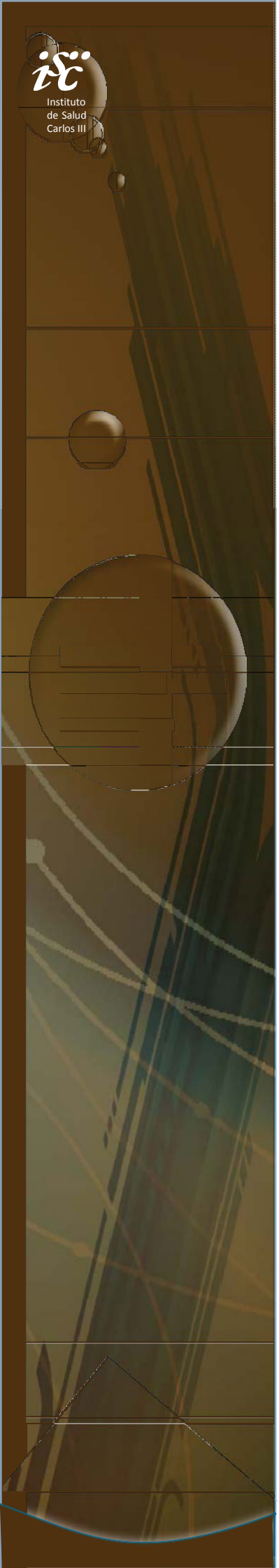

Red Biobancos
Instituto de Salud Carlos III

Code of Good Practices applicable to Spanish Biomedical Research Biobanks

Madrid, 2012

CODE of GOOD PRACTICES applicable to Spanish Biomedical Research Biobanks

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MOST FREQUENTLY USED ABBREVIATIONS

CREC: Clinical Research Ethics Committee

ICF: Informed Consent Form

BRL: Spanish Biomedical Research Law 14/2007, dated July 3, governing Biomedical Research

SOLPPD: Spanish Organic Law on the Protection of Personal Data. Spanish Organic Law 15/1999, dated December 13, governing the Protection of Personal Data

SOPs: Standard Operating Procedures

QMS: Quality Management System

1. INTRODUCTION

Biomedical research is a key tool for improving our current understanding of diseases, and for developing methods to diagnose, prevent and treat them so as to improve the qualitiy and expectancy of human life. Thus, in recent years, various sectors of our society, from donors to the scientific community, have developed a growing interest to establish the necessary means to ensure the availability of human biological samples of good quality:

- Samples obtained in compliance with the authorizations required by our legal framework to guarantee the safeguarding of the donors' rights and available to promote biomedical research.
- Samples with associated information (clinical, epidemiological, etc.) registered securely.
- Samples obtained and processed in a standardized way, and preserved in optimal conditions.

The biological samples (blood, urine, tissue, etc.) are classified, according to the purpose (from a broad purpose to a specific one) for which they were collected, in samples from biobanks, collections or specific projects (article 22 of Spanish Royal Decree 1716/2011).

Biobanks serve as research support infrastructures that house collections of biological samples under strict ethical and scientific supervision, and which currently play a fundamental role in biomedical research. They act as a link between donors, clinicians and researchers to ensure a safe and effective treatment of the biological samples and associated data, favoring the access to high quality samples.

The "traditional model" of informed consent (notification of all the details of the research activities to which a sample will be subjected; see Section 2.1) must currently face the new challenges linked to the recent advances made in biomedical research technology, particularly those associated with the creation of the biobanks. In this new context, it is hard to provide subjects with information concerning the research, as the biobanks are designed to be used by several researchers, as well as many current and future projects. Therefore, the biological samples that they house must be linked to an informed consent applicable to various research purposes enabling the use of the samples for any research approved both scientifically and ethically.

Biotechnological development has opened the door to the discovery of new therapeutic targets; however, to continue progressing in this field, large case series, including perfectly collected samples and data (since the samples, per se, have no value if they are not accompanied by accurate clinical information) and enabling the conduct of high quality multidisciplinary and multicentric studies, are needed. This demand has been largely covered by biobanks, which, among other aspects, allow for improving methods for the early prediction and diagnosis of diseases, the discovery of new drugs selectively aimed at specific variants of certain pathological processes, and the early detection of the susceptibility of each person to toxicity or resistance to certain treatments (see Riegman et al. 2008).

Broadly speaking, we can classify biobanks for human biomedical research into two main types:

- Population biobanks: whose main purpose is to obtain susceptibility biomarkers. To this end, they store samples and data of a great number of healthy donors, establishing a long-term follow-up.

- Disease-oriented biobanks: the purpose of these biobanks is to improve the current knowledge on the mechanisms and biomarkers of a specific pathology. To this end, they store samples and data, often from clinical medical records.

This Code of Good Practices aims to gather the consensus on the recommendations, standards and obligations of the Spanish Biomedical Research Biobanks.

1.1 Purpose and Scope

This Code of Good Practices aims to develop a consensual procedure guide describing the operating guidelines of the Biomedical Research Biobanks, based on past experience and framed by the ethical-legal standards in force. Therefore, this document is applicable to all staff employed by the Biomedical Research Biobanks, as well as those working at health care institutions or research centers, who, in the exercise of their professional activity, carry out biomedical research with human biological material and/or data.

The Management Department of the Centers featuring Biomedical Research Biobanks belonging to the National Biobanks Networks (see www.redbiobancos.es) must enable the dissemination and implementation of this Code of Good Practices among its staff. Likewise, it is advisable that the website of these biobanks include a link to this Code of Good Practices in order to facilitate its availability and consultation.

1.2 Scope of Application

This Code of Good Practices shall be applicable to scientific research projects involving humans, human samples, human data, and human embryonic or fetal material. With respect to biological samples, this Code applies to all biological samples obtained for biomedical research, including those used in the context of a clinical trial, as well as samples obtained for diagnostic or medical purposes, which will also be used for research purposes (article 3 of Spanish Royal Decree 1716/2011).

1.3 Applicable Legislation and Regulations

- Article 44.2 of the Spanish Constitution, which entrusts public authorities with the promotion of science and scientific and technical research for the benefit of the public interests.
- Spanish Organic Law 15/1999, dated December 13, governing the Protection of Personal Data. Official Gazette of the Spanish Government (BOE) number 298, dated December 14, 1999.
- Spanish Law 14/2007, dated July 3, governing Biomedical Research. BOE number 159, pages 28826-28848.
- Spanish Law 41/2002, dated November 14, regulating the autonomy of the patient, and the rights and obligations relating to clinical information and documentation. BOE number 274, pages 40126-40132.
- Spanish Royal Decree 1716/2011, dated November 18, which establishes the basic requirements for the authorization and operation of biobanks for biomedical research purposes and the processing of human biological samples, and regulates the operation and organization of the National Biobank Registry for Biomedical Research. BOE number 290, pages 128434-128454.
- Spanish Royal Decree 1720/2007, dated December 21, approving the Regulation implementing Organic Law 15/1999, dated December 13, on the Protection of Personal Data. BOE number 17, pages 4103-4136.
- Spanish Royal Decree 65/2006, dated January 30, which sets out the requirements for the import and export of biological samples. BOE number 32, pages 4626-4636.

- Order SAS/3166/2009, dated November 16, replacing the annexes of Spanish Royal Decree 65/2006, dated January 30, which sets out the requirements for the import and export of biological samples. BOE number 286, pages 100514-100523.
- Guide on the regulations concerning the transport of infectious substances 2009-2010. World Health Organization.

The various Autonomous Regions that make up the Spanish State are authorized to regulate this activity in their territory; hence, the local legislation of the regions where each biobank resides must also be complied with.

The following conventions and declarations are also applicable: Universal Declaration on the human genome and human rights (UNESCO 1997), Convention on Human Rights and Biomedicine (European Council 1997), International Declaration on Human Genetic Data (UNESCO, October 2003), Universal Declaration on Bioethics and Human Rights (UNESCO, October 19, 2005), and Recommendation of the European Council R(2006)4 on research with human biological material, dated March 15, 2006.

The recommendations of the Spanish Bioethics Committee (see www.comitedebioetica.es/documentacion/index.php), and the Codes of Good Practices outlined below, were considered to develop this code of good practices:

- Code of Good Practices of the Carlos III Institute (see www.isciii.es/htdocs/terapia/terapia_comiteetica.jsp).
- The Guideline Documents on Good Practices in Biomedical Research Biobanks of the Clinical Research Managing Bodies Network (REGIC, www.regic.org).

The following Guides on Good Practices were also used as a source for preparing this document (see the References Section: Codes of Good Practices):

- The National Tumor Banks Network (promoted by the Spanish National Cancer Research Center [CNIO])
- The International Society for Biological and Environmental Repositories (ISBER)
- The Organization for Economic Cooperation and Development (OECD)

2. DEFINITIONS

2.1 General Definitions

- Material transfer agreement: a document where the terms and conditions under which samples and materials shall be exchanged between two institutions are specified.
- Biobank for biomedical research purposes: a public or private, non-profit establishment that houses one or several collections of human biological samples for biomedical research purposes, organized as a technical unit with quality, order and destination criteria, regardless of whether or not it stores samples for other purposes.
- Network biobank: a biobank with a single type of organization and decentralized activity.
- National biobank for biomedical research purposes: biobank for biomedical research purposes created by the head of the Ministry of Science and Innovation because of its special public interest.
- Transfer of human biological samples for biomedical research purposes: transfer of biological samples to a third party for biomedical research purposes.
- Consent: a manifestation of the free and conscious will, validly issued by a capable person, or by their authorized representative, preceded by the appropriate notification of information. Within the framework of this research project, it would correspond to the act of assenting/granting authorization to participate in a research project.
- Informed consent form: The informed consent form for biomedical research involving the collection of biological samples is a document that includes all information relating to the requested biological samples, the sampling procedure, and the purpose and use of these for biomedical research purposes. This document serves as proof of the authorization (consent) of the source subject/donor and offers the possibility of refusing or withdrawing the authorization (consent refusal or withdrawal).
- Biological sample: any biological material of human origin susceptible to preservation, regardless of whether it contains information on a person's genetic endowment.
- Source subject or donor: subject from whom the biological sample was collected.
- Traceability: ability to follow the history, application or location of everything under consideration (ISO standard 9000:2005). In the specific case of biological samples, traceability is defined as the ability to associate specific biological material with information recorded during each step of the collection process, as well as throughout the entire research process.

2.2 Definitions of the Identification Systems and Tagging of Samples or Data

According to the association between the biological samples or data and the identity of the source subject/donor, these identification and sample or data tagging systems can be classified as:

- Identified samples or data: those cases in which there is a direct link between the samples or data and the donors' identity. Examples: a document including the donors' name or the number of their medical record and their diagnostic information; a biological sample tagged with the donors' name or medical record number.
- Coded samples or data: those cases in which the link between the donors' identity and the samples or data is indirect and based on either a simple or double code. Example: a document or sample identified by an alphanumeric code that does not reveal any information that can link the document or sample with the donor, and which requires access to a protected record or document that allows for establishing a relationship with the donors' code and the sample or document.

This coding constitutes a reversible dissociation process.

- Anonymous samples or data: those cases in which there was never a link between the samples or data and the donors' identity.
- Anonymized samples or data: these are samples or data that were previously identified or coded, but whose identification, code or code key has been destroyed and for which there is consequently no longer a link with the donor.

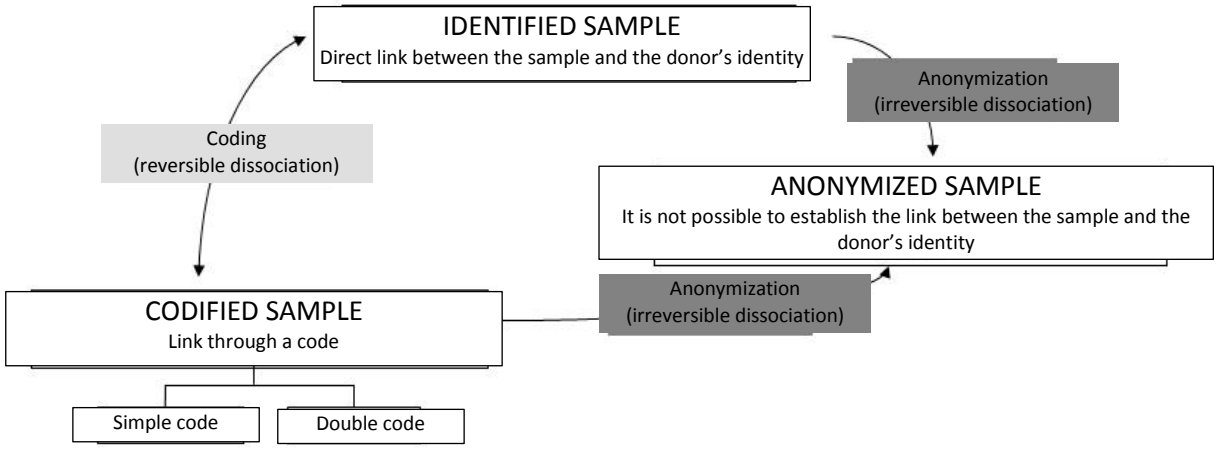

Figure translation:
IDENTIFIED SAMPLE (direct link between the sample and the donor's identity
Anonymization (irreversible dissociation)
ANONYMIZED SAMPLE (it is impossible to establish a relationship between the sample and the donors' identity)
Anonymization (irreversible dissociation)
CODED SAMPLE (linked to the donor by a code): Simple code / Double code
Coding (reversible dissociation)

The samples or data may be subjected to a dissociation, coding or anonymization process allowing for decoupling the donor's identifying data:

- Dissociation: a process by which the link between the sample/data and the donors' identity is destroyed. This dissociation may be reversible (coding) or irreversible (anonymization).
- Coding: this is the process whereby a code (simple or double) is assigned to a sample/datum to mask the relationship between the sample and the donor.
- Anonymization: this is the process whereby it becomes impossible to ascertain, by reasonable means, the relationship between a datum/sample and the identity of the source subject or donor. Therefore, this is an irreversible dissociation process.

The coding of samples/data can be simple or double:

- A simple code constitutes a direct link to the subjects' identity and is generally made up of a random set of numbers and letters, or a barcode;
- A double code implies that a second code is needed to link the sample/datum to the persons' identity.

3. RESEARCH INVOLVING HUMAN BEINGS

3.1 General Principles and Rules Governing Research Involving Human Subjects or their Biological Material

The general principles for the conduct of research projects with human beings are as follows (article 2 of the Spanish Biomedical Research Law [BRL]):

a) The dignity and identity of the human subjects must be safeguarded during any research involving the conduct of any procedures on the human subjects in the field of biomedicine, guaranteeing all individuals, without any type of discrimination, respect of their integrity and other rights and fundamental freedoms.

b) The health, interests and well-being of the human participant in a biomedical research project will prevail over the interests of society or science.

c) Research studies involving the use of human biological samples shall be carried with the utmost respect to fundamental rights and freedoms, guaranteeing confidentiality during the processing of the personal data and biological samples, and particularly during the conduct of the genetic analyses.

d) Freedom of research and scientific production in the field of biomedical science shall be guaranteed.

e) The authorization and development of any research project involving human subjects or their biological material will require a prior and mandatory favorable report granted by the Research Ethics Committee (REC).

f) The research study must be carried out in accordance with the precautionary principle to prevent and avoid risks to the subjects' life and health.

g) The research study must be subject to evaluation.

Based on these principles, the general rules that must be met for the collection, storage and use of human biological samples in research projects are:

- Protect the rights of subjects whose biological samples will be included in a collection. Because of this, it is crucial to duly notify the source subject/donor of the purpose and use of the biological samples submitted, and to obtain their informed consent.
- Guarantee the confidentiality of the information and data supplied by the source subject/donor.
- Guarantee the traceability and quality of the samples donated for biomedical research.
- Guarantee the safe and appropriate long-term storage of the biological samples.
- Facilitate the accessibility and availability of the collections for their use in research projects with a favorable opinion on the part of the scientific and ethics committees.
- Submit the proposals for biomedical research projects and protocols for scientific and ethical review to obtain scientific and ethical approval for their implementation.

3.2 Authorization and Development of Research Projects Involving Human Subjects or their Biological Material

The authorization and conduct of any research study involving human subjects or their biological material shall require a prior and mandatory favorable report granted by the Research Ethics Committee (or the Clinical Research Ethics Committee [CREC]). Biomedical research projects involving human subjects shall be detailed in a written document that must include, at least, the following information: background, specific objectives, methodology used and staff involved. Additionally, the document must include a work plan, with the associated planned schedule for each of the research phases, describing the human and material resources that are expected to be used during each phase. The research project must be accepted and signed by the principal investigator, and if the use of certain assistance services is expected, the collection of prior written approval through the person in charge of the project, including economic agreements if the study involves expenses for these, is advised.

The participation of a subject in a biomedical research project, as well as the collection and use of biological samples for use in research, requires the provision of sufficient information to the source subject/donor, in writing and in understandable terms, in order for them to have enough time to exercise their right to autonomy, consult the proposal and make an informed decision (articles 4, 58, 60 and 69 of the BRL; article 23 of Spanish Royal Decree 1716/2011; see Section 4.3). Likewise, the legislation governing patients' autonomy and the protection of personal data also sets outs the requirements to obtain the informed consent of the source subject/donor. This informed consent form to be submitted to the Research Ethics Committee for its review and authorization must be prepared according to the purpose of the project and the samples requested to the source subject/donor (see Section 3.5)

3.3 Biomedical Research in Specific Situations

Biomedical research can occasionally involve subjects who, due to their condition or state, are more vulnerable than others, or they may be carried out in situations in which it is impossible to inform and obtain the donors' consent. This is the case of research involving embryos or fetuses, pregnant or breastfeeding women, subjects unable to provide their consent (either because of their clinical situation or other circumstances) or deceased subjects.

Human embryos that have lost their capacity for biological development, as well as embryos or dead human fetuses, may be donated for biomedical research purposes or other diagnostic, therapeutic, pharmacological, clinical or surgical purposes, provided that the donors grant their consent for this (articles 28 and 29 of the BRL). In addition, any research project involving the use of biological material from a human embryo or fetus shall request the authorization of the competent regional or state authority, and must have been granted a favorable report by the Guarantees Committee for the Donation and Use of Human Cells and Tissues (articles 31, 34 and 35 of the BRL). In addition, the principal investigator must have previously requested the approval of the Research Ethics Committee (or the Clinical Research Ethics Committee) of the center where they exercise their professional activity.

Research involving pregnant or lactating women may also be carried out, provided that the benefits/risks ratio justifies their participation in the study, and if the donor has provided her consent (article 19 of the BRL).

In the case of subjects who are unable to grant their consent (underage subjects or disabled patients), this research study may be carried out, with the prior authorization of their legal representatives, provided that the results of the research can produce real or direct benefits for their health. If the research is not expected to produce directly beneficial results this must be notified to the Prosecuting Authority (article 20 of the BRL). In the case of subjects unable to grant their consent because of their clinical condition, their legal representatives must be informed and/or the donors must be asked to provide their consent as soon as they are able to do so (article 21 of the BRL).

Finally, biological samples of deceased subjects may be collected if they provided their consent for this when they were alive, or if they had not provided an express record of their opposition to such collection,

and after receiving a favorable opinion from the Research Ethics Committee (article 26 of Spanish Royal Decree 1716/2011).

3.4 Biomedical Research Using Samples Stored Prior to the Entry into Force of the Biomedical Research Law, or Performed in the Absence of the Express Consent of the Source Subject

Biological samples obtained prior to the entry into force of the Biomedical Research Law may be treated for biomedical research purposes when the source subject/donor has granted their consent or when the samples have been previously anonymized (see Section 2.2). However, coded or identified samples can also be treated for biomedical research purposes without having obtained the consent from the source subject/donor, when the collection of said consent represented an unreasonable effort or was impossible or unreasonable because the source subject/donor was deceased or unlocatable. In this case, a favorable opinion must be granted by the corresponding Research Ethics Committee (second transitory provision of the BRL). Both similarly and exceptionally, in the case of samples obtained after the entry into force of Spanish Royal Decree 1716/2011, and for which an express consent has not been granted, these may be used when the collection of the consent was not possible or entailed an unreasonable effort, and if the Research Ethics Committee granted a favorable opinion (article 24 of Spanish Royal Decree 1716/2011).

3.5 Donors' Consent for Biomedical Research

A subject's consent to participate in a research project constitutes a communicative process which requires that the details be notified to the participants in terms that they can understand. Both Nürnberg's Code (1947) and the Declaration of Helsinki (1964) establish (although not enough) the need to obtain the subjects' consent for the research involving human subjects to be ethically acceptable.

The information described in the informed consent form (ICF) for biomedical research (article 59 of the BRL; article 23 of Spanish Royal Decree 1716/2011) includes the following items:

- The purpose, nature, scope and duration of the procedures of the research study;
- The expected benefits (either for the source subject/donor or other parties), risks and discomforts, along with a statement that compensation for the potential damages or losses derived from the subjects' participation in the study will be ensured;
- The identity of the person in charge of the research study or a description of the biobank or biobanks that will receive the samples;
- The site where the analyses will be performed and the samples will be sent after ending the research: dissociation, destruction, future uses or transfer to other researchers, destination of the sample in case of the closure or authorization withdrawal of a biobank, and the sample destination chosen by the source subject among the various options offered at the end of the project or research study involving samples from collections or specific research projects;
- The possibility of including a restriction on the use of the sample;
- Information on the right to refuse or withdraw the consent;
- A statement on the right to be informed of the genetic data obtained throughout the study, and a warning on the implications that this information may have for the source subjects/donors or their relatives;
- A statement on the right to be informed of the projects in which the samples will be used;

- A guarantee of access to the information once the underage participant reaches adulthood;
- A guarantee of the confidentiality of the data, samples and results obtained;
- A statement on the possibility of contacting the source subject/donor;
- A waiver of any economic, patrimonial or optional rights on the results or potential benefits that could result from the research.

In addition, the informed consent concerning biological samples collected for genetic analyses shall include, among other items, the purpose of the genetic analysis and the commitment to provide genetic counseling (articles 47 and 54 of the BRL).

In the event of using anonymized samples, the informed consent will only include information on the purpose, the benefits, the potential inconveniencies and the identity of the person in charge of the research study.

3.6 Biobanks, Collections and Human Biological Samples for use in Biomedical Research

Human biological samples for use in biomedical research may be stored in a biobank, preserved for use in a specific research project, or kept as a collection for research purposes outside the organizational scope of a biobank (article 22 of Spanish Royal Decree 1716/2011). Collections of samples that are expected to be stored in biobanks may be linked to an ICF with a broader or generic purpose, provided that the source subjects or their legal representative have provided their consent. Samples included in collections or projects outside the organizational scope of a biobank can only be used for the purpose for which the collection was created or for a specific project.

3.6.1 Biological Samples Stored at Biobanks

Both the biobanks and the biological samples they house are characterized by the following:

- The samples can be used for any biomedical research project: the biological samples stored at biobanks can be used for any type of biomedical research; therefore, the potential use of these samples in other research projects and their potential transfer to third parties in broader terms must also be detailed in the informed consent form (article 22 of Royal Decree 1716/2011).
- The samples can be transferred to third parties: the biobank is authorized to transfer the samples for biomedical research projects that have been granted a positive opinion by external research and ethics committees, not belonging to the biobank (article 34 of Spanish Royal Decree 1716/2011).
- They need an authorization for their constitution and operation: the biobank must request an authorization for its constitution and operation to the corresponding body of the Autonomous Region who, in turn, shall notify the biobank's information to the National Biobank Registry (articles 4 and 37 of Spanish Royal Decree 1716/2011).
- The destination of the samples in the event of closure of the biobank: the informed consent form must indicate that the information on the destination of the samples in the event of closure of the biobank will be available at the National Biobank Registry (article 23 of Spanish Royal Decree 1716/2011).
- They are responsible for providing information on the use of the samples: the biobank must inform the source subjects/donors of the availability of the information concerning the use of their sample by third parties, unless they were previously anonymized (article 32 of Spanish Royal Decree 1716/2011).

3.6.2 Biological Samples Stored at Collections

The biological samples belonging to collections for the purpose of biomedical research comprise an ordered set of human biological samples intended to be permanent and preserved outside the organizational scope of a biobank (article 2 of Spanish Royal Decree 1716/2011). Human biological samples preserved exclusively for use in a specific research project are excluded from this concept, provided that their preservation does not exceed the date of completion of the research project and that they are not intended to be transferred.

The collections and samples stored in these collections are characterized by the following:

- The samples can only be used for the specific purpose described in the informed consent form, except if the source subjects grant their consent for their use for another purpose (article 22 of Spanish Royal Decree 1716/2011).
- The destination of the samples following study completion: the informed consent shall describe the destruction of the sample, its anonymization, its free transfer to a biobank, or its use in a research line along with a warning note that the subject will be asked to sign a specific informed consent form for such purpose (article 27 of Spanish Royal Decree 1716/2011).
- The transfer of samples to third parties requires the signing of a specific consent form for this transfer (page 128435 and article 34 of Spanish Royal Decree 1716/2011).
- They are responsible for providing information on the use of the samples: the person responsible for the collection must inform the source subjects/donors of the availability of the information concerning the use of their sample, unless the sample was previously anonymized (article 32 of Spanish Royal Decree 1716/2011).

Moreover, those responsible for the collections must inform of their existence to the head of the establishment in whose facilities the collection or samples are kept and, if necessary, communicate data relating to the collection to the National Biobank Registry (articles 28 and 37 of Spanish Royal Decree 1716/2011). In the event of a transfer of the collections of samples to biobanks, this must be formalized by means of a documented agreement (article 33.2 of Spanish Royal Decree 1716/2011).

3.6.3 Biological Samples from Specific Research Projects

This category includes human biological samples preserved outside the organizational scope of a biobank exclusively for their use in a specific research project, provided that their preservation will not exceed the date of completion of the research project and that they will not be transferred.

The characteristics of the biological samples for specific research projects are:

- The samples can only be used for the specific research project described in the informed consent form, except if the source subjects grant their express consent for their use for another purpose (article 22 of Spanish Royal Decree 1716/2011).
- The destination of the samples following the completion of the specific research study: the informed consent form shall describe the destruction of the sample, its anonymization, its free transfer to a biobank, or its use in a research line along with a warning note that the subject will be asked to sign a specific informed consent form for such purpose (article 27 of Spanish Royal Decree 1716/2011).
- The transfer of samples to third parties: a new express consent form signed by the source subject/donor will be required to use the samples in other research projects or lines, in which case these samples shall be deposited in a biobank or integrated into a collection; this shall be notified to the National Biobank Registry (article 22 of Spanish Royal Decree 1716/2011).

- Information on the use of the samples: the person responsible for the project in which the human biological samples will be used must inform the source subjects/donors of the availability of the information concerning the use of their sample, unless they were previously anonymized (article 32 of Spanish Royal Decree 1716/2011).

Those responsible for preserving the biological samples for their use in a specific research project must inform of their existence to the head of the establishment in whose facilities the collection or samples are kept, although their existence does not need to be notified to the National Biobank Registry (article 28 of Spanish Royal Decree 1716/2011). In the event of a transfer of the samples to biobanks or collections, this must be formalized by means of a documented agreement (article 33.2 of Spanish Royal Decree 1716/2011).

3.7 Protection of Personal Information and Confidentiality Guarantees

Research studies involving the use of human biological samples must be performed respecting fundamental rights and liberties, guaranteeing confidentiality during the processing of the personal data and biological samples, particularly in the case of genetic analyses (article 5 of the BRL). Thus, Spanish Organic Law 15/1999, dated December 13, governing the Protection of Personal Data (SOLPPD) shall be applicable to all documents and files including personal information of the source subjects/donors of which the samples for use in biomedical research are taken. The degree of safety level applicable (basic, medium or high) will depend on the type of personal information contained in the documents and files. If these data only contain personal information, the applicable safety level will be basic. If, in contrast, they contain information on a subject's health, for example, such as a diagnosis or clinical data, the level of safety must be high. The SOLPPD shall also apply to the informed consent forms and their copies, regardless of their location. If the consents do not contain information on the potential diseases of a source subject/donor, then the safety level will basic; otherwise, it will be high. As for biological samples, as these can potentially contain data on the current or future health of a source subject/donor, their safety level shall be considered high.

Biobanks must register a biobank file in the General Data Protection Registry of the Spanish Agency for Data Protection (https://www.agpd.es/portalwebAGPD/index-ides-idphp.php) or, when applicable, the Registry of the regional Agency for Data Protection. In addition, a Safety Plan must be prepared along with the corresponding Safety Document associated with the files and subject to the SOLPPD. It is advisable that the person in charge of preparing the Safety Plan use the guidelines provided by the Spanish Agency on Data Protection (see https://www.agpd.es/portalwebAGPD/index-ides-idphp.php).

Researchers who carry out biomedical research must be explicitly committed to duly safeguarding confidentiality, especially concerning all information associated with a participant in a project, in accordance with the provisions of the legislation on the protection of personal information. In general, the anonymity of the participants must be guaranteed, both during the execution of the project and during the recording and preservation of the resulting data.

3.8 Responsibilities of the Centers

The Management Department of the Centers featuring biobanks or collections of samples for biomedical research must guarantee its staff that the infrastructures meet the requirements and that they have been granted the relevant authorizations for the conduct of any scientific practice subject to specific regulations, such as the case of scientific research involving human subjects, samples or data, or human embryonic or fetal material.

3.9 National Biobank Registry for Biomedical Research

The Spanish legislation governs the operation and organization of the National Biobank Registry for Biomedical Research, of public and informative nature, under the authority of the Carlos III Health Institute (article 67 of the BRL; articles 35-39 of Spanish Royal Decree 1716/2011). This Registry will be comprised by:

- All information concerning the biobanks (authorization for their constitution and operation, amendments, authorization withdrawals or closure of biobanks, as well as data relating to their activity and the networks to which they belong). The competent body to grant authorizations for the constitution of these biobanks shall notify the data relating to these biobanks to the National Biobanks Registry.
- All information relating to the collections of human biological samples for biomedical research purposes preserved outside the organizational scope of a biobank. These collections must be notified by the people, or public or private entities, boasting one or more collections.

A catalog featuring updated information from the National Biobank Registry for Biomedical Research will be published in the website of the Carlos III Health Institute.

4. BIOMEDICAL RESEARCH BIOBANKS

4.1 Description of the Biobanks, their Organization, and the Authorization for their Constitution

Biobanks constitute a public or private, non-profit establishment that house a collection of biological samples for diagnostic or biomedical research purposes, and are organized as a technical unit with quality, order and destination criteria. The purpose of a biobank is to provide the scientific community with the necessary biological material stored in optimal conditions so as to ensure the competitiveness and excellence of their research, while safeguarding the rights of the source subjects/donors.

The manager of the biobank is responsible for requesting the authorization for its constitution and operation, as well as for modifying the authorization and closing the biobank, if necessary (article 12 of Spanish Royal Decree 1716/2011). The requirements for the granting of the authorization for the constitution and operation of these biobanks demand that the organization, objectives and means available justify its biomedical interest; that those responsible for the organization of the biobank have been duly assigned; that the biobank be affiliated with a scientific and research ethics committee; that the activity of the biobank does not involve a profit motive; that the data file has been recorded in the General Data Protection Registry of the Spanish Agency for the Protection of Data or in the competent body; and that it features the crucial facilities and means to guarantee the preservation of the samples in adequate quality conditions (article 5 of Royal Decree 1716/2011). Furthermore, there is also a special regimen for the creation of national biobanks according to their special interest, in which case the authorization for their creation must be issued by the Ministry of Science and Innovation (articles 4 and 18 of Spanish Royal Decree 1716/2011).

The basic structure of the organization of a biobank must include a scientific director and a file manager, and must be affiliated with two external scientific committees, one scientific and one ethical, respectively, that shall assist biobank directors in the exercise of their functions (article 66 of the BRL). The external scientific and ethics committees of the biobank are each comprised by less than four members with sufficient knowledge on the matter and who do not participate directly in the biobank's activity. Both the scientific and ethics committee must exercise their functions under the regulations of an internal operating regulation (article 15 of Royal Decree 1716/2011). The functions of the external ethics committee may be assumed by an existing Research Ethics Committee. In addition to the staff requested by law, the biobanks must be comprised by a biobank coordinator that shall assist the biobank's manager in the exercise of their responsibilities, and by specialized technical staff boasting an adequate training in the processing and storing of samples, and in the handling of databases.

1. The responsibilities of the biobank's manager are (article 13 of Spanish Royal Decree 1716/2011):
    a. Ensuring compliance with the current legislation;
    b. Keeping a record of the biobank's activities;
    c. Guaranteeing the quality, safety and traceability of the data and biological samples stored, as well as of the procedures associated with the biobank's operation;
    d. Preparing an annual report of the biobank's activities, including, among others, a reference to the agreements signed to obtain and transfer samples;
    e. Addressing inquiries or claims sent to the biobanks;
    f. Directing the ordinary management of the biobank;
    g. Preparing the biobank's good practices document;
    h. Preparing the amendments to the descriptive report describing the characteristics of the collections, the inclusion criteria and the purposes for which the collection was

constituted, the way in which the historical collection was obtained, and the information associated with the samples;

i. Managing the transfer of samples.

2. On the other hand, the file manager is responsible for answering requests relating to the exercising of rights of access, rectification, cancellation or opposition, made by the source subjects/donors, according to the provisions of the regulation in force on the protection of personal data (SOLPPD).

3. The responsibilities of the external scientific and ethics committees include (article 15 of Royal Decree 1716/2011):

   a. Performing the scientific and ethical assessment of the biobank's requests for the transfer of samples and associated data.

   b. Counseling the head of scientific management on the adequacy of the procedures set forth to guarantee the quality, safety and traceability of the data and samples stored at the biobank, and of the procedures associated with the biobank's operation.

   c. Counseling the head of scientific management on the biobank's document of good practices.

   d. Assisting the head of the biobank's management in other proposed matters.

4.2 Good Practice Procedures of Biomedical Research Biobanks

4.2.1 Collections and Organization of the Biobanks

The biological samples organized and grouped according to one or more common characteristics make up the biobank collections. These biobanks must describe, document and publicize the collections that they store, as well as the conditions to access them in order to optimize their use and ensure the transparency of their activities. Thus, each biobank is advised to publish a "catalog" including a description of each collection, along with the minimum data associated with the samples that comprise them and that will be available for potential users. For each collection, the catalog usually describes the following information:

- Name of the collection, project or pathology it encompasses.
- Number of donors/cases/samples in each collection.
- Type of biological samples available (blood, tissue, serum, plasma, etc.).
- Minimum data associated with the samples that could be of interest for research purposes.

The biobanks are advised to plan which samples will be collected and held at the biobank based on the needs of the research projects and the researchers requesting the samples, on the availability of samples of high scientific value, on the cooperation in projects concerning rare diseases and on the available resources. It is also recommended that the biobanks cooperate and set out consensus measures for the collection of biological samples that would allow for complementing the activities of the different biobanks.

These biobanks must identify their priorities and strategies when creating new collections:

- Collections of specific pathologies

- Population collections, with adequate diversity and demographic characteristics for multiple scientific purposes
- Historical collections
- Prospective collections
- Control case collections

It is also advisable that the members that make up the biobank's organization be made public, and that the identity of the members that comprise the external committees also be publicized.

The biobanks must design strategies to ensure their long-term economic sustainability by searching public or private funding, and setting rates for the services rendered.

4.2.2 Biosafety Measures for the Biobank Staff

Any work involving the use of human biological samples entails a potential risk of exposure to biological agents such as the human immunodeficiency virus, the hepatitis B and C viruses, etc. To this end, the human biological samples must be obtained, handled and stored under biosafety conditions in order to avoid the staff's exposure to potentially infectious agents (see the References Section: Technical guides and manuals: Biosafety manuals of the World Health Organization and the Centers for Disease Control (CDC) of the National Institute of Health (NIH); Díaz and Muñoz-Fernández, 2008).

The biobanks must have a biosafety plan (article 6 of Spanish Royal Decree 1716/2011) describing the procedures whereby the traceability of the samples and data collected by the biobank will be ensured, and stating that the collection, transport, storage, manipulation and transfer of samples will be performed under biosafety conditions (see Section 5.2.11).

The biobanks must inform and train their staff on the dangers and safety procedures that must be taken into account when manipulating human samples, and their facilities must be adequate to establish the necessary safety measures.

The staff employed at the biobanks must be included in a health surveillance program and shall be offered the possibility of undergoing screening and serology tests in order to determine their immune status, as well as active immunization by means of a vaccination, in those cases for which a vaccine with proven efficacy is available.

The biobanks and other repositories of biological samples must establish clear policies regarding the inclusion or exclusion of high-risk biological samples, and adapt their facilities according to the biosafety level required based on the biological samples stored in them.

Apart from the biosafety precautions, the biobanks must establish safety measures due to the possible exposure to chemical agents, and adhere to the basic safety principles of a laboratory.

Spanish Royal Decree 664/1997, dated May 12, on the protection of workers against the risks related to the exposure to biological agents at their work place, sets out the minimum provisions applicable to the activities during which the workers are, or may be, exposed to biological agents owing to the nature of their profession. Additionally, the Technical Protection Notes (TPN) published by the National Institute of Occupational Safety and Hygiene must also be taken into account (see the References Section: Technical Guides and Manuals). Furthermore, in the context of biobanks and other repositories of biological samples, the following also deserve particular mention: TPN 376 on Good Laboratory Practices, TPN 725 on chemical products, TPN 233 on biological safety cabinets and TPNs 517 and 518 on PPI safety equipment (personal protective equipment [PPI]).

4.2.3 Obtaining Consent to Collect Biological Material and Associated Data

One of the main bioethical pillars refers to the principle of autonomy of the source subject/donor. For a source subject/donor to be able to exercise their right to autonomy, they must be provided with complete, specific and adapted information that will allow them to understand such right. The granting of this consent by the participant must be free, voluntary, express, specific and documented.

The purpose for which consent is requested for the collection of the biological samples and associated data must be described in the informed consent. A separate informed consent must be prepared for those biological samples included in biobanks and that can be used for any type of biomedical research (article 70 of the BRL; article 22 of Spanish Royal Decree 1716/2011).

The biobanks must provide the necessary means to obtain the subjects' consent before or after collecting the sample and the personal or clinical data, as well as the means needed for the registry and custody of the informed consents. If the source subjects/donors are unable to write, the consent may be granted through any means admitted by law that will allow for recording their will.

The signature sheet of the informed consent form shall be issued in triplicate (article 23.4 of Spanish Royal Decree 1716/2011):

- One copy for the source subject/donor;
- Another copy to be kept by the site where the sample was collected;
- A third copy to be kept by the biobank or the person in charge of the collection or the research study.

The consent shall be kept, at least, for the samples' life-time, and always for a period of no less than five years. The maximum term of conservation shall be set according to the national and regional regulations governing clinical documentation, informed consents, and documentation concerning research matters and the protection of personal data.

The biobanks must inform the donor and establish the procedures to be followed to guarantee the exercising of the following rights:

- Refusal or withdrawal of the consent;
- Access to general information on the research studies performed with the biobank samples (article 32 of Spanish Royal Decree 1716/2011);
- Access, rectification, cancellation and opposition to the personal data linked to the samples.

The biobanks must set out measures to limit the access to the personal information linked to the samples by means of the use of safe and structured bioinformatic resources, with clearly defined accesses and permits (see Section 4.2.5).

In addition, adequate backups must be kept, and periodic updates shall be made to prevent data loss. All staff employed at the biobanks who have access to the donors' personal information will be required to maintain the confidentiality of this information while they exercise their profession, and even after their career and for life (article 10 of SOLPPD; article 5 of the BRL).

4.2.4 Processing of Biological Material

It is advisable that human biological samples collected for biomedical research projects be processed according to procedures described in the scientific literature or to procedures agreed upon by professionals of the sector with a view to minimizing the samples' degradation and deterioration, and to enabling research of the utmost quality and excellence. The general recommendations of good practices applicable to the processing of biological samples are:

- All human biological samples must be deemed potentially infectious; therefore, it is crucial that the biobank staff work in biosafety conditions.
- The staff in charge of the processing of samples must be duly trained and skilled, and must safeguard the traceability of the samples from their receipt to their storage.
- Prepare and implement the Standard Operating Procedures (SOPs) of all processes applied to biological samples, and ensure that they are accessible to the entire staff. These SOPs must be consensual, based on scientific evidence, documented in an understandable way, and updated regularly to be available for the laboratory staff. Harmonization of the SOPs among the different biobanks is recommended in order to facilitate the conduct of multicentric studies and those requiring a greater number of samples. Because of all the information that must be contained in these SOPs, they are usually not very manageable in the laboratory; therefore, it is advisable to also provide work flowcharts describing the different steps involved in the processing of a biological sample.
- Define and collect all preanalytical variables that will affect the results of the assays to which the samples will subsequently be subjected to: sampling method, primary conditioning, storage temperature prior to the processing, date and time of the collection, and time elapsed between the sample's collection and its storage, use of anticoagulants or stabilizers, or the freezing method (see the References Section: Other publications: Betsou et al., 2010).
- Process and preserve the sample in the most stable state possible for the greatest number of macromolecules that shall subsequently be analyzed so as to ensure long-term stability.
- Define the analytical objectives of the different types of samples stored at the biobank when deciding which SOP is applicable to the sample's processing. To define these objectives, it is advisable to consider both the current biomedical research needs and the expected future uses in the framework of the development of new technologies.
- Determine the quality controls to be performed upon receipt of the samples, and verify that these are performed prior to the sample's processing. These quality controls shall include samples linked to an informed consent and a series of minimum associated data, in addition to its correct identification and integrity.
- Process the samples in the minimum possible time after their collection and, when this is not possible, use stabilizing agents.
- Assign separate areas in the laboratory according to the type of samples to be processed in each.
- Use sterile material and change it after processing each sample in order to avoid cross-contamination between samples.
- Automatize, as much as possible, the sample's processing and label the samples correctly so as to ensure their standardization and traceability.
- Optimize the use of samples based on the biobank's capacity with the aim of obtaining the greatest number possible of samples derived from the primary sample.
- The labeling and coding of the samples must be resistant to common laboratory solvents and the storage conditions.

4.2.5 Sample Identification, Tagging and Traceability

The biological samples and their associated data obtained for research purposes are subjected to their registry, processing, storage and use in research procedures that require the implementation of a tagging and identification system for the samples, documentation, data and operators responsible for the conduct of each process carried out, so as to ensure the traceability (article 8 of the BRL) and protection of the personal data.

The biobanks must feature inventory and traceability systems that allow for keeping a detailed and well-documented record of all the samples (and associated data) that comprised their collections, from the time of their donation to the end of their lifespan, as well as for recording the location and condition of each sample. The databases must rely on safety systems capable of setting accessibility levels according to the user category to comply with the regulations in force on the protection of personal information.

The biobanks are advised to code the samples with unique and unambiguous identifiers that do not reveal any personal information of the source subject/donor, but that allow for identifying, through highly protected records, the information associated with the samples, such as the donor's information, the type of sample, etc. There are currently specific IT tools that enable the collection of information on samples and their associated data in compliance with the legislation in force regarding the protection, traceability and coding of the personal information linked to the biological samples. The biobanks are advised to make use of such software tools or to develop proprietary IT tools that meet the specific needs of each biobank. The software systems linked to the inventory and traceability system must be validated and subject to quality assurance audits.

4.2.6 Standardization During the Collection of Data and Minimum Data associated with a Sample

Although no general consensus has been reached on the minimum personal/clinical/epidemiological data associated with human biological samples for use in biomedical research, as these depend on factors such as the type of collections (population groups, donors with pathologies, etc.), the type of samples, the pathologies associated with the samples, etc., agreeing upon and harmonizing these minimum data is deemed good practice. Overall, collecting data on the donors, their health status, the biological samples, their traceability and on the informed consent is recommended:

- Data on the donors and their health status: including identifying personal information that allow the unequivocal identification of the source subjects/donors (name and surname, age, sex, ethnicity) and any data allowing for verifying the clinical/pathological information associated with the sample (medical record number, referral center, etc.), as well as health information, risk factors, lifestyle habits, family history or genetic data.
- Data on the biological sample: these data include the date, time and procedure used to obtain the sample, the time elapsed between the sample's collection and its processing, the method and temperature used to store the sample, the total volume or amount of sample, the processing method, the specimens obtained from each source sample, the number of aliquots, the type of storage vial used, the storage temperature, and data associated with the analysis of the samples, such as concentration and quality data.
- Data on the sample's traceability: these data include, among others, data on the location of the sample and on transfers for its use in research projects.

- Consent information: these data usually refer to the type of consent whereby the sample was obtained (specific project/research line or generic consent), and the dates on which the consent was obtained or withdrawn.

It is advisable to create a coding logbook or manual for the written data of each sample collection (for example: diagnosis). This coding logbook or manual shall describe all data recorded in writing, as well as the required format of such information, and the language that must be used to record the information. This coding logbook or manual must be made available to all staff who record or use the biobank's sample database.

The P3G (Public Population Project in Genomics; http://www.p3gobservatory.org/) is a non-commercial non-profit organization whose purpose is to promote cooperation among researchers in the field of population genomics. It also seeks to promote the cooperation, design optimization and harmonization of biobanks, as well to facilitate the transfer of knowledge. Its website features a series of tools (DataSHaPER) designed to ease the harmonization and design of questionnaires for biological samples from biobanks.

4.2.7 Biological Sample Storehouses, Alarm Systems and Restricted Access

The importance of storing the biological samples, and the biological materials derived from these, determine the need to use specific storage equipment. To prevent or minimize potential losses or damages to the biological samples, it is advisable to establish the policies and procedures, as well as the equipment inspection, maintenance, repair and calibration programs, according to the following recommendations:

- Access to the samples stored in the collections must be restricted to authorized staff in order to minimize the likelihood of contamination of the staff or environment, and to ensure the quality of the biological samples. Access controls requiring the use of identification cards by authorized staff may be installed in the storage rooms, or freezers and nitrogen tanks equipped with a mechanism to restrict their access may be purchased.
- The storage rooms and their equipment must be monitored by registry and alarm systems designed to constantly control and register temperatures. These systems must remain operational for 24 hours a day, seven days a week, and employ staff authorized to respond to alarm situations to prevent or minimize potential losses or damages to the collections. The computer or system that controls and records the temperatures, and manages the alarms, must be connected to additional energy sources to avoid the loss of temperature recordings or failures in the alarms system.
- Operating procedures must be established in the event of an alarm. These must describe the empty and available storage areas and, optionally, an alternative power generator and/or an uninterrupted power supply (USP) capable of supplying electrical power in the event of a failure or loss of the electrical supply.
- It is also advisable to install a CO_2 supply system in freezers reaching a temperature of up to -80 ºC to replace interruptions in the electrical supply for up to two days.
- In the event of an emergency, these freezers and nitrogen tanks used for spare storage must be kept at the corresponding temperature. It is advised that 10% of the surface of each storage area be covered by freezers, and 1.5-3% be equipped with nitrogen tanks.

- When using liquid nitrogen to freeze the samples, either a 3-day supply or 20% of the storage tank's capacity must be kept.
- The cryopreservation rooms must feature air renewal and air conditioning systems to guarantee the extraction of heat, excess moisture and condensation (the optimal temperature of the room holding the cooling equipment must be kept at a temperature of 15-22 ºC), as this range will enable the correct operation of the equipment and the elimination of toxic or asphyxiating gases for the operators. In cases of cryopreservation rooms with liquid nitrogen tanks, these must be equipped with oxygen sensors.
- Routine preventive maintenance, calibration and repair protocols must be designed for the storage equipment, following the manufacturer's recommendations.

4.2.8 Request, Evaluation and Follow-up of Sample Transfers for Biomedical Research Projects. Material Transfer Agreements (MTA)

The biobanks may transfer their samples to any biomedical research project that complies with the legally established requirements (article 69 of the BRL; article 34 of Spanish royal Decree 1716/2011), provided that this possibility was detailed in the informed consent form signed by the samples' source subjects/donors.

Sample requests issued to the biobanks must include:

- Information on the project to be carried out with the requested samples;
- A favorable report issued by the Research Ethics Committee of the center where the applicant researchers conduct their work;
- The explicit commitment of the requesting research center and/or project researchers to not use the requested material for a use other than that described in the request;
- Information on the funding sources available for the conduct of the research project or a favorable report attesting the applicant researchers' capacity to carry out the project from both a technical and financial perspective, issued by the research center where the applicant researcher will carry out the project.

All requests for the transfer of samples received by the biobanks shall be examined by the biobank's external scientific and ethics committees, who will then issue a report on the applications. The regulations applicable to these committees set out the adequate mechanisms to ensure the independence and absence of conflicts of interest during the decision-making process.

The requests for samples issued to a biobank may be refused either total or partially by the responsible person by means of a reasoned decision that shall take into account relevant previous reports issued by the biobank's external scientific and ethics committees. In the event that the scientific or ethics committees issue an unfavorable report, such document will be binding in nature.

If the opinion of the scientific and ethics committees is favorable, a document of agreement to transfer biological samples (Material Transfer Agreement), which will regulate the transfer of research material between the applicant researcher's site and the biobank, and describing the consensual cooperation conditions, rights and obligations of both parties, shall be signed (article 34.5 of Spanish Royal Decree 1716/2011). The amount of sample to be transferred shall correspond to the minimum necessary to carry out the project for which it was requested. The Material Transfer Agreement must describe all agreements made regarding the intellectual and commercial property (see Section 4.2.9), as well as the publication rights and costs of the transfer of material between the requesting and donor institution. The research project to which the samples will be transferred may be monitored through periodic or final reports on the publications or patents resulting from the use of the samples, or a final report on the results obtained, as deemed appropriate in the Material Transfer Agreement. All these documents shall

be submitted to the biobank for its records.

In general, the samples and their associated data will only be transferred in an anonymous and dissociated manner and, when deemed necessary because of the specific nature of the research project, they may be accompanied by additional clinical data, in which case the biobank shall coordinate the collection of this information with the research center where the sample was taken. The specific measures to be applied to guarantee the confidentiality of the personal information that could accompany the transfer must be detailed in these cases.

The shipment and transport of the biological samples must be carried out under biosecurity conditions, as set out

in the national and international transport regulations, as applicable (see Section 5.2.11).

Biobanks are advised to keep a record of the requests for biological samples received, the arrangements made and the results obtained (approved or rejected), as well as a record of each transaction carried out with the requested samples (destination, use, etc.) to guarantee their traceability.

4.2.9 Intellectual and Industrial Property Rights and Publishing Practices

According to the ethical and legal consensus, no property rights are applicable to parts of the human body once they have been detached from the donor. Any person possessing parts of a body acts as the samples' custodian and, as far as possible, must comply with the donor's intentions. For their part, the source subjects/donors waive their property rights; therefore, the donation and use of the human biological samples shall be free, and any compensation provided for the inconveniences resulting from the samples' collection may not have a profitable or commercial intent (article 7 of the BRL). Although the biological sample in itself does not have an economic value, its collection, handling, storage and shipment does involve certain costs; hence, during the transfer, the biobank may request payment for the expenses derived from the samples (article 69.3 of the BRL; see Section 4.2.10).

The researcher requesting biological samples to a biobank must mention the source of these samples in all publications featuring the results of the research study performed with these. Following the typical structure of a scientific article, the biobank's contribution must be indicated as follows:

- Materials and Methods: the source of the samples and data used in the study must be stated.
- Acknowledgments: the biobank from which the samples were requested must be mentioned following the pre-established format set out by the biobank.

It is also advisable to establish the intellectual and industrial property rights derived from the project's results in those research studies in which the conduct of the research project with the transferred samples involves research work performed by part of the staff of the institution that donated the samples.

The biobanks are advised to make use of inventory/tracking systems to assess the work performed by the biobank and the impact of its activity based on the number of samples donated, as well as the number of projects and publications in which it participated. This analysis/assessment of the biobank's activity may be relevant for the biobank's evaluation by financing entities.

4.2.10 Costs Associated with the Samples

The biobanks may charge for the costs of obtaining, maintaining, handling and sending the transferred samples, as well as for other costs of similar nature related to the samples, which shall allow them to recover all or part of the expenses incurred by the organization and the biobank's operation (article 69.3 of the BRL).

The fees associated with the transfer of samples must be linked to the real expenses of the work needed to acquire, store and supply these samples, and must not be determined by other factors such as the rarity of the biological sample, the supply and demand, etc.

The biobanks are usually supported by the institutions that promote them, which are frequently of public nature. Therefore, it is legitimate for an organization to consider charging different fees based on the final user, discriminated, for example, by whether the researcher belongs to the institution itself, to non-profit academic institutions or if the samples will be used in an activity or institution with commercial interests.

4.2.11 Biosafety Measures for the Shipment and Transfer of Samples

The shipment and transfer of human biological samples must be carried out under biosafety conditions. The specifications of the biological material to be sent must be determined prior to packaging and sending the biological samples. For transport purposes, infectious substances are defined as substances which are known or justifiably believed to contain pathogens. These pathogens are microorganisms (such as bacteria, virus, rickettsia, parasites, and fungi) and other agents such as prions, that may cause diseases in animals or humans. The infectious substances can be divided into two categories: category-A infectious substances and category-B infectious substances.

- Category-A infectious substance: an infectious substance transported in a form that, upon exposure, may cause a permanent disability, be life-threatening or constitute a deadly disease for otherwise healthy humans or animals. Infectious substances that meet these criteria and cause diseases in both humans and animals shall be assigned code UN2814, whereas those that only cause diseases in animals will be assigned code UN2900.
- Category-B infectious substance: an infectious substance that does not meet the criteria for inclusion in category A. This category includes: crops, patient samples, biological products, genetically modified microorganisms, and medical or clinical waste. Category-B infectious substances are assigned code UN3373.

The corresponding conditioning/packaging, labeling and documentation requirements will depend on the classification of the infectious substance and may be consulted in the recommendations of the World Health Organization (http://www.who.int/csr/resources/publications/biosafety/WHO_HSE_EPR_2008_10_ES.pdf), as well as in the International Civil Aviation Organization (ICAO) and local transport regulations (Spanish Royal Decree 65/2006).

The conditioning/packaging system to be used for all infectious substances must be comprised by the following three layers:

- Primary container: a watertight and waterproof container containing the sample.
- Secondary conditioning/packaging: a secondary sealed, waterproof and durable container enclosing and protecting the primary container or containers. Sufficient absorbent material must be used to absorb any fluid spills in case of rupture.
- External conditioning/packaging: an external packaging composed of an adequate shock-absorbing material. None of the sides of the external conditioning/packaging must measure less than 10 x 10 cm.

The applicable legislation concerning the import and export of biological samples is Spanish Royal Decree 65/2006, dated January 30, which sets forth the requirements for the import and export of biological samples. Importers and exporters (natural or legal persons) who regularly (at least once every quarter) import or export samples, may request their registration in the Registry of importers and exporters of biological samples created by the Spanish Ministry of Health and Consumer Affairs affiliated with the General Directorate of Public Health, and managed by the General Subdirectorate of Foreign Health.

To import biological samples, the interested party must submit a request to the General Subdirectorate of Public Health stating the type of sample they intend to import. On the other hand, to export biological samples, the interested party must submit a declaration to the General Directorate of Public Health including relevant information needed to identify the sample and its destination. The annexes to this regulation on the import and export of biological samples have been replaced by Order SAS/3166/2009, dated November 16.

4.2.12 Quality Management

The Biomedical Research Law makes specific reference to the need to follow quality criteria (article 3 of the BRL: biobank definition) and implement the necessary means to guarantee the quality, safety and traceability of the samples, data and work protocols (article 66 of the BRL) of a biobank.

The need to ensure compliance with these legal requirements, in addition to those affecting the rest of parties involved (researchers, donors and society in general), warrant the implementation of a Quality Management System (QMS) allowing for improving the operation of the biobanks with the available resources, which are usually limited or even scarce. In general, a QMS serves as a tool that guarantees compliance with certain quality standards, optimizes the available resources and seeks to achieve continuous improvement and client satisfaction.

Of the quality management standards available, the one that best adapts to a research biobank is the UNE-EN-ISO 9001:2008 (ISO 9001) (see Haro et al., 2006; García-Montero and Regalado, 2010).

The starting point for the implementation of the ISO 9001 standard is an adequate planning, involving an analysis of the actual status of the biobank with respect to the standard's, legal and internal requirements, to determine which requirements are met by the organization.

Once the biobank's starting point has been established, the steps that must be followed to implement the QMS are as follows:

1. Establish the quality and strategic objectives required to achieve results according to the provision of the biobank's quality policy. These objectives must be ambitious but, at the same time, achievable so as to facilitate the biobank's continuous improvement.
2. Define the processes involved, that is, the tasks that form part of the biobank's activities, and the interrelationships between them, identifying the key processes for achieving the set objectives.
3. Provide a detailed description of the processes (define the work protocols or SOPs). All support documentation of the QMS must be clear, concise and properly identified and organized to ensure its correct use.
4. Establish control mechanisms that should allow for: a) evaluating the implementation of the processes and, b) detecting weaknesses in the system and/or opportunities for improvement.
5. Define the procedures that will enable the implementation of corrective and preventive actions, as well as their analysis and follow-up, as a commitment towards the continuous improvement of the biobank's activity.

Any biobank that chooses to implement the QMS according to the provisions of ISO standard 9001 must bear in mind that the final goal is not to obtain certification, but to define a quality policy and plan that will ensure the quality of the processed samples and compliance with the applicable requirements. In addition, obtaining the ISO standard 9001 certification will improve the users' perception of the biobank because of the following:

1. It serves as evidence that the biobank has established a quality management system that ensures its ability to regularly provide samples that will satisfy the final user's requirements and the applicable legal and regulatory requirements;

2. It reflects the biobank's commitment to increase the satisfaction of the research groups that will use the available samples.

4.2.13 Biobanks and Networking

Biobanks achieve their greatest degree of operability and usefulness when they work in a coordinated way within a cooperative network (network biobank; see Section 2.1). The Spanish National Biobank Network is an initiative promoted by the Carlos III Health Institute (Spanish Ministry of Science and Innovation) through the Spanish Cooperative Health Research Thematic Networks (RETICs), to add value to all Spanish biobanks whose work is focused on managing human samples as a service to biomedical research. This network is mainly comprised by biobanks of the hospitals of the Spanish National Health System and their associated centers (www.redbiobancos.es).

The network aims to serve as a meeting point for these biobanks in order to promote an improvement in the quality and homogeneity of their services: the access to human biological samples and their associated data by the scientific community, with the greatest quality standards, scientific adequacy and safeguarding of the donors' rights in the context of the legislation in force.

Through this networking, the biobanks can homogenize technical procedures and ethical requirements, promote common quality policies, facilitate the exchange and enrichment of experiences, and other potential aspects that may have an impact on the usefulness of the institutions. In addition, because of this networking, the biobanks may address scientific challenges that require, or benefit from, a multicentric source of the samples, thus minimizing the risks and biases associated with this type of studies.

5. REFERENCES

5.1 Laws

- Spanish Law 14/2007, dated July 3, governing Biomedical Research. BOE No. 159, pages 28826-28848.
- Spanish Organic Law 15/1999, dated December 13, governing the Protection of Personal Data. BOE number 298, dated December 14, 1999.
- Spanish Law 41/2002, dated December 15, regulating the autonomy of the patient, and the rights and obligations concerning clinical information and documentation. BOE number 274, pages 40126- 40132.

5.2 Spanish Royal Decrees

- Spanish Royal Decree 1716/2011, dated November 18, which establishes the basic requirements for the authorization and operation of biobanks for biomedical research purposes and the processing of human biological samples, and regulates the operation and organization of the National Biobank Registry for Biomedical Research. BOE number 290, pages 128434-128454.
- Spanish Royal Decree 1720/2007, dated December 21, approving the Regulation implementing Organic Law 15/1999, dated December 13, on the Protection of Personal Data. BOE number 17, pages 4103-4136.
- Spanish Royal Decree 65/2006, dated January 30, which sets out the requirements for the import and export of biological samples. BOE number 32, pages 4626-4636.
- Order SAS/3166/2009, dated November 16, replacing the annexes of Spanish Royal Decree 65/2006, dated January 30, which sets out the requirements for the import and export of biological samples. BOE number 286, pages 100514-100523.
- Spanish Royal Decree 664/1997, dated May 12, on the protection of workers against the risks related to the exposure to biological agents at their work place. BOE No. 124, dated May 24, 1997.
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5.3 Codes of Good Practices

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- OECD Best Practice Guidelines for Biological Resource Centers. Organization for Economic Co-operation and Development (OECD).
- Common minimum technical standards and protocols for biological resource centers dedicated to cancer research. 2007. International Agency for Research on Cancer (IACR), World Health Organization.

5.4 Technical Guides and Manuals

- Practical guide for the use of biological samples in Biomedical Research (Roche Institute).
- Guide on the regulations concerning the transport of infectious substances 2009-2010. World Health Organization.
- Laboratory biosafety manual. World Health Organization (WHO).
- Biosafety in microbiology and biomedicine laboratories. Center for Disease Control and Prevention. CDC NIH 4th version.
- Biosafety manuals for HIV Research laboratories. Díaz L, Muñoz- Fernández MA. Report from the Foundation for Innovation and Health (FIPSE).
- TPN 376: Exposure to biological agents: Safety and Good Laboratory Practices. Spanish National Institute of Occupational Safety and Hygiene.
- TPN 25: Laboratory safety: Storage of chemical products. Spanish National Institute of Occupational Safety and Hygiene.
- TPN 233: Biological safety cabinets. Spanish National Institute of Occupational Safety and Hygiene.
- TPN 517: Laboratory risk prevention. Use of individual protection equipment (I): General aspects. Spanish National Institute of Occupational Safety and Hygiene.
- TPN 518: Laboratory risk prevention. Use of individual protection equipment (II): Management. Spanish National Institute of Occupational Safety and Hygiene.
- TPN 276: Disposal of laboratory waste: General procedures.
- TPN 399: Laboratory safety: Actions to be taken in case of leaks or spills.
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- TPN 447: Actions to be taken in the event of an accident entailing a biological risk.

5.5 Other publications

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- García-Montero AC, Regalado AM. “Políticas de calidad de un biobanco” in Volume 83 of Viure en Salut. Generalitat Valenciana, Consellería de Salut. Pages 14-15. (2010).
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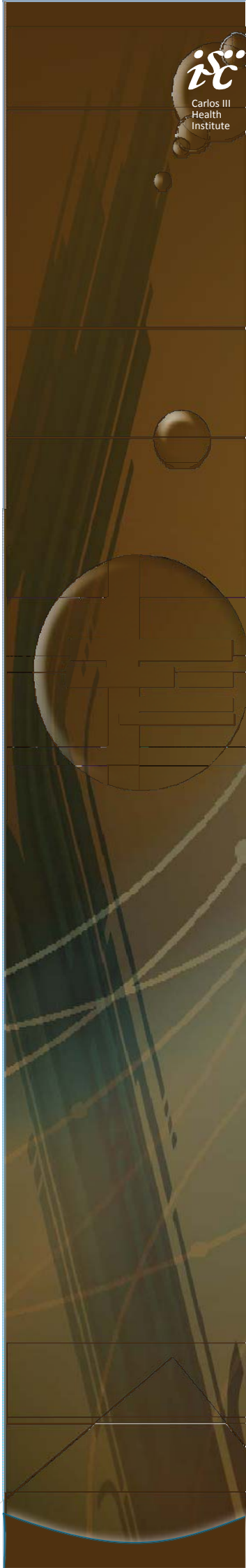

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