later stage. Furthermore, a research ethics committee must provide a report for each of the studies involving human biological samples or their related data. This Law also introduced the need for insurance against possible damages that participants may suffer when studies involve invasive procedures. It adopts the principle of gratuity throughout the process (donation, storage, awarding access, and sample use) both for source subjects and the store developers. It also establishes the need to create quality and safety standards in treating and handling samples. Biobanks for biomedical

research deserve special mention, but more details on this matter will be given below.

Invasive procedures and insurance

The LBR considers an invasive procedure to be any intervention performed for research purposes that involves physical or psychological risk to the subject involved. It is based on the general principle that research must not cause the participant risk or discomfort disproportionate to the expected potential benefits. Any risk or discomfort must be minimal for the subject, as deemed by the research ethics committee assessing the research project, weighing up the risks/benefits for each individual case.

As has been previously mentioned, and in the ambit of the LBR's protective nature, studies which entail invasive procedures on human beings require insurance against possible adverse effects or unforeseen damages that could occur during research, as well as meeting the requirements necessary for any given project.

With regard to this matter, the LBR makes reference to the Spanish royal decree 223/2004 regulating clinical trials with drugs.²² It established that unforeseen events that negatively affect the study participant's health will be considered a consequence of the research, except when proven otherwise, whether they occurred during the project or the year after it has been completed. The research developer, main researcher and the research centre will jointly accept responsibility for the damage, although they may not be at fault. As such, the burden of proof is reversed, meaning that the defendant has to prove that the damage has not been produced as a result of the research, which could cause a difficult situation for the researcher.

From a practical point of view, it is important, however, to take into account the main purpose for taking the sample. If it is taken for diagnostic or therapeutic purposes, we would not have to consider the invasive procedure to be performed solely for research purposes, meaning that it would be exempt from most of the ethical/legal issues described. As such, it would be a good idea to obtain samples for research purposes during other healthcare tasks, i.e. when taking blood, so as to avoid direct expenses and potential conflicts.

Informed consent

Subjects must be informed about why their samples are being taken and must give consent before they are taken and used, no matter the research purpose, whether it is anonymously stored or codified, or stored in a collection or a biobank.

The informed consent process is described in a document consisting of a form and an information sheet, on numbered pages. This document should at least include the information on the following:

- 1) The purpose and objectives of the research project;
- 2) The procedure and the possible disadvantages associated with giving samples;
- 3) Identity of the researcher and the person in charge of the collection or biobank;

- 4) The subject's right to express whether he/she consents to future use of his or her samples, whether he/she consents to other researchers having access to his or her samples and/or related data and, where applicable, access conditions;
- 5) Guarantee that confidentiality of information will be maintained;
- 6) The right to withdraw consent at any moment, and right to dispute, rectify, and cancel his or her data in accordance with current legislation;
- 7) The right to decide if he/she wishes to receive information about the research results and, where applicable, when, how and by whom he/she shall be informed;
- 8) The expected benefits from participating in the research (for him/her, his/her family, if there are any, for science and the health system);
- 9) The measures taken to assure appropriate compensation if the subject were to suffer an adverse effect or unforeseen damage.

If the sample is to be included in a biobank or collection, the subject should also be informed of the following:

- 1) The biobank or institution where the sample shall be stored;
- 2) The collection or biobank's purpose and objectives;
- 3) That the biological material or the research results may generate profits, and that the subject will not receive any financial compensation.

The subject must consent to any surgical act and/or sample taking for diagnosis and separate consent must be obtained for research purposes. A patient may consent to giving a sample for diagnostic but not research purposes. If this were to occur, the surplus sample must be destroyed, except if it were to be required for possible future diagnostic reviews.

Historical samples collected before the LBR, which were obtained for purposes other than research, must be made anonymous before being used. This means that any link or code associated with the source subject must be destroyed. When the research requires the link to be maintained, the LBR, as an exception, ascertains that codified or identifiable samples can be used when it is impossible to obtain consent, or if it represents an unreasonable effort. The research ethics committee must issue a report permitting the research project.

Sample donation from minors and people unable to consent for themselves

In these cases, consent should be granted by legal representatives. Donation of tissues or samples for research purposes can only be allowed when research results can directly benefit the participant's health. For this matter, The LBR makes reference to the Spanish Law 41/2002, a basic regulatory law on patient autonomy. It establishes a greater level of protection as it orders research developers to inform the tax ministry of the authorisations granted for research on underage subjects.

Research ethics committees

The professional member organisations changed when the research ethics committees were created. Before the LBR was approved, ethics was mainly evaluated by clinical research ethics committees. The LBR outlines that the research ethics committee should assess the ethics associated with all research involving human beings, biological samples or personal data.

With regard to samples to be used in research, the research ethics committees must ensure that:

- They have been consented to by the source subject.
- When using samples collected before the LBR came into force, the best alternative for making the research possible must be sought without violating the source subjects' rights.
- Using samples from diagnostic archives for research purposes must not compromise the source subjects' rights to health.
- Appropriate measures must be established to ensure that related information and participant's privacy is maintained confidential.
- Appropriate measures have been taken to insure possible unforeseen damages.
- As far as is practical, the project shall be monitored by means of relevant progress reports and a final report, and the incidences that could entail ethical repercussions during the study are to be assessed.

Taking or using biological samples from deceased people

The LBR states that biological samples from deceased people can be taken for research if the subject gave consent when he/she was alive, or at least if the subject had not expressly opposed against such practice in writing. In principle, the subject's family is not be able to dispute it without good reason, and provided that it is not against the deceased person's will, the samples can be used. If this is to be the case, the researchers should find out the subject's wishes, meaning that researchers should find out if the patient gave previous instructions and if not, the deceased person's family and healthcare providers shall be consulted.

Prior agreement between the researcher or the biobank and the centre storing the cadaver, (healthcare centre, funeral parlour, forensic institute or morgue) is also required for taking samples from deceased subjects, whether for a specific use or to be stored in a biobank.

Biobanks

Law on biomedical research and biobanks

With the creation of biobanks, the LBR pursues the objective of aiding researchers access to the most samples. Its essential quality, preservation and gratuity requirements ensure that high-quality research projects are possible. The

Registro Nacional de Biobancos (Spanish biobank register) was also created for this same purpose, publishing information on accredited biobanks, also making it easier to consult the material stored in it. The LBR states that biobanks must have a specific structure to ensure that the ethical and legal requirements are met: a scientific director, two external committees, (a scientific committee and an ethics committee), and someone that is in charge of filing data. The law also states that for the biobank to be able to function it must undergo an administrative authorisation procedure.

This regulation expects that samples to be used for biomedical research are preferably included in a biobank, as they can subsequently be employed in any type of biomedical research, provided that the source subject has given consent to these storage terms, and that the scientific and ethical committee has issued a report justifying the action. In contrast, the samples stored in collections may only be used for the purpose that the subject consented to, meaning that for any new project, researchers must request specific consent from the source subject. The *Registro Nacional de Biobancos* must also be informed of sample collections for research.

The source subject maintains ownership of its sample, and the biobank acts as a safekeeper or deposit, ensuring that it is used in a "safe" manner in accordance with the donor's wishes. Samples and related data stored in biobanks can only be provided to researchers on an anonymous and dissociated basis to ensure that the source subject's personal data are protected. However, it also states that if the research project needs additional clinical data from the source subjects, then the biobank or person in charge of the collection can contact the centre from where the sample was obtained in order to obtain this information.

Future perspectives

With the aim of promoting and providing quality research, biobanks have become essential technological platforms and one of the most essential tools for basic and clinical research. They make accessing and exchanging biological material easier and are one of the most important strategic infrastructures for the Spanish national health system's health centres.

Subsequent to the LBR, and with the same objective, the *Instituto de Salud Carlos III* (Carlos III Health Institute) kick-started the Spanish biobank network, as a cross-sectional structure within the thematic networks for cooperative research, mainly focusing on Spanish National Health System's health centres. This was how Spanish biobank networks started to integrate into international platforms, such as the Biobanking and Biomolecular Resources Research Infrastructure, funded by the 7th Framework Programme. Its aim is to create an infrastructure of biobanks and biomolecular resources for research purposes at a Pan-European level. Spain has actively participated in this project.

Discussion

The LBR has presented a regulatory framework designed to provide the researcher with legal security and to protect the source subject's rights in an attempt to harmonise the researchers' and the community's interests. However, some of the points concerning taking and handling samples for research have aroused controversy among the research ethics committees:

- 1) The need for damage insurance for projects that imply invasive procedures and the reference to the insurance regime established for clinical trials in the Spanish Royal Decree 223/2004. This aspect is especially disputed when the procedure to be carried out is minimally invasive, e.g. venipuncture. Furthermore, the definition of invasive procedure covers any intervention performed for research purposes which implies a physical or psychological risk for the participant. The Law does not establish precaution differences or risk levels, as are defined, for example, in the European Parliament document for implementing guidelines on the Directive 2001/20/EC.²³ Nor does it follow the recommendation in the Additional Protocol, which urges the creation of guidelines that describe interventions and establish a scale for possible damages. The reference to the Spanish Royal Decree 223/2004 entails contracting an insurance policy with compensation for damages which will guarantee a minimal sum of €250,000 per participant in the study, which could substantially increase the projects' expenditure.
- 2) Another of the most debated aspects is the difficulty to define the line of research and the repercussion that this has on requesting informed consent or not for a specific research project developed within this framework. For certain innovative areas, it is increasingly difficult to define their limits. An example of this is the complex relation between cancer and ageing or between some degenerative diseases and basic inflammation mechanisms. However, for this last matter, the LBR establishes an ideal framework that provides great flexibility when using samples, i.e. the biobanks. The guarantees that an accredited biobank offers (donor consent to storage, ethical and scientific supervision of the research project, sample and data protection, more effective use of resources, etc.) comply with the most demanding ethical requirements and also provides legal security for the researcher, without hindering access to samples.

Surgeons have to be increasingly aware of the participants' rights (requesting consent, right to information and provision of results, including genetic counselling when necessary) and must take them into consideration when designing, implementing and managing the research project.^{24,25} Developing clear and participative practices will have an impact on patients' trust, benefiting an increase in their tendency to donate samples or participate in research that implies invasive procedures.²⁶

Lastly, the growing complexity of biobanks' activity, and its scientific, ethical and legal connotations has revealed

the need to professionalise biobanking. Biobanks are not the final purpose, but the instruments that support biomedical research of excellence. In this respect, the LBR provides biobanks with a structure for developing policies that can optimise the circulation of samples and related data among researchers, adapting biobanking to the ethical and legal framework and guaranteeing best practice. The scientific and ethical committees associated with the biobank must contribute to achieving the biobank's objectives, without forgetting that its quality should not be measured by the number of samples that it stores, but by their utility.²⁷

Conflict of interest

The authors affirm that they have no conflict of interest.

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