ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH

(Ethics Committee of the Instituto de Investigación de Enfermedades Raras - CEIIER)

Ministerio de Ciencia e Innovación

Instituto de Salud Carlos III

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ETHICAL GUIDELINES GOVERNING THE CREATION AND USE OF REGISTRIES FOR BIOMEDICAL RESEARCH PURPOSES

Ethics Committee of the Instituto de Investigación de Enfermedades Raras (CEIIER)

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1. INTRODUCTION

Until a few years ago, there were hardly any limitations on the creation and use of epidemiological registries or the use of information drawn from pre-existing records for research purposes. This situation has changed substantially, due basically to two factors: on the one hand, there is the growing importance that modern laws attach to the protection of privacy and confidentiality of personal data, reflecting keener social concern for such protection;(1) and, on the other hand, there is the ease of access to clinical information which has resulted from progressive computerisation and which will presumably render us more vulnerable to our privacy being invaded by third parties.(2) To these factors, one could arguably add a third element that is acquiring ever increasing prominence, namely, the possibility of subjects' genetic data being used and the additional degree of vulnerability which society perceives this would imply.(3) Indeed, there has been no lack of critical voices complaining about the disproportion that exists between restriction of access and use of clinical information for research purposes in cases where the subjects are identifiable, and the real risk of abuse. In addition, the alert has been sounded as to the impact that such a restriction could have on the advance of knowledge.(4)

Clinical information stored in records of various types has been a fundamental tool for biomedical research in general and for epidemiological research in particular, with judicious use of such information leading to innumerable contributions to clinical medicine.(5)

(1) Sánchez Caro J, Abellán F. Datos de salud y datos genéticos – su protección en la Unión Europea y en España. Derecho Sanitario Asesores, Granada: 2004.

(2) Welch C. Sacred secrets – the privacy of medical records. N Engl J Med 2001; 345:371-372.

(3) It should be noted that genetic data constitute a type of health information that, in principle, is neither more nor less sensitive than any other kind of clinical-history data. A European Commission committee of experts has found so-called "genetic exceptionalism" –namely, the perception that genetic data differ from other types of medical information- to be incorrect, though it does acknowledge the existence of a greater degree of sensitivity in society which could render specific treatment appropriate. McNally E, Chambón-Thomsen A, Brazell C, Cassiman JJ, Kent A, Lindpainter K et al. 25 recommendations on the ethical, legal and social repercussions of genetic testing. Office for Official Publications of the European Communities, Luxembourg, 2004.

(4) Kulyinch J, Korn D. The effect of the new federal medical-privacy rule on research. N Engl J Med 2002; 346: 201-203. Strobl J, Cave E, Walley T. Data protection legislation: interpretation and barriers to research. BMJ 2000; 321:890-892. Peto J, Fletcher O, Gilham C. Data protection, informed consent and research. BMJ 2004; 1029-1030. Ingelfinger JR, Drazen JM. Registry research and medical privacy. N Engl J Med 2004; 350:1452-1453.Roberts L, Wilson S. Argument for consent may invalidate research and stigmatise some patients. BMJ 2001; 322:858. Cox P. Obtaining individual consent may hinder studies. BMJ 2001; 322:858. Kaiser J. Privacy rule creates bottleneck for US biomedical research. Science 2004; 305: 168-169. Regidor E, de la Fuente L, de Mateo S. Restricción al uso de datos personales en la práctica y en la investigación sanitaria: a propósito de una sentencia sobre el registro de infecciones por el virus de la inmunodeficiencia humana. Med Clin (Barc) 2004; 123:624-626.

(5) Ingelfinger JR, Drazen JM. Registry research and medical privacy. N Engl J Med 2004; 350:1452-1453. Melton LJ. The threat to medical-records research. N Engl J Med 1997; 337:1466-1470.

As its prime aim, research involving human beings seeks to obtain generalisable knowledge, the principal beneficiary of which is society as a whole rather than the specific research subject. The fundamental ethical problem that this raises, therefore, is that the attainment of collective benefit requires the "sacrifice" of a few, whether in direct health terms (the possible physical or mental risks of research) or in terms of disclosure of their data to third parties. The predominant thesis is that both interests –those of the individual and the group- apparently in collision, converge when the research subject expressly consents to research, once he has been duly informed of the risks and benefits involved. Even so, the solution does not appear to be so simple. On the one hand, the ethical sufficiency of informed consent for justifying research is debatable, and other ethical values or principles have been brought into play,(6) and on the other hand, there are a number of circumstances in which informed consent may be unobtainable (e.g., patients below legal age, subjects having no capacity to consent or deceased), unfeasible (e.g., epidemiological research requiring access to records of tens of thousands or hundreds of thousands of persons), or prove so difficult to obtain as to place the validity of the study at risk (where a relevant number of subjects withhold it).

Although the legal framework is already very explicit with respect to the use of clinical information, there is some room for ethical deliberation and prudent advice, so that such information can be used for the purpose of doing research which is valid and useful and, at the same time, respects the rights of subjects and the law. Sight should not be lost of the fact that, while complementary, the scope of ethics and legislation is neither superimposed nor mutually exclusive. The principal aim of this document is to analyse the problems that derive from the use of registries in research, inasmuch as situations may arise which may violate principles or values essential for the respect of the dignity of human subjects. By extension, this implies: reflecting on the validity of possible practices; evaluating the legitimacy of the purposes pursued and the means employed; deciding on the most appropriate procedures for observing the respect due to persons and their interests, as well as social assets and values regarded as fundamental; and justifying the suitability of proposals for the introduction of changes that redound to the benefit of all, and result in improved quality and greater responsibility. Finally, these guidelines in no way seek to impose a criterion, but rather to stimulate and foster prudent deliberation on these issues.(7)

(6) **National Commission for the Protection of Humans Subjects of Biomedical and Behavioral** Research. Belmont Report. Accessible at: http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm.

(7) **Epidemiological registries are increasingly accompanied by collection of biological samples** and creation of biobanks. The ethical issues raised by biological samples are specifically addressed in other guidelines issued by the Committee (see: Ethics Committee of the Rare Disease Research Institute. Recommendations on the Ethical Aspects of Specimen Collections and Human Biobanks for Biomedical Research Purposes. Rev Esp Salud Pública 2007; 81: 95-111.) Accessible at: http://www.scielosp.org/scielo.php?script=sci_arttext&pid=S1135-57272007000200002&lng=&nrm=iso

2. GLOSSARY(8)

Release or communication of data (LOPD):(9) any disclosure of data to a person other than the interested party.

Consent of interested party (LOPD): any free, unequivocal, specific and informed expression of will whereby the owner of information consents to personal data concerning him being handled and processed.

Anonymous data (LIB):(10) data recorded without any nexus to an identified or identifiable person.

Data of a personal nature (LOPD):(11) any information concerning identified or identifiable physical persons.

File (LOPD): any organised set of data of a personal nature, whatever the manner or mode of its creation, storage, organisation and access.

Clinical history (LAP):(12) set of documents containing data, evaluations and information of any type on the status and clinical progress of a patient over the course of the health-care process.

Biomedical research: set of activities designed to develop or contribute to generalisable knowledge relating to the health of human beings or populations.

Clinical research: type of biomedical research conducted on human subjects for the purpose of obtaining knowledge, which will enable useful medical technology to be developed for the diagnosis, prevention or treatment of disease. This comprises, not only studies undertaken to validate such technology, but also those designed to obtain the information required for its conception and development.

Epidemiological research: type of biomedical research undertaken on human populations and aimed principally at studying disease distribution (including routine

(8) The definitions offered in this document must be seen as being merely intended to ensure greater ease of comprehension of what the Committee wishes to say in its recommendations. In some instances, the definitions have been drawn from legal texts, mainly from Spain, and in such cases, the text from which they come is cited.

(9) This indicates that the definition comes from the Personal Data Protection Act 15/99 of 13 December (LOPD) (*Ley Orgánica de Protección de Datos de Carácter Personal*).

(10) Biomedical Research Act 14/2007 of 3 July (*Ley de Investigación Biomédica, LIB*).

(11) Data of a personal nature are: name and surname(s); ID number (*Documento Nacional de Identidad - DNI*); telephone number; address; hospital clinical-history number; health card code; etc. In contrast, personal data are not deemed to include sex, age, country of birth or residence, health district/area where the patient is attended, etc., because, at least when these are used separately, they do not enable persons to be identified or render them identifiable. It would have to be decided whether, on combining several such items of data, there would be a real risk of identifying a person by using reasonable methods.

(12) Basic Act 41/2002 of 14 November governing patient autonomy, rights and obligations in matters of clinical information and documentation (*Ley básica reguladora de autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica, LAP*).

output of disease frequency measures), identifying the causative factors underlying a given disease, ascertaining its prognosis and assessing clinical practice.

Anonymisation procedure: term equivalent to "disassociation procedure".

Disassociation procedure (LOPD): processing personal data in such a way that any information obtained cannot be associated with any identified or identifiable person.

Registry(13)**:** in the context of these guidelines, a registry is understood to mean any document that contains health data on any person, along with his personal identification in any format (paper, electronic, audio, video, etc.). Documents that contain a patient's clinical history or any set of clinical histories of patients attended at a health-care institution, death certificates issued in a specific geographical area, or cases of any given disease or health condition occurring over a period of time in a community, are all examples of registries that contain data on the health status of persons.

Computerised or irreversibly disassociated record (or registry) (LIB): a record in which health data cannot be linked to an identified or identifiable person, either because the link with all information that might identify the subject has been destroyed, or because linkage requires an unreasonable effort [on the researcher's part], with this being understood to mean the use of a disproportionate amount of time, expense and work.

Coded or reversibly disassociated record (or registry) (LIB): a record in which health data are not associated with an identified or identifiable person, as a result of the information that identifies the person having been replaced or unlinked, by means of a code that enables the operation to be reversed [by the researcher].

Registrar: Natural or legal person, whether public or private, that is tasked with the safekeeping of a record or registry and puts the necessary means in place to ensure compliance with the ethical and legal requirements governing the creation, maintenance and use of such record or registry.

Minimum risk: commonly construed as "the risk assumed by any person in his daily life and activities". In the case of groups with specific diseases, however, it could also be understood to mean "the risk to which persons are normally exposed in the community or group to which the subject belongs". In the Biomedical Research Act 14/2007 of 3 July (*Ley de Investigación Biomédica*), "*Minimal risk and burden*" are deemed to exist where "the effects of the health impacts and discomfort that research subjects may suffer will only be mild and temporary in nature".

Data-processing (LOPD): technical operations and procedures, whether or not computerised, which enable the collection, recording, storage, processing, amendment, barring and cancellation, as well as the release of data issuing from communications, consultations, interconnections and transfers.

(13) **Note added to the English version: The Spanish word "registro" can be translated in English** as "register", "registry" or "record", which are not exactly synonymous. In Epidemiology the word "registry" is widely used to mean collections of data from populations and the Committee agreed for practical reasons to favour its use. The word "record" has been reserved to mean the data pertaining to a single person (e.g. medical record) as well as to refer to the store of data in a generic manner.

3. REGISTRIES: TYPES AND USES

Registries with health data of a personal nature contain information considered sensitive and are therefore subject to special protection. The most relevant types of registries for clinical and epidemiological research are described below.

1. CLINICAL HISTORY

Clinical histories inevitably contain data of a personal nature, since such data are essential for being able to record and manage a patient's overall health care. Clinical histories are normally found in paper format, but with the growing use of new information technologies, the existence of computer files or records is becoming increasingly frequent.

A clinical history's fundamental purpose is to help in the patient's health care. Patients do not give express consent to their data being collected, it being taken for granted that tacit agreement or implicit consent exists, based on the trust between patients and health professionals and between patients and the health-care institutions which safeguard the information. Indeed, it is this that confers ethical legitimacy on the practice.

Patients' clinical histories are also frequently used for health-planning studies and, in particular, for clinical and epidemiological research, e.g., to analyse the relationship between individual characteristics and the risk of developing certain diseases (such as the relationship between smoking and respiratory diseases). In general, use of information of a personal nature for research purposes cannot be deemed to be encompassed by the tacit agreement or implicit consent that is given for healthcare.

2. HEALTH CARE, MEDICAL AND ADMINISTRATIVE REGISTRIES

In modern societies, personal records are increasingly kept for a variety of reasons, be they civil, social or health-related. Instances of these are birth and death certificates at the civil registry, hospital-discharge diagnosis registries, or records of medications prescribed and dispensed. All these data-collections require the subject's identification, whether by means of his name and surname(s), Identification Card number, clinical history code, etc., as well as other demographic (sex, age) and social data (marital status, home address, etc.), which render the subject identifiable with the little ambiguity.

While many such registries have an overriding administrative purpose or have been conceived with health management or planning in mind, they have also been -and continue to be- frequently used for epidemiological research. Record linkage can be very valuable for research; for instance, drug prescriptions and hospital discharge diagnoses can be linked to investigate the association between certain

diseases and use of medications. This linkage necessarily requires an unequivocal subject identifier.

Informed consent is not needed for the creation and maintenance of some of these registries because its requirement is determined by law. Ethical and legal problems arise when the use to which such registries are put differs from that which was originally designated as the justification for their creation.

3. EPIDEMIOLOGICAL REGISTRIES

Coming within this third type are records created *ad hoc*, in which all or most of the subjects who belong to a specific geographical or administrative area and present with a given disease, health condition or characteristic, are included and followed-up over time. Identification of subjects is necessary in order to be able to conduct this kind of follow-up and avoid duplication of information. The registries of rare diseases which are starting to be kept in Spain are typical examples. Standard practice in these cases is for specific informed consent to be sought from the subjects whose data are targeted for collection, or from their legal guardians, thus lending the registry its ethical and legal legitimation. At times, however, serious problems with the registry's scientific validity have arisen when a high proportion of subjects withhold consent, because the patients included in the registry in such cases may not be representative of the population affected by the disease.(14)

(14) **Tu J, Willison DJ, Silver FL, Fang J, Richards JA, Laupacis A, Japral MK. Impracticability of** informed consent in the registry of the Canadian Stroke Network. N Engl J Med 2004; 350:1414-1421. Roberts L, Wilson S. Argument for consent may invalidate research and stigmatise some patients. BMJ 2001; 322:858.

4. ETHICAL PRINCIPLES AND MORAL NORMS

Although a number of theories have been formulated to underpin bioethics, the principlist theory is commonly accepted, particularly in ethics applied to research involving human subjects. This theory postulates the existence of 4 principles which would act as the co-ordinates of any moral problem that might be posed by research involving human subjects, namely, the principles of *non-maleficence, justice, autonomy and beneficence*.(15) In practical terms, these principles are applied through moral norms, such as assessment of the benefit-risk ratio, informed consent, equitable sample selection and protection of confidentiality. Annexe 1 sets out the principles and moral norms deriving from these, along with their interpretation for ethical analysis of the creation and use of registries for research purposes. It should be borne in mind here that none of the principles is absolute in nature, which means that exceptions could arise in specific cases when, in the light of the consequences, there could be cogent reasons for justifying the fact that respect for the dignity of the human being is better served by non-observance than by observance of the principle.(16)

(15) The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research Ethical Principles and Guidelines for the Protection of Human Subjects of Research. Accessible at: http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm.. Beauchamp TL, Childress JF. Principles of biomedical ethics, 6th ed. Oxford University Press, New York:2008. Gracia D. Procedimientos de decisión en ética clínica. Eudema Universidad- Textos de Apoyo. Madrid: 1991 (reedition with a new prologue in Ed. Triacastela, Madrid: 2007).

(16) Gracia D. Procedimientos de decisión en ética clínica. Eudema Universidad- Textos de Apoyo. Madrid: 1991. (reedition Ed. Triacastela, Madrid: 2007). Gracia D. La deliberación moral: el método de la ética clínica. Med Clin (Barc); 2001; 117:16-17. Feito L. Principios vs. consecuencias. In: Alvarez JC, ed, Principios y aplicaciones de la bioética. Asociación de Bioética Fundamental y Clínica, Madrid 2005, pp: 125-130.

5. LEGAL PROVISIONS IN FORCE IN SPAIN AND INTERNATIONAL GUIDELINES

The fundamental rules and regulations to which reference must be made vis-à-vis the handling of medical or other types of records that contain data of a personal nature are the: Personal Data Protection Act 15/99 of 13 December (*Ley Orgánica de Protección de Datos de Carácter Personal*); Basic Act 41/2002 of 14 November governing patient autonomy, rights and obligations in matters of clinical information and documentation (*Ley básica reguladora de autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica*); Instrument of Ratification of the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine (Convention on Human Rights and Biomedicine), done at Oviedo on 4 April 1997; and Act 14/2007 of 3 July concerning the additional biomedical research protocol (see Annexe 2 for the most relevant provisions relating to these guidelines).

International Guidelines that refer to research involving human subjects in general are the Helsinki Declaration VI and the 2002 CIOMS Guidelines (Annexe 3).

6. METHOD OF EVALUATION OF ETHICAL PROBLEMS

The method employed by ethics is deliberation, that is to say, thorough and thoughtful analysis of each case, taking ethical principles into account but also responsibly evaluating their consequences and endeavouring to ascertain all the relevant points of view.(17) To ensure that a prudent and reasonable decision is made, it is advisable for deliberation to follow a set procedure, such as:(18) 1) identifying the different ethical problems (for this purpose, a check-list that includes the relevant elements can be useful); 2) once the problem has been identified, specifying the different possible courses of action; 3) contrasting each of these courses of action against ethical principles and identifying possible conflicts between them. To resolve any such conflict, it may be useful to consider grading the principles according to whether the values that they defend are essential for the survival of the individual or the community (e.g., non-maleficence and justice) (see Annexe 1); 4) assessing the consequences and justification of possible exceptions to the principles, where there are weighty reasons for this, such as the protection of a superior value; and, 5) choosing the course of action. To these "moments" of moral reasoning, a further two should be added, namely, evaluating the course of action with respect to: 6) the prevailing law (see Annexe 2); 7) any possible guidelines applicable, e.g., the 2002 CIOMS Guidelines, Helsinki Declaration or specific guidelines, such as those contained in this document (see Annexe 3). Lastly, while deliberation must be individual, it must also be collective, particularly within the context of multidisciplinary committees.

(17) Gracia D. La deliberación moral: el método de la ética clínica. **Med Clin (Barc); 2001;** 117:16-17.

(18) Alvarez JC. Procedimiento y metodología de la decisión. In: Alvarez JC, ed, Principios y aplicaciones de la bioética. Asociación de Bioética Fundamental and Clinica, Madrid 2005, pp: 125-130.

7. RECOMMENDATIONS

Registries constitute a fundamental tool for biomedical research, and to this end, both their creation and use should be encouraged. Nevertheless, researchers must follow certain ethical principles, such as showing respect for the dignity of the human being, and comply with prevailing legal obligations. The following recommendations seek to serve as guidance for researchers, sponsors and members of Research Ethics Committee (REC) for the drawing-up and evaluation of research projects that include the use of registries or records. There are times when the subject of ethical appraisal is the registry's creation *per se*, e.g., where the intention is to set up an epidemiological registry. The creation and use of records, albeit overlapping, are distinct actions and may thus have different ethical connotations. It is feasible for the creation of a registry to be justified and acceptable from scientific and ethical points of view respectively, and at the same time, for some specific research project that seeks to make use of such a registry to be devoid of scientific or ethical justification, or both.

CONCERNING THE JUSTIFICATION FOR THE CREATION OF A REGISTRY FOR BIOMEDICAL RESEARCH PURPOSES

1. The creation of a registry for biomedical research purposes must be justified in terms of its scientific pertinence and social utility.

As with any scientific activity, the creation of a registry for research purposes must be grounded in the need to attain knowledge that will enable greater well-being to be achieved for society as a whole or, at the very least, for the population on the basis of which the registry is to be set up or from which the sample is to be drawn for said purpose. The aims and uses of the registry must be defined from the outset. If the registry's primordial purpose is health care or planning rather than research, but the possibility of releasing the data to third parties for research purposes is nevertheless envisaged, it is advisable for this potential use to be specifically defined from the start.

Registries set up by private sponsors (e.g., pharmaceutical companies for the purpose of orphan drug follow-up) must bear in mind that the justification for their creation is their public utility rather than the attainment of private goals. The possibility of these records being used by other researchers ought to be envisaged from time of the registry's creation.

2. Data collected from subjects for a registry's creation must be justified in the light of the designated research purposes.

Information collected from subjects must be consistent with the registry's goals. Researchers must carefully weigh and evaluate the data to be collected in terms of their utility for research, particularly if such data should pertain to some type of information deemed especially sensitive (e.g., ethnic group, religious beliefs, sexual

inclinations, etc.). Any sensitive information that is not justified by the registry's designated goals must not be collected.

CONCERNING THE ORGANISATION OF A REGISTRY FOR BIOMEDICAL RESEARCH PURPOSES AND DEFINITION OF RESPONSIBILITIES

3. All registries must have a designated registrar and a public or private institution to house and safeguard it.

The institution that houses a registry is liable for its safekeeping, and must provide it with a structure, organisation and internal set of written rules and regulations which govern its operation and define the relevant responsibilities, quality policy and scientific aims. The institution must appoint some person to hold the position of "Registrar", with functions that are clearly set out and defined in the internal rules and regulations.

Before operational data-collection for the registry comes into effect, the registrar must lay down certain standardised work procedures that ensure the quality of the information and the mechanisms for protecting confidentiality.

The registrar must be informed of all research that is being undertaken with data which are contained in the registry and may previously have been released for the purpose (see Recommendation 13 below). Likewise, he must ensure that, for review purposes, the Research Ethics Committee is fully informed about the registry and specific research projects.

4. All information relating to a registry must be documented in a registry-implementation protocol to facilitate internal management and auditing by third parties.

The creation of a registry for biomedical research purposes requires a protocol stipulating the registry's goals, the need it seeks to meet, and the means available for its implementation. Similarly, it should record the data to be collected, whether these are to be subjected to a process of anonymisation and, if so, the justification for such a process. It is important that the protocol specify: which party or parties is/are to be responsible for recording and processing the data and for quality control; any security measures (see Recommendation 6 below); who is to have access to the data; and whether release to third parties is envisaged. A registry-implementation protocol can be independent or part of the research project. In the latter case, it should be possible for it to be read in isolation, regardless of the research project.

5. Registrar and researchers must ensure that health information which contains data of a personal nature is exclusively handled by health professionals or members of staff who, like them, are under a duty of secrecy.

The protection of confidentiality and the good use made of the information contained in a registry must be one of the priorities of the registrar and the organisation charged with its safekeeping. All persons who have access to registry data of a personal nature must be informed of the obligations entailed therein and sign a confidentiality agreement. In all cases, they should have access to only such information as is strictly necessary for performance of their designated function.

6. Registrars and researchers must ensure that the security measures implemented are adequate to prevent breaches of confidentiality.

The rules and regulations governing security measures for automated personal-data files should be taken into account. In Spain, the Royal Decree 994/1999 of 11 June, renders it mandatory for files containing personal health data to be allocated security measures defined as top-level, in addition to those defined as standard- and medium-level.

CONCERNING THE SCIENTIFIC VALIDITY OF THE RESEARCH PROJECT

7. Any research using registries must be well-founded, undertaken with suitable methodology, conducted by competent teams and have the potential for leading to social utility.

The first ethical norm governing any scientific research is its technical correctness. Without this, no research has any possibility of affording any benefit whatsoever either for the research subjects or for society, and any risk -no matter how small or remote- would lack justification. The social utility of clinical or epidemiological research must be measured, not in terms of direct or indirect benefits for the research subjects, but rather in terms of the usefulness of the knowledge which can be generated, and which could possibly be applicable to clinical or public health practice. Any knowledge obtained should at least be useful for the population from which the sample of research subjects is drawn.

8. Every research project must have a protocol listing its justification, the method(s) to be followed, source of information, data to be collected, procedure of analysis, and the identification and definition of the responsibilities of the principal researcher and remaining members of the research team.

Research involving human subjects, or the use of documents pertaining to or material drawn from human subjects for research purposes, should be the result of mature reflexion about what is already known regarding the targeted research topic, and about the research team's means and ability to render the proposed project viable. The research team must possess proven expertise in the application of the intended method. There must be a work plan and a clear definition of each team member's appointed tasks and responsibilities. All the above must be evidenced in writing in a research protocol, which will enable all the research processes to be internally monitored and evaluated by third parties (internal audits or inspections by health authorities).

CONCERNING THE ETHICAL REQUIREMENTS FOR ANONYMOUS DATA COLLECTIONS AND ANONYMISED RECORDS

9. Anonymous data collections and anonymised records may be used and released without subjects' informed consent. Where data refer to diseases that may have a negative social impact, special caution must be had with respect to any ensuing prejudicial effects for the populations affected.

It is assumed here that anonymous data are collected as such at the point of origin. Anonymised data are drawn from an information source with data which are of a personal nature but have undergone a disassociation procedure, with the result that the subject's identity is definitively severed from the personal data or, alternatively, its association with the person is not within the researcher's reach or demands an unreasonable effort from him. In both cases, the handling of this type of information falls outside the requirements stipulated by the Personal Data Protection Act 15/99 of 13 December.

Anonymous collection, like anonymisation, must be justified in the registry-implementation protocol or research project protocol, whichever of the two is applicable.

A relevant element from an ethical point of view is the procedure used for disassociating the information. The best of all scenarios would be if patients themselves consented to such disassociation, but this might well prove an excessive requirement if sought to be applied systematically.(19) There may, however, be cases, where requesting consent for anonymisation of data may be necessary, e.g., where research may give rise to important consequences that affect the diagnosis, prognosis, prevention or treatment of diseases of specific subjects: it is assumed that this could occur with genetic testing, and hence, while irreversible anonymisation may *a priori* be regarded as ideal for protecting the privacy of data, it may prove counterproductive for subjects who provide their data and biological samples, if the research were to reveal that they evinced certain risks that could be prevented.(20)

The possible harm to the community from which subjects come must be carefully assessed, if such a community is clearly defined by social characteristics (a given ethnic or cultural group, etc.), geographical limits (town, city, island, country, etc.) or any other feature that enables it to be identified. To this end, the group of patients with a rare disease could be regarded as the members of a specific community whose potential harm must be evaluated.

(19) See the lack of logic in the argument: "Subjects' data may only be used without their consent if these do not contain data of a personal nature, but for their disassociation consent will be necessary". Wilson P. Commentary: Legal issues of data anonymisation in research. BMJ 2004; 328: 1300-1301.

(20) See Ethics Committee of the Rare Disease Research Institute. Recommendations on the Ethical Aspects of Specimen Collections and Human Biobanks for Biomedical Research Purposes. Rev Esp Salud Pública 2007; 81: 95-111.) Accessible at: http://www.scielosp.org/scielo.php?script=sci_arttext&pid=S1135-57272007000200002&lng=&nrm=iso

CONCERNING THE ETHICAL REQUIREMENTS OF REGISTRIES THAT CONTAIN DATA OF A PERSONAL NATURE

10. The creation and/or use for research purposes of registries containing personal data is something that calls for adequate and clear justification of the need for such data.

A certain number of epidemiological studies, particularly those that are longitudinal, need to collect data of a personal nature in order to be able to conduct a follow-up and preserve the integrity of the information. Furthermore, it may be necessary for the registry to contain some item of information which unequivocally identifies the person, if the intention is to cross-check the data against other records that use the same individual identifier (e.g., cancer and death registries via the ID number). Coded records would also come within this category, since researchers could, at their discretion, access subjects' identity details. Researchers must specifically justify the need for such information in the protocol, and the personal data as well as all the remaining information registered must be strictly necessary, inasmuch as the study's designated objectives would be otherwise unachievable.

11. The creation and/or use for research purposes of registries containing personal data is something that requires the registrar or the researcher, as the case may be, to seek the consent of subjects, after having duly informed them of all the relevant scientific aspects concerning such data, along with the security procedures to be adopted for their handling, and such persons who are to have access.

Data of a personal nature may only be collected or used for research purposes in the case of subjects who have expressly given their consent, save in those cases in which an exception can be justified (see Recommendation 12 below).

Informed consent must in all cases be deemed a process requiring information, comprehension and voluntariness. Both researchers and Research Ethics Committees must ensure that the process meets these three conditions. The information must be clear, using words suited to the subject's level of comprehension. It must be furnished in writing and supplemented orally. Subjects must, at minimum, be informed of the following aspects:

a) the underlying reason for the registry and/or research project, and its stated aims;
b) the expected benefits to be obtained from the registry and/or research project;
c) the risks and distress to which they expose themselves;
d) the processing and analysis that their data will undergo;
e) who is to have access to the information;
f) how confidentiality is to be ensured;
g) whether it is envisaged that their data might be released to third parties; and,
h) their statutory rights under currently prevailing legal provisions (including the rights of access and objection to, and cancellation and rectification of information).

It is advisable that the written information to be furnished to patients and the consent form be in the same document, with the pages numbered consecutively.

The person tasked with obtaining informed consent must give the subject the necessary time and opportunity to think about his decision, and must place himself at the subject's disposal to clarify any queries that may arise or provide fuller information. It would be advisable if the registrar or the principal researcher, as the case may be, or in their absence, one of the team members furnished the necessary information and sought consent. In certain cases, provided always that the subject gave his authorisation, it might be prudent if his family and general practitioner were also informed.

Any coercion or undue influence must be avoided. If the subject has a strong relationship of dependency with the researcher, e.g., because the former depends on the latter for any health care and/or social benefits he/she receives, it would be prudent for consent to be sought by some other, less involved member of the team or by the subject's own family doctor.

12. Consent for the creation and/or use for research purposes of registries containing personal data could only be waived in exceptional circumstances. The exception would have to be justified by the principal researcher for the specific case to which it was to be applied, and would have to be discussed and approved by a Research Ethics Committee.

Informed consent is a fundamental ethical requirement and may only be waived when it clashes with other overriding norms and principles. This should only happen as an exception and in very specific situations.

One of the reasons put forward for dispensing with informed consent in the creation or subsequent use of certain registries was the latter's validity. For instance, certain records are used to ascertain the incidence or prevalence of a disease, and to this end must be complete, i.e., they must cover the majority, if not all, of the patients affected by the disease. Accordingly, if a high proportion should withhold consent, the registry would be invalidated, thereby rendering the efforts of the researchers useless, the investment of public funds a waste and, what is worse, yielding information that was not valid and that, if used, might lead to highly costly errors in any subsequent decision-making. This possibility should be borne in mind when it comes to setting up a registry.

On other occasions, it has been argued that the request for consent might itself be a reason of sufficient concern to merit considering whether it would be more appropriate to make an exception, and the hypothetical example is cited of a study which might seek to ascertain the relationship existing between child mortality due to unknown causes and parents' mental health. In such circumstances, approaching the subject to obtain consent might prove ethically less acceptable than making an exception to consent.

The Medical Research Council Guidelines on the handling of clinical information in medical research suggests that regard be had to a number of criteria, when it comes to making an exception to consent, namely:(21)

— *Necessity*: Are there any alternative, practicable, ways of conducting the study? Could anonymous data be used?

(21) *Medical Research Council*. "*Personal Information in Medical Research*" Accessible at: http://www.mrc.ac.uk/Utilities/Documentrecord/index.htm?d=MRC002452

— *Sensitivity*: What and how sensitive is the information required for research?
— *Importance*: Is the research well designed, and likely to make a significant contribution to knowledge in the area?
— *Safeguards*: Are security measures envisaged that will prevent leaks of information and prevent distress to patients?
— *Independent review:* Has a Research Ethics Committee evaluated the proposal and supported the exception?

Whatever the reasons adduced, researchers must make them explicit, and the Research Ethics Committee will then decide whether or not it supports the proposal. Researchers should nevertheless be aware that the Research Ethics Committee's approval, though important, in no way exempts them from fulfilling their legal responsibilities. In such cases, it is essential that researchers inform the management of the institution.

13. Data of a personal nature can only be released to third parties if the interested party has given his consent before any such release is made, unless: a) the release has been envisaged, explained and authorised by the interested party in the initial consent; b) the legally stipulated exceptional circumstances are present; or, c) disassociation is made prior to release.

If the release of data to third parties is envisaged at the date of a registry's creation, it would be advisable for this possibility to be included in the initial consent procedure. Subjects must be informed of the reasons for the release, the data that are to be released, and the identity of those destined to receive the information. In all cases, researchers must ensure, and duly advise subjects, that the recipient will apply the same or more stringent security measures to any data that are transferred.

Local law concerning data protection should be consulted in order to ascertain the exceptions accepted to the request for informed consent in the case of release to third parties. For instance, in Spain the Article 11 of the Personal Data Protection Act 15/99 of 13 December provides the following exceptions: 1) where this is authorised by law; 2) where the release is to take place between public authorities, with the intention of subsequently processing the data for historical, statistical or scientific purposes; or alternatively, 3) where the release is necessary to resolve an emergency that requires accessing a file or conducting epidemiological studies on the terms stipulated in national or regional health legislation.(22)

If data, once collected, are then disassociated for subsequent processing, this would amount to a *de facto* anonymised record. Disassociation must result in it being impossible for the end-user of the information to identify the subjects by reasonable means.

14. Subjects are entitled to withhold their consent to research and revoke their consent at any time, without having to give explanations for their decision and without this entailing penalisation or discrimination of any type whatsoever.

The right to refuse consent, as well as the possibility of revoking consent once granted, must be acknowledged in the written information handed to subjects and

(22) It is taken for granted that, in the event of release to researchers, there would be additional compliance with the requirement that such release be made for purposes directly related with the legitimate functions of the party releasing the information and the party to whom such information is released.

reinforced orally. Revocation may affect any processing to which data are subjected or be specific to certain operations, such as release to third parties. Moreover, subjects must be informed of their rights under the local law (including the rights of access and objection to, and cancellation and rectification of information).

In those cases in which analysing the reasons for non-participation or revocation might be scientifically justified, any request for information about such reasons shall be made after a time lag of sufficient length to ensure that no influence is exerted on the decision.

In the event that cancellation of subjects' data might have a relevant impact on research, there would be the possibility of raising an exception based on the criteria and considerations discussed under Recommendation 12 above.

15. If the registry created or from which personal data are used, includes minors or subjects lacking capacity to consent, the need to include such populations in research must be scientifically justified. Where it is deemed justified for the data of such subjects to be collected, consent will be sought from their parents or legal representatives, as the case may be. Furthermore, assurances must be given that the research risk is non-existent or minimal, and that relevant knowledge, which would not otherwise be obtained for this population, will be obtained from this research.

In principle, research involving vulnerable groups can only be justified if this yields direct benefits for the research subject, which could not otherwise be obtained. Where no direct benefit for the subject is to be gained from research -a situation particularly frequent in observational studies- the research could only be justified if the knowledge could not be obtained in any other way (e.g., the research cannot be undertaken on non-vulnerable groups) and assurances are given that the risk is minimal. The Research Ethics Committee must appraise the level of risk posed by participation in the registry.

Research that entails a higher-than-minimal risk for subjects will not be acceptable, unless: a) the importance of the knowledge that might be obtained is extremely high; b) the group to which the subject belongs might benefit considerably from same; and c) full assurances are given during the process of informed consent. In these exceptional circumstances, justification could be found for the consent procedure to be supervised by an auditor appointed by the Research Ethics Committee.

At all events, every effort should be made to ensure that subjects participate in the consent procedure as far as possible. Similarly, in the case of minors aged twelve years or over, their informed consent will also be requested. Refusal to participate in research must be respected, though the Research Ethics Committee will weigh and consider the different circumstances surrounding each individual research project.

CONCERNING THE USES OF CLINICAL HISTORY FOR RESEARCH PURPOSES

16. All information of a personal nature deriving from medical care must be treated confidentially. At the time when such information is gathered, subjects should be informed that their data may possibly be used for research purposes, and be given the chance to object to same.

A clinical history should be regarded as just another record containing data of a personal nature. The creation of a clinical history does not require informed consent,

inasmuch as it is seen as an indispensable tool for the provision of health care and patients are deemed to consent to it implicitly when requesting such care. It is assumed, however, that the data contained in the clinical history are not going to be used for purposes other than those for which they are recorded. In Spain, the creation of records needed for health care (i.e., clinical histories) is covered by Article 7.6 of the Personal Data Protection Act 15/99 of 13 December.

In view of the fact that clinical history data are often used for research purposes, it is considered good practice to inform subjects of this possibility. Subjects' refusal to their health data being eligible to form part of clinical or epidemiological studies must be noted in their clinical histories.

17. Where the information needed for clinical or epidemiological research is sought to be obtained from a clinical history, the subject's express consent will not be required if the researcher forms part of the medical team that attends him, though once the necessary information has been extracted and incorporated into the data-collection file, it must be appropriately coded or anonymised to prevent any breach of confidentiality. At all events, both the study and the data-collection procedure will have to be approved by a Research Ethics Committee.

18. If the subject's medical team needs to transfer the information to third parties for research purposes, this may only be done with the subject's prior consent or by applying an appropriate disassociation procedure. In all cases, however, both the research and the release of data will have to be justified and approved by a Research Ethics Committee.

19. If the researcher is external to the institution that has custody of the subject's clinical history, express informed consent for this study must be requested, unless the extraction of data is performed by the subject's medical team and an appropriate disassociation procedure is incorporated before the information is released to the researcher. In every case, however, both the research and the procedure for obtaining the information will have to be approved by a Research Ethics Committee.

If access to data corresponds to the medical team that attends the research subject, then the necessary confidentiality is at no time violated, but the team is naturally under a duty of secrecy and may not disclose such data to third parties, unless an appropriate disassociation procedure is first incorporated. Where this is not so, however, specific informed consent must be sought.

If the person seeking to access the clinical history is not part of the medical team, then the patient's consent is necessary, save where the researcher wishes to consider the possibility of raising an exception, based on: a) the inviability of consent, or the harm that this could cause to the validity of the registry or the specific research project, or to the patient himself; b) the impossibility of collaboration on the part of the patient's usual medical team; and, obviously, c) the absence of any risk of inappropriate use being made of such information. In Spain, mention should be made of the exception envisaged under Article 11 (2.f) of the Personal Data Protection Act 15/99 of 13 December, with respect to the undertaking of epidemiological studies.(23)

(23) In clinical trials, the rules of good clinical practice demand that the trial monitors, who act on behalf of the research sponsor, as well as the official health inspectors, have access to patients' clinical histories in order to be able to verify the veracity and completeness, as per the protocol, of the data collected by the physician-researcher. The ethical legitimacy of this monitoring and

CONCERNING THE USE OF HISTORICAL RECORDS AND INFORMATION ABOUT DEAD PEOPLE FOR RESEARCH PURPOSES

20. Historical records containing data of a personal nature may only be used for research purposes when one or more of the following circumstances is present: a) the subject's express consent; or, b) there has been disassociation of personal data prior to the record's release for use. In exceptional cases, historical records may be used without the subject's informed consent, bearing in mind the determining factors described in Recommendation 12 above.

There are a many records that have been used in the past without subjects' express consent and, while some of these are covered by statute, others are not, at least specifically. Where the personal data contained in the record are not strictly necessary, an easy alternative would be to render them anonymous. If this is not viable, however, and the personal data must be retained, consideration should be given to the possibility of informing subjects prospectively (and, if at all feasible, retrospectively too) of the record's existence, setting out and explaining their rights. Where this possibility of informing subjects or requesting their consent is inviable, either because it requires a disproportionate effort or because it may seriously affect the record's validity, the possibility of justifying an exception might well be considered. The risk of inappropriate use being made of the data and the security measures to be implemented are fundamental elements which the Research Ethics Committee will have to take into account.

21. Records containing personal data on dead people may only be used where prior consent has been given, either by the subject or, where this is lacking, by his relatives or legal representatives.

Where the record is or forms part of the subject's clinical history, the terms of Recommendations 17 to 19 will apply.

Where the subject's prior consent is absent and seeking it from his relatives or legal representatives is not considered feasible, the researcher can propose to the Research Ethics Committee the possibility of making an exception to this rule. The importance of the research, along with the risk of inappropriate use being made of the data and the security measures to be implemented, are fundamental elements to be borne in mind. In no case, however, may personal data pertaining to a deceased person be collected or used where there is evidence that he had objections to this.

CONCERNING CONTACT WITH SUBJECTS DURING THE COURSE OF RESEARCH

22. Researchers must have procedures that minimise the risk of causing harm to persons contacted during the course of research and have a plan for dealing with this.

Contact with research subjects or their legal representatives (in those cases where the former have no legal capacity, are minors or deceased) may be necessary in order

inspection system's derives from the patient being informed of its existence at the time when his consent to participate in the clinical trial is sought. In epidemiological studies that use clinical histories as a data source, prior consent is not usually present because such studies normally tend to be retrospective. Furthermore, a specific request for informed consent may prove unfeasible due to: the high number of subjects involved in the study; subjects' vital status (death, disability etc); or the risk of introducing consent-related selection biases.

to request informed consent or obtain more detailed information. In both cases, interviews must be conducted by experts and, as far as possible, be protocolised, particularly when the interview or data-collection procedure can be assumed to constitute a source of distress for the subject or his representative. The impact that such an approach may have on the subject should not be underestimated. Not only will it enable any foreseeable psychological harm to be ameliorated, particularly in cases where subjects are questioned about especially sensitive matters but, at the same time, it will also facilitate participation in the study.

CONCERNING THE COMMUNICATION OF RESEARCH RESULTS

23. In studies in which informed consent is sought, researchers must decide what information about the results should be made known to the participants once the study has been concluded or, in exceptional cases, during the course of same. Similarly, there should be a management procedure for handling findings that arise during the course of research and are applicable to individual subjects; from the outset, subjects or their representatives should be offered the possibility of deciding whether or not to receive such information.

Subjects who have consented to furnishing or permitting access to their personal data are entitled to be told at first hand of the results of research in which they have participated and to what extent such results can benefit them, the group to which they belong, or society in general. This would seem to be only fair recompense owed by researchers to those without whose contribution, the research would not be possible.

A distinction must be drawn between scientific research results that are applicable to population groups, and specific findings that concern individual subjects who have taken part in the study. The latter may be unexpected or, alternatively, they may be foreseen, though precisely which subjects are going to display said characteristic is not known at the start of the study. For instance, in a study one might be evaluating the hypothesis of the relationship between exposure to a given environmental pollutant and a disease. If certain subjects were then to be identified as having a high exposure to this toxin, regardless of whether or not the study hypothesis is confirmed, this finding should probably be made known to the subjects and to the health authorities. To forestall improvisation, it is recommended that researchers have a procedure for announcing research results and individual findings, and that this procedure be assessed by a Research Ethics Committee.

The same principle of autonomy that covers the "right to know", would also cover the "right not to know", though the latter, rather than being presumed, must be expressly declared by the subject (or his representative). The "right not to know" may have restrictions if it affects the interests of third parties.(24) The Research Ethics Committee should advise researchers as to how to proceed in such cases.

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(24) This circumstance may be especially relevant in research that includes genetic testing. To explore this matter in greater depth, see Ethics Committee of the Rare Disease Research Institute. Recommendations on the Ethical Aspects of Specimen Collections and Human Biobanks for Biomedical Research Purposes. Rev Esp Salud Pública 2007; 81: 95-111.) Accessible at: http://www.scielosp.org/scielo.php?script=sci_arttext&pid=S1135-57272007000200002&lng=&nrm=iso

CONCERNING REVIEW BY A RESEARCH ETHICS COMMITTEE

24. The scientific and ethical aspects both of the creation of registries and of the use of pre-existing records for research purposes should be assessed by a Research Ethics Committee. The Committee's appraisal will be particularly important in cases where research calls for the handling of data of a personal nature.

At minimum, the following items should be discussed by the Committee: 1) pertinence of the registry and/or research project; 2) its social utility; 3) its technical correctness; 4) the research team's competence; 5) the benefit-risk ratio for the research subjects; 6) selection of research subjects; 7) assessment of vulnerability; 8) the completeness, veracity and comprehensibility of the information furnished to subjects; 9) appropriateness of the informed consent procedure; 10) evaluation of subjects' capacity and substitution decisions in the case of minors and/or subjects lacking legal capacity; 11) the privacy and confidentiality of the data; 12) contacts envisaged with the subject and communication of results. Finally, the Committee must conduct a follow-up of the study via the progress and final reports that the researchers undertake to submit, and evaluate any incidents having ethical repercussions which may arise.

The Committee must have adequate multidisciplinary representation. It should at least include clinicians, epidemiologists, experts in bioethics, lawyers and lay members.(25)

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(25) **In Spain there is great legal vacuum regarding which Committee should evaluate** epidemiological research of an observational nature. Although the Clinical Research Ethics Committees regulated by the Medical Drugs & Health Care Products Guarantee and Rational Use Act (*Ley de 29/2006 de Garantías y Uso Racional de Medicamentos y Productos Sanitarios*) (which replaces the Medical Drugs Act - *Ley 25/1990 del Medicamento*) can perform this function, this is not altogether clear in cases where the research is undertaken by non-health care institutions. Similarly, outside the provisions laid down in the regulations applicable to clinical trials, it is unclear what competencies such Committees would have vis-à-vis these studies, e.g., in the creation and/or use of a disease registry. This is important, for example, when it comes to evaluating possible exceptions envisaged under the Data Protection Act, since the Act is silent as to who is to judge exceptions to specific cases or in what forum these are to be judged, other than the courts of law themselves, a procedure that is obviously rather inefficient for resolving specific issues, in view of the important number of registries that there could be in Spain. In other countries, such as the USA, the *Privacy Rule* lays down that *Institutional Review Boards* (the equivalent of the Clinical Research Ethics Committees that operate in Spain) are to decide upon exceptions to informed consent. This is likewise envisaged under the 2002 CIOMS Guidelines. This proposal would be both interesting and necessary for Spain, at least as a standard procedure, i.e., Research Ethics Committees or those set up in institutions with capacity to do so, would evaluate and guide the researcher as to how to proceed with the creation and/or use of registries. Where the record goes beyond an institution's scope, one would have to consider the possibility of ethical issues being debated in committees at a regional or national level. The recently promulgated Biomedical Research Act 14/2007 of 3 July likewise fails to resolve the problem, firstly because observational research is excluded from its provisions, and secondly because the Research Ethics Committees that it establishes are only formally mentioned and will require subsequent development.

ANNEXE 1
ETHICAL PRINCIPLES AND MORAL NORMS

The principlist theory of bioethics postulates the existence of 4 principles which would serve as the framework for analysis of any moral problems that may be posed by the practice of medicine and research involving human subjects.(26) These principles and the main moral norms deriving from them will now be outlined below, as will their interpretation for ethical analysis of the creation and use of registries and records for biomedical research purposes.

4.1. PRINCIPLE OF NON-MALEFICENCE

This principle lays down that, as a general rule, harm should not be caused to other persons. Harm may be of different types, i.e., physical, psychological, moral, financial, etc. Needless to say that an overly literal interpretation of this statement would bar any medical intervention, given that inevitably there is a certain implicit risk of inducing harm. For this reason, in a medical context it is more appropriate to speak of the benefit-risk ratio or balance of interventions. Hence, maleficence is construed as being present where *a priori* the *benefit-risk ratio* of an intervention must be deemed unfavourable. For instance, an intervention would be judged maleficent where it offered no possibility whatsoever of securing a benefit for the person undergoing it, but did, in contrast, entail a significant risk for such a person; generically, an intervention would have to be deemed maleficent where it was held to be proved that the ensuing risks considerably exceeded the potential benefits for the person who was to undergo it.(27)

This same line of argument could also be extended to populations. Just as there are a number of *microethical principles* which are defined from the standpoint of the individual, certain *macroethical principles* could be formulated, which would be

(26) National Committee for the protection of human biomedical and behavioural research subjects. Belmont Report. Accessible at: http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.htm. Beauchamp TL, Childress JF. Principles of biomedical ethics, 6th ed. Oxford University Press, New York: 2008. Gracia D. Procedimientos de decisión en ética clínica. Eudema Universidad-Textos de Apoyo. Madrid: 1991 (reedition Ed. Triacastela, Madrid: 2007). Gracia D. La deliberación moral: el método de la ética clínica. Med Clin (Barc); 2001; 117:16-17.

(27) Epidemiological research is basically observational and, unlike experimental research, does not tend to pose any risk to patients in addition to that posed by clinical practice itself, other than the risk stemming from inappropriate use of health information associated with personal identifying data (data of a personal nature). Hence, if the study guarantees that inappropriate use is not going to be made of data and that no data are going to be released to third parties unless they too subscribe to these same assurances, such research will comply with the principle of non-maleficence. Some epidemiological studies call for certain diagnostic tests or follow-up methods that do not form part of standard clinical practice. Where this occurs the need for such tests must be assessed in accordance with the designated research goal and the risks that this entails. Such risks may be physical (extraction of blood, biopsy etc.), psychological (questionnaires targeted at very sensitive aspects of psychological or biographical life, such as sexual relations, drug use, relationships with parents, etc.) or, alternatively, may relate to invasion of the individual's privacy.

defined from the stance of populations(28) and would also have to be respected. In other words, an epidemiological study may be non-maleficent vis-à-vis persons at an individual level and yet be maleficent vis-à-vis the populations of which those individuals form part, e.g., if health data pertaining to a well-defined population group were to be published.

The *technical adequacy* of the study and the *competence of the research team* are ethical norms that come within the principle of non-maleficence, since both are necessary premisses for avoiding unnecessary damage of whatever type to patients. Research that lacks a scientific basis, or is conducted using inappropriate methods or by incompetent people, must be deemed maleficent, in view of the benefit being nil and the risks involved unpredictable.

4.2. PRINCIPLE OF JUSTICE

This principle was defined in the Belmont Report as fairness in distribution of the burdens and benefits of research among all individuals (and, one should add, among all the communities) affected by the problem under investigation, to prevent exploitation of certain vulnerable groups, such as minors, the incapacitated, racial minorities, the socially disadvantaged, third world communities, etc., something that was unfortunately an all too characteristic hallmark of research involving human subjects prior to the 1970s. In practical terms, this translates as *equitable selection of research subjects*.(29) It is not fair, therefore, for research subjects to be drawn from a given social group only because they may be more easily accessible or more easily manipulable. Transferring this to the sphere of medical records, attention must be paid to the fact that the registry may be justified by a specific social condition (e.g., public vs. private health, particularly in countries with a charity-based public health), which may place registered individuals in a position of inequality.

An ethical norm, rooted in the principle of justice, though interpreted more widely than that contained in the Belmont Report, would be the *social utility* of research. A research study could only be deemed fair if the ensuing results were for the benefit of all, or at least, of the population group from which the sample of study subjects were drawn.

4.3. PRINCIPLE OF AUTONOMY

The principle of autonomy comes within individuals' right to freedom and demands respect for the criteria, considerations, preferences and actions of autonomous persons. An autonomous person is an individual capable of deliberation about personal goals and of acting under the direction of such deliberation. To respect

(28) **CIOMS. International guidelines for ethical review of epidemiological studies, 1991.** Accessible at http://www.cioms.ch/1991_texts_of_guidelines.htm. At the date of writing, these guidelines were in the review phase.

(29) **Principle 19 of the Helsinki Declaration VI would be a practical application of this rule:** "Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research". De Abajo FJ. La Helsinki Declaration VI: una revisión necesaria, pero suficiente? Rev Esp Salud Pública 2001; 75: 407-420. Available at: <http://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1135-57272001000500002&lng=es&nrm=iso>

autonomy means, not only regarding autonomous persons' choices seriously, but also refraining from obstructing their actions unless these are clearly detrimental to others. Compliance with this principle naturally requires that the individual be in possession of the information necessary to make a considered judgment.

"However, not every human being is capable of self-determination. The capacity for self-determination matures during an individual's life, and some individuals lose this capacity wholly or in part because of illness, mental disability, or circumstances that severely restrict liberty. Respect for the immature and the incapacitated may require protecting them as they mature or while they are incapacitated" (the Belmont Report). The protection of non-autonomous, and thus, vulnerable persons is the other side of the principle of autonomy, though this is in many ways connected with the principle of justice.

The principle of autonomy can manifest itself in a variety of ethical and legal forms. For instance, when one speaks of personal data relating to health or other facets of life, it is very useful for this principle to be spelt out in three interlinked but independent concepts, i.e., intimacy, privacy and confidentiality:(30)

— *Intimacy.* Intimacy is the spiritual area of a human being which encompasses his innermost, most closely-guarded self. Intimacy is perceived today as an inherent right belonging to every individual, a right that does not have to be won in order to be possessed, is not lost because of lack of knowledge as to its existence, and can be assumed to have the following features,(31) namely, it is: a) unassignable, i.e., cannot be transferred by acts *inter vivos* or *mortis causa*; b) unrelinquishing; c) inalienable and inseparable; and, d) imprescriptible.

— *Privacy.* Privacy is every person's right to decide and control what information about himself is disclosed, to whom and why. Privacy is a need that arises as a consequence of living in society. Needless to say, privacy is a necessary prerequisite for intimacy yet in some way also goes beyond it, inasmuch as certain aspects of personal life or relationships that are not necessarily intimate, may nonetheless be considered private. If "intimate" is everything that is innermost and most closely-guarded about a person (such as thoughts, feelings, desires, beliefs, "intimate" personal relationships, physiological acts, genetic data, health data, etc.), then "private" would include all that was intimate *plus* everything of a personal nature which, without being intimate, a person would not want to see made public, e.g., external features such as race or the existence of some handicap or disability.

— *Confidentiality*. Confidentiality is the right of every subject whose private data are disclosed in a setting of trust, to ensure that anybody who receives such private information (a "confidant") does not communicate it to third parties, unless so authorised by the subject himself. To the extent to which such information may be recorded in some type of file or registry, the confidant is thereby bound to ensure its custody and protection. That is to say, the subject's right to the confidentiality of his private data is correlative with an obligation of discretion about, safekeeping and protection of such data on the

(30) Júdez J, Nicolás P, Delgado MT, Hernando P, Zarco J, Granollers S. La confidencialidad en la práctica clínica: historia clínica y gestión de la información. Med Clin (Barc) 2002; 118:18-37.

(31) Sánchez Carazo C, Sánchez Carazo JM. Protección de datos de carácter personal relativos a la salud. Agencia de Protección de Datos, Madrid: 1999.

part of the confidant. In the healthcare sphere, physicians, nurses, pharmacists, etc., are necessary confidants, to the extent that, in order to provide health care, they need to know private –and thus confidential- information about the subject or patient. In the health professions, this is what has traditionally been known as the "duty of secrecy". Nowadays, in view of the fact that health-care relationships include more than one person (the "medical team") or even an institution, it would seem more appropriate to talk of confidentiality than of secrecy, though in the legal field the latter term continues to be used.

The practical form of expressing the subject's moral autonomy is *informed consent*, and hence this will also serve to define the scope of privacy and confidentiality, i.e., to whom and under what conditions access to private data is authorised by the subject. Accordingly, the wording of informed consent, both in clinical practice and in the sphere of research, should in all cases state who may have access to the data, how such data is to be safeguarded and protected, and what rights he will have to continue exercising control over same (objection, access, rectification and cancellation).

Privacy and confidentiality are also protected if health information is unlinked from personal data by means of an appropriate procedure of disassociation. In such a case, informed consent becomes unnecessary.

4.4. PRINCIPLE OF BENEFICENCE

The Belmont Report states that, "Persons are treated in an ethical manner not only by respecting their decisions and protecting them from harm, but also by making efforts to secure their well-being. (…) The term *beneficence* is often understood to cover acts of kindness or charity that go beyond strict obligation. In this document, beneficence is understood in a stronger sense, as an obligation". Indeed, the principle of beneficence imposes a heavier obligation in the health care context than it does in other areas of civil society.

Unlike clinical practice, biomedical investigation does not have the research subject' benefit as its primary goal, and so the principle of beneficence should be interpreted somewhat differently in a research context. In investigative research, respect for the principle of beneficence consists of the research team safeguarding the subject's well-being, by ensuring that he is given all the medical care that he would otherwise receive if he did not form part of the study, unless such care were to be incompatible with the research itself, something that would have to be duly reported. It would be appropriate for the research subject to receive some type of benefit or privilege in return for participating in the study (special or more personalised attention, more stringent follow-up, etc.), provided that this did not influence the subject's decision or prejudice third parties.

The principle of beneficence is a private matter for the individual subject and is, as a consequence, linked to his ideal of perfection as a human being. Within these confines, a subject may judge that his participation in research can benefit others to whom he feels close. It is essential that the principle of beneficence also be viewed in this light, i.e., where, rather than merely being a passive research subject, the individual is also an active subject who values the attainment of a benefit for third parties.

4.5. EXCEPTIONS TO THE PRINCIPLES

All the bioethical principles formulated are *prima facie* mandatory, so that an effort must be made to observe them. There are authors who feel that the decision as to which of these should give way in the event of conflict, can only be based on an analysis of the consequences deriving from a specific course of action in a given situation. Nevertheless, levels can be distinguished within the principles, thereby enabling a hierarchy to be established. The principles of non-maleficence and justice are binding regardless of personal opinions, since they safeguard minimal, essential elements: the principle of non-maleficence ensures the protection of the lives of individuals inasmuch as these are persons warranting equal respect; similarly, the principle of justice refers to non-discrimination and equity, not in the context of biological life, but rather in that of social life. In this regard, these two principles thus enjoy a certain pre-eminence over the other two, which refer to private domains. Such ranking would justify allowing possible courses of action to be rated in each case, according to the principle to which they responded and by which they were legitimated.

Notwithstanding the above, it remains true that all the principles are *prima facie* mandatory, so an attempt must necessarily be made to respect them. On the other hand, however, despite their possible ranking, none of the principles is absolute in nature, and there could be specific situations in which it would be possible for exceptions to be made, i.e., when, in the light of the consequences, there could be cogent reasons for justifying the fact that respect for the dignity of the human being would be better served by non-observance than by observance of the principle. One example is that of the "white lie", where flinging the truth in a subject's face might be more harmful than telling a discreet lie.(32) Another example concerns the duty of confidentiality pertaining to private data disclosed in a professional relationship. It is obvious, that to the health professional this is a *prima facie* duty and must thus be unfailingly fulfilled: clearly, however, this would be on the condition that observance did not entail a higher cost, something that might occur when the well-being or health of third parties was manifestly prejudiced. An exception to this duty of confidentiality would also have to be considered where social interests might be adversely affected. Circumstances of this nature would justify the mandatory reporting of infecto-contagious diseases or adverse drug reactions, though, even in these cases, one would have to consider whether it was essential for personal identifying information to be reported. Along these same lines, an appeal could be made to social interests in the case of epidemiological studies needed to resolve health problems.(33)

Obviously, principles and ethical norms are there to be followed and in many situations it is feasible for all of them to be observed. Exceptions to ethical principles should thus be raised as a last resort and only in particular cases: the exception can

(32) For a discussion of the matter, see: Gracia D. Procedimientos de decisión en ética clínica. Eudema Universidad- Textos de Apoyo. Madrid: 1991 (reedition Ed. Triacastela, Madrid: 2007). Gracia D. La deliberación moral: el método de la ética clínica. Med Clin (Barc); 2001; 117:16-17. Feito L. Principios vs. consecuencias. In: Alvarez JC, ed, Principios y aplicaciones de la bioética. Asociación de Bioética Fundamental and Clinica, Madrid 2005, pp: 125-130.

(33) This at least would seem to be the interpretation that would have to be given to the exception envisaged by the Personal Data Protection Act 15/99 of 13 December, for the release of data for epidemiological research purposes (Article 11.2.f).

never be raised to the category of a rule. Finally, it seems obvious that the party proposing the exception bears the burden of proving that the dignity of the human is better respected by making an exception than by observing the principle. Needless to say, the appropriate forum for ethical deliberation in such cases is the Ethics Committee.

ANNEXE 2: LEGAL PROVISIONS IN FORCE IN SPAIN GOVERNING THE USE OF REGISTRIES FOR BIOMEDICAL RESEARCH PURPOSES

PERSONAL DATA PROTECTION ACT 15/99 OF 13 DECEMBER

(Ley Orgánica de Protección de Datos de Carácter Personal)

This is the most important statutory enactment governing the use of personal data for research purposes. The Act does not refer to collections of anonymous data or anonymised records, inasmuch as these do not allow for persons to be identified.

Insofar as these guidelines are concerned, the most relevant provisions are:

Article 3. *Definitions.*

For the purposes hereof, the terms shown below shall be construed as follows:

a) Data of a personal nature: any information concerning identified or identifiable physical persons.

b) File: any organised set of data of a personal nature, whatever the manner or mode of its creation, storage, organisation or access.

c) Data-processing: technical operations and procedures, whether or not computerised, that enable the collection, recording, storage, processing, amendment, barring and cancellation as well as release of any data resulting from communications, consultations, interconnections and transfers.

e) Affected or interested party: natural person who is the owner of the data subjected to the processing referred to in subsection c) hereinabove.

f) Disassociation procedure: processing personal data in such a way that any information obtained cannot be associated with any identified or identifiable person.

h) Consent of interested party: any free, unequivocal, specific and informed expression of will whereby the owner of information consents to personal data concerning him being handled and processed.

i) Release or communication of data: any disclosure of data to a person other than the interested party.

Article 4. *Data quality.*

1. Data of a personal nature may only be collected for processing, and subjected to such processing, where they are appropriate, pertinent and not excessive with respect to the specific, express and lawful scope and purposes for which they were obtained.

2. Data of a personal nature subjected to processing may not be used for any purpose incompatible with that for which the data were collected.

The subsequent processing of such data for historical, statistical or scientific purposes shall not be deemed incompatible [...].

5. Data of a personal nature shall be cancelled when they have ceased to be necessary or pertinent for the purpose for which they were collected or recorded.

They shall not be kept in any manner that might permit the identification of the interested party for a period exceeding that necessary for the purposes on the basis of which they were collected or recorded.

The procedure shall be laid down by law whereby, as an exception and with due regard for historical, statistical or scientific values pursuant to specific legislation, it is decided that given data are to be maintained whole and intact [...].

Article 5. *Right to information in data collection.*

1. Interested parties from whom personal data are sought must be previously informed, expressly, accurately and unequivocally, of:

a) The existence of a file or processing of data of a personal nature, the purpose of collecting these and the recipients of the information;
b) The compulsory or optional nature of their replies to any questions that may be asked;
c) The consequences of obtaining the data or refusal to furnish them;
d) The possibility of exercising the rights of access, rectification, cancellation and objection; and,
e) The identity and address of the person in charge of data-processing, or, as the case may be, of his representative.

Where the person in charge of data-processing is not based within the territory of the European Union, and means situated in Spanish territory are used in the processing of the data, then, save that such means should be used for the purpose of formalities, a representative in Spain must be appointed, without prejudice to any such action as may be brought against said person in charge of data-processing.

2. Where questionnaires or other forms are used for data-collection, these shall advise the reader of the items listed in the above Section, in a manner that is clearly legible.

3. The information referred to in subsections b), c) and d) of Section 1 hereinabove shall not be required if the content thereof can be clearly deduced from the nature of the personal data sought or the circumstances in which these are collected.

4. Where the data of a personal nature are not collected from the interested party, the latter must, within a period of three months following the date of recording the data, be expressly, accurately and unequivocally informed by the person in charge of the file or his representative, save where said interested party has already been previously informed, of the content of the processing and the source of the data, along with the information envisaged under subsections a), d) and e) of Section 1 hereinabove.

5. The above Section shall not apply in cases where this is expressly envisaged by law, the processing has historical, statistical or scientific purposes, or informing the interested party may prove impossible or require disproportionate efforts, in the

opinion of the Data Protection Agency or the equivalent regional body, having due regard for the number of interested parties, the age of the data and any possible compensatory measures [...].

Article 6. *Consent of affected party.*

1. The processing of data of a personal nature shall require the unequivocal consent of the affected party, save where the Act provides otherwise [...].

Article 7. *Specially protected data.*

[...] 3. Data of a personal nature that make reference to racial origin, health and sex life may only be collected, processed and released where, for reasons of general interest, this is provided for by law or expressly consented to by the affected party [...]

6. Notwithstanding the provisions contained in the above Sections, data of a personal nature referred to in Sections 2 and 3 hereof may be the subject of processing, where such processing should prove necessary for prevention or medical diagnosis, provision of healthcare or medical treatment, or management of health care services, provided that such data-processing is performed by a health professional subject to professional secrecy or by any other person likewise subject to an equivalent duty of secrecy.

The data to which the above paragraph refers may also be the subject of processing when such processing is necessary to safeguard the vital interest of the affected party or any other person, in a case where the affected party is physically or legally unable to give his consent.

Article 8. *Health-related data.*

Without prejudice to the provisions laid down in Article 11 hereinbelow with respect to release of data, public and private institutions and health care centres, as well as their corresponding professionals, may proceed to process data of a personal nature relating to the health of any persons who seek attention or have been treated at same, pursuant to the provisions laid down in national or regional health legislation.

Article 10. *Duty of secrecy.*

Any person in charge of a file and those persons who intervene in any phase of the processing of data of a personal nature are bound to professional secrecy with respect thereto and to a duty to safeguard such data, obligations that shall endure even after their relationship with the owner of the file or, where applicable, the person responsible for same has terminated.

Article 11. *Disclosure of data.*

1. Data of a personal nature subjected to processing may only be disclosed to a third party for purposes directly related with the lawful functions of the party releasing the information and the party to whom such information is released, subject to the interested party's prior consent.

2. The consent required by the above Section shall not be necessary:

a) where the release is authorised by law;

b) where the data concerned have been collected from publicly accessible sources [...];

e) where the release is to take place between public authorities, with the intention of subsequently processing the data for historical, statistical or scientific purposes; or

f) where the release of health-related data of a personal nature is necessary to resolve an emergency that requires accessing a file or conducting epidemiological studies on the terms stipulated in national or regional health legislation [...].

6. Where disclosure is made subject to a prior disassociation procedure, the provisions laid down in the above Sections shall not be applicable.(34)

BASIC ACT 41/2002 OF 14 NOVEMBER GOVERNING PATIENT AUTONOMY, RIGHTS AND OBLIGATIONS IN MATTERS OF CLINICAL INFORMATION AND DOCUMENTATIO

(*Ley básica reguladora de autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica*)

The most relevant Articles relating to the use of clinical histories for research purposes are as follows:

Article 14. *Definition and filing of clinical history.*

1. A clinical history comprises a set of documents relating to an individual patient's health care process, along with identification of any physicians and other

(34) **One would thus have to conclude that the LOPD covers the creation, maintenance and use** of records containing personal health data, provided that one or more of the following circumstances are present:

1. the subject has been informed and given his express consent;
2. it is authorised by statute; or,
3. provision of health care or medical treatments or management of health care services is necessary for prevention or medical diagnosis, provided that data-handling of this type is performed by a health professional subject to a duty of professional secrecy or by any other person likewise subject to an equivalent obligation of secrecy.

Where the data, rather being collected from the interested party, have instead been collected from another source, the Act lays down that the person in charge of the file must inform said interested party, but provides for possible exceptions where: this is envisaged by law; processing the data has historical, statistical or scientific purposes; or informing the interested party is impossible or requires disproportionate efforts, though this last case may only be established by the National Data Protection Agency or its counterpart in a regional context. This is understood to be generally applicable.

Once health-related personal data have been collected, these may then be released to third parties, such as researchers, provided that one or more of the following circumstances are present:

1. the affected party expressly consents thereto;
2. the release is necessary for, among other purposes, undertaking epidemiological studies on the terms stipulated in national or regional health legislation; or,
3. the release is made subject to prior disassociation of data of a personal nature.

It is taken for granted that, in the event of release to researchers, there would be additional compliance with the requirement that the release be made for purposes directly related with the legitimate functions of the party releasing the information and the party to whom such information is released.

professionals who have intervened therein, designed to secure the maximum integration possible of each patient's clinical documentation, at least within the scope of the [health] centre.

2. Each centre shall file its patients' clinical histories in whatever format recorded, be it paper, audiovisual, computerised or of any other type, such that the security, proper safekeeping and retrieval of the information are guaranteed.

3. Health administrations shall establish such mechanisms as will guarantee the authenticity of a clinical history's content matter and of any amendments made thereto, as well as the possibility of the future reproduction thereof.

Article 16. *Uses of clinical history.*

1. A clinical history is an instrument fundamentally aimed at ensuring suitable health care for patients. The centre's health professionals responsible for the patient's diagnosis or treatment have access to the latter's clinical history as a fundamental instrument for providing him with suitable care.

2. Each centre shall establish such methods as may at all times enable access to each patient's clinical history by the professionals that attend him.

3. Access to clinical histories for legal, epidemiological, public health, research or teaching purposes is governed by the provisions of the Personal Data Protection Act 15/99 of 13 December [*Ley Orgánica 15/1999, de Protección de Datos de Carácter Personal*] and the General Health Act [*Ley 14/1986, General de Sanidad*], and any other such provisions as are applicable in each case. Access to clinical histories for these purposes imposes an obligation to preserve the patient's personal identification data separated from those of a clinico-health care nature, so that, as a general rule, anonymity is ensured, save where the patient himself has given his consent to such data not being separated [...]. Access to clinical history data and documents is strictly delimited to the specific purposes of each case [...]

Article 23. *Professional obligations pertaining to technical, statistical and administrative information.*

Aside from the obligations outlined with respect to clinical information, health professionals are under a duty to complete any such protocols, records, reports, statistics and other health care or administrative documentation as may be related to the clinical procedures in which they intervene or be required by the competent health centres or services and health authorities, including any documents linked to medical research and epidemiological information.(35)

(35) **Access to clinical histories for research purposes is thus guaranteed, provided that measures** to separate or disassociate clinico-health care data from personal identification data are adopted. At all events, the LAP refers to the LOPD; and, as was previously seen, the latter allows for the release of clinical history data for epidemiological research without the need for the subject's consent to be sought, particularly where the release is preceded by a procedure to disassociate any data of a personal nature.

INSTRUMENT OF RATIFICATION OF THE CONVENTION FOR THE PROTECTION OF HUMAN RIGHTS AND DIGNITY OF THE HUMAN BEING WITH REGARD TO THE APPLICATION OF BIOLOGY AND MEDICINE (CONVENTION ON HUMAN RIGHTS AND BIOMEDICINE), DONE IN OVIEDO ON 4 APRIL 1997.

(Instrumento de Ratificación del Convenio para la protección de los derechos humanos y la dignidad del ser humano con respecto a las aplicaciones de la Biología y la Medicina (Convenio relativo a los derechos humanos y la biomedicina), hecho en Oviedo el 4 de abril de 1997.)

Also called Oviedo Convention, which has been law in Spain since 1 January 2000(36). Special mention should be made of Article 10:

Article 10. *Private life and right to information*

1. All persons shall be entitled to have their private lives respected insofar as information about their health is concerned.

2. All persons shall be entitled to be advised of any information collected about their health. However, the wishes of individuals not to be informed are to be observed.

3. In exceptional cases, restrictions may be imposed by law, in the patient's interest, on the exercise of the rights contained in Section 2 hereinabove.

BIOMEDICAL RESEARCH ACT 14/2007 OF 3 JULY

(*Ley de Investigación biomédica*).

Although the Act lays down that only research which entails invasive procedures is subject to regulation, the definition given to these types of procedures is very wide. Furthermore, the Act makes relevant contributions as regards many of the elements addressed in these guidelines. Insofar as these guidelines are concerned, the most relevant articles in the Act are as follows:

Article 1. *Aim and scope of application.*

1. With full respect for human dignity and identity and the rights inherent in the person, this Act seeks to regulate biomedical research, and in particular:

a) human health-related studies that entail invasive procedures;
b) donation and use of ovocytes, spermatozoids, pre-embryos, embryos and human foetuses or their cells, tissue or organs for biomedical research purposes and their possible clinical applications;
c) processing and handling of biological samples;
d) storage and transfer of biological samples;
e) biobanks;

(36) **INSTRUMENT of Ratification of the Convention for the Protection of Human Rights and** Dignity of the Human Being with regard to the Application of Biology and Medicine (Convention on Human Rights and Biomedicine), done in Oviedo on 4 April 1997. Official Government Gazette (*Boletín Oficial del Estado – BOE*) No. 251, 20 October 1999.
Chapter V devoted to scientific experimentation must be understood as being solely applicable to research of an experimental or interventional nature.

f) the Bioethics Committee of Spain and other bodies having competence in the field of biomedical research; and,

g) mechanisms for the fostering and promotion, planning, evaluation and co-ordination of biomedical research.

2. In like manner, and exclusively within the ambit of health care, this Act regulates the undertaking of genetic analysis and processing of genetic data of a personal nature.

3. The biomedical research to which this Act refers includes research of a basic and clinical nature, with the exception in the latter case of clinical trials with medications and health products, which shall be governed by provisions specific thereto.

Article 3. *Definitions.*

For the purposes hereof, the terms shown below shall be construed as follows:

— *Genetic analysis:* procedure aimed at detecting the presence, absence or variants of one or more segments of genetic material, which includes indirect tests for detecting a genic product or specific metabolite that is primarily indicative of a given genetic change.

— *Genetic-population analysis:* research aimed at comprehending the nature and magnitude of genetic variations within a population or among individuals in a single group or different groups.

— *Anonymisation:* procedure whereby it ceases to be possible for the nexus to be established between an item of information and the subject to whom it refers, by reasonable means. It is also applicable to biological samples.

— *Consent:* conscious expression of free will validly made by a person with the necessary capacity therefor or by his authorised representative, after duly receiving appropriate information.

— *Anonymous data:* data recorded without any nexus to an identified or identifiable person.

— *Anonymised or irreversibly disassociated data:* data that cannot be linked to an identified or identifiable person, either because the nexus with all information that might identify the subject has been destroyed, or because linkage requires an unreasonable effort, with this being understood to mean the use of a disproportionate amount of time, expense and work.

— *Genetic data of a personal nature:* information about the hereditary characteristics of an identified or identifiable person, obtained by analysis of nucleic acids or other scientific analyses.

— *Coded or reversibly disassociated data:* data not associated with an identified or identifiable person, as a result of the information that identifies the person having been replaced or unlinked, by means of a code that enables the operation to be reversed.

— *Observational study:* study conducted on individuals in respect of whom no treatment or intervention that they may be otherwise undergoing is modified and no other treatment or regimen that may affect their personal integrity is prescribed.

— *Invasive procedure:* any intervention undertaken for research purposes which entails a physical or psychological risk for the subject affected thereby.
— *Minimal risk and burden:* any health impacts and distress which study subjects may suffer, and the effects of which can only be of a mild and temporary nature.

Article 4. *Informed consent and right to information.*

1. Respect shall be shown for the free autonomy of any persons who may participate in or contribute biological samples to biomedical research, for the purpose of which they must have previously given express written consent after duly having received appropriate information.

Information shall be furnished in writing and shall cover the nature, importance, implications and risks of the research, on the terms set forth herein.

Information shall be conveyed to persons with disability under conditions and in formats that are accessible and adequate to their needs.

If the research subject should be unable to write, consent may be given by any means permitted by law which enable his wishes to be placed on record.

2. Consent shall be given by proxy where the person has no legal capacity or is a minor, provided that there are no other research alternatives.

The giving of consent by proxy shall be proportionate to the research to be undertaken and shall be effected with respect for the dignity of the person and for the benefit of his health.

Persons having no legal capacity and minors shall participate as far as possible and in accordance with their age and capacity in decision-making throughout the research process.

3. Any person who participates in biomedical research shall be entitled to revoke his consent at any time, without prejudice to the limitations established hereunder. Persons or bodies that have received such consent shall make available such measures as may be necessary for the effective exercise of this right.

4. Lack of consent or revocation of consent that has been previously given, shall have no adverse effect whatsoever on the subject's healthcare.

5. All persons are entitled to be informed of their genetic data and any such other data of a personal nature as may be obtained during the course of biomedical research, on the terms in which they expressed their wishes. Any person who, for the purpose indicated herein, has contributed biological samples, or in respect of whom other biological materials have been obtained from such samples, is recognised as having the selfsame right.

Respect shall be had for the right of any person to decide that the data referred to above, including any unexpected discoveries that might arise, are not to be communicated to him. Notwithstanding this, where such information, in the opinion of the physician responsible, is necessary to prevent serious harm to the person's health or that of his biological relatives, a near relative or a representative shall be informed, subject to previous consultation with the health care committee, if there be one. At all events, such communication shall be confined exclusively to the data necessary for these purposes.

Article 5. *Protection of personal data and guarantees of confidentiality.*

1. The protection of personal privacy and the confidential handling and processing of personal data resulting from biomedical research activity shall be guaranteed, pursuant to the provisions of the Personal Data Protection Act 15/99 of 13 December [*Ley Orgánica 15/1999, de Protección de Datos de Carácter Personal*]. The same guarantees shall be applicable to any biological samples that are the source of information of a personal nature.

2. Any release of data of a personal nature to third parties unconnected with the medico-health care activity or biomedical research, shall require the interested party's express written consent.

Should that the data obtained from the source subject reveal information of a personal nature about his relatives, release to third parties shall require the express written consent of all interested parties.

3. Any use of data relating to the health of persons for purposes other than those for which consent was given is prohibited.

4. Any person who, in the exercise of his functions in connection with a medico-health care activity or biomedical research, whatever their scope, should gain access to data of a personal nature, shall be under a duty of secrecy. This duty shall endure even though the research or activity may have ceased.

5. Should it not be possible for the results of a research project to be published without identifying the person who participated in or contributed biological samples to it, such results may only be published when said person has given his prior, express consent thereto.

Article 12. *Research Ethics Committees.*

1. To ensure their independence and impartiality, Research Ethics Committees corresponding to those centres that conduct biomedical research must be duly accredited by the competent body in the pertinent Autonomous Region [*Comunidad Autónoma*] or, in the case of centres coming under central Government administration, by the competent body concerned.

For the purposes of accrediting a Research Ethics Committee, the following criteria shall, at minimum, be weighed: its members' independence and impartiality with respect to the sponsors of and researchers engaged in biomedical research projects; and their interdisciplinary composition.

The competent authorities may decide on the creation of Research Ethics Committees designated to perform their functions at two or more centres that conduct biomedical research.

2. The Research Ethics Committee corresponding to any centre shall exercise the following functions:

a) evaluating the qualifications of the principal researcher and research team as well as the feasibility of the project;

b) weighing the methodological, ethical and legal aspects of the research project;

c) weighing the balance of envisaged risks and benefits emanating from the study;

d) monitoring compliance with procedures that enable the traceability of samples of human origin to be ensured, without prejudice to the provisions laid down by personal data protection legislation;

e) reporting, subject to assessment of the research project, any biomedical research which may entail interventions involving human subjects or the use of biological samples of human origin, without prejudice to other reports that may have to be issued. No research project may be authorised or implemented without the prior, mandatory, favourable report from the Research Ethics Committee;

f) drawing up good practice codes in accordance with the principles established by the Bioethics Committee of Spain, and handling any conflicts and dossiers that non-compliance therewith may generate;

g) co-ordinating its activity with that of similar committees of other institutions; and,

h) monitoring confidentiality and performing whatsoever other functions the regulations implementing this Act may assign to it.

3. For the performance of their functions, Research Ethics Committees may demand any information that they may require and, in particular, such information as addresses the sources and amount of funding for studies and the manner in which expenditure is distributed.

4. Research Ethics Committee members must make a statement of their activities and interests and shall abstain from taking part in any deliberations and votes in which they may have a direct or indirect interest in the matter under review.

Article 13. *Consent.*

The conduct of research involving a person shall require the express, specific, written consent of the latter or his legal representative, in accordance with the general principles set forth in Article 4 hereof.

Article 14. *General principles.*

1. Research involving human subjects may only be undertaken in the absence of an alternative of comparable efficacy.

2. Research must not entail disproportionate risks and distress for the human being in relation to any potential benefits to be obtained.

3. Without prejudice to the provisions of the above Section, where research has no possibility of producing results of direct benefit for the research subject's health, such research may only be initiated in the event that it represent a minimal risk and burden for said subject, in the opinion of the Research Ethics Committee tasked with evaluating same.

Article 15. *Information for research subjects.*

1. Any person whose participation in a research project is sought shall previously receive the necessary information, duly documented and in a manner that is

comprehensible, and in cases where persons with disability are involved, in a manner adequate to their circumstances.

2. The information shall include the purpose, detailed plan, distress and possible risks and benefits of the research. Said information shall specify the following points:

a) nature, extent and duration of procedures to be used, and in particular any that may affect the subject's participation;

b) available preventive, diagnostic and therapeutic procedures;

c) measures to respond to adverse events insofar as the subjects who participate in the study are concerned;

d) measures to ensure respect for private life and the confidentiality of personal data in accordance with the requirements envisaged under the legislation governing protection of personal data;

e) measures for gaining access, on the terms envisaged under Article 4.5 hereinabove, to any information of relevance to the subject, which may arise from the study or the overall results;

f) measures to ensure adequate compensation in the event that the subject suffer from some harm;

g) identity of the professional in charge of the research;

h) any future potential use, including commercial use, of the research results; and,

i) source of funding for the research project.

Should these points not be known, there shall be an express commitment to complete the information when such data become available.

3. In the event that the future or simultaneous use of genetic data or biological samples be envisaged, the provisions laid down in Chapters II and III of Title V hereof shall apply.

4. In addition, any person whose participation in a research project is sought shall be informed of the rights and safeguards prescribed in the Act for his protection and, specifically, of his right to refuse consent or withdraw it at any time, without his right to healthcare being in any way affected thereby.

Article 20. *Protection of persons having no capacity to express consent.*

1. In the case of a minor or person with no legal capacity, save where, having due consideration for his degree of judgement, the judicial ruling on said person's lack of capacity should authorise him to give consent to research, investigative research may only be undertaken if the following conditions are met:

a) the research results may produce real or direct benefits for their health;

b) a study of comparable efficacy cannot be undertaken on individuals with capacity to consent;

c) the person who is to participate in the study has been informed in writing of his rights and the limits prescribed herein, as well as the regulations implemented hereunder for his protection, unless said person should not be in a position to receive the information; and,

d) the legal representatives the person who is to participate in the study have given their consent in writing, after duly having received the information stipulated under Article 15 hereinabove. The legal representatives shall take any wishes or objections previously expressed by the person affected into account. In such cases, moreover, all parties shall proceed in accordance with the provisions of Section 1 of Article 4 hereinabove.

2. Where it is foreseeable that research may not produce results of direct benefit for the health of subjects referred to in Section 1 hereof, the study may be authorised by way of exception if, in addition to the requirements contained in subsections b, c and d of the above Section, the following conditions are met:

a) the research seeks to contribute, through significant improvements in the understanding of the individual's disease or condition, to a beneficial result for other persons of the same age or with the same disease or condition, within a reasonable period of time;

b) the research entails a minimal risk and burden for the individual participant; and,

c) authorisation for the research is placed on record with the Attorney General's Office.

Article 21. *Research involving persons unable to consent owing to their clinical situation.*

1. For the undertaking of an investigation in emergency clinical situations, in which the person involved is unable to give consent, the following specific conditions must be fulfilled:

a) research of comparable efficacy cannot be undertaken on persons that are not in this emergency situation;

b) if the research is foreseeably not going to produce beneficial results for the patient's health, then such research should seek to contribute to improving the understanding of the patient's disease or condition significantly, with the aim of benefiting other persons with the same disease or condition, provided that it entail the minimal risk and discomfort for said patient; and,

c) authorisation for the research is placed on record with the Attorney General's Office.

2. Respect shall be had for any objection previously expressed by the patient, which is known to the physician responsible for his care, the researcher or the pertinent Research Ethics Committee at the centre.

3. For the purposes of Section one hereof, investigations in emergency situations shall be deemed to be those in which the person is in no condition to give his consent and, by reason of his state and the urgency of the situation, authorisation cannot be obtained from the patient's legal representatives in time or, where there are no such legal representatives, from any persons who may cohabit with him.

4. Any person who participates in an investigation in an emergency situation or, where applicable, his legal representatives, must be informed as quickly as possible on the terms laid down under Article 4 hereof. In like manner, consent must be sought to continue participating in the research as soon as the patient is in a position to give same.

Article 26. *Duty to inform.*

Pursuant to Article 4.5 hereinabove, if research yields relevant information for the health of participants, said information must be made available to them, something that shall be made effective within the framework of ongoing care or, in the absence thereof, by giving specific counselling and advice.

Article 27. *Information about results.*

1. Once the study has been concluded, the researcher in charge shall submit a summary thereof to the competent authority that issued the authorisation and to the relevant Research Ethics Committee.

2. Research results shall be communicated to the participants, where so requested.

3. On conclusion of the study, the researchers must make the general results of the research known to the public, having due regard to the requirements relating to data of a personal nature referred to by Article 5.5 hereinabove and without detriment to any corresponding intellectual and industrial property rights which may flow from the research.

ANNEXE 3
INTERNATIONAL GUIDELINES AND RECOMMENDATIONS

HELSINKI DECLARATION (EDINBURGH VERSION, 2000)(37)

The principles or rules in which reference is made to the privacy and confidentiality of health data or medical records as a source of information are as follows:

1. .... Medical research involving human subjects includes research involving identifiable human material or identifiable data.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research involving human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail.(38)

2002 CIOMS GUIDELINES

The Council for International Organizations of Medical Sciences (CIOMS) is a non-governmental organisation founded in 1949 with the mandate to collaborate with the UNO and its specialised agencies, and the WHO and UNESCO in particular. This organisation has drawn up a series of guidelines on the ethics governing research involving human subjects. The most relevant are the 1991 International Guidelines for Ethical Review of Epidemiological Studies (currently being reviewed and revised)(39) and the International Ethical Guidelines for Biomedical Research

(37) Two notes of clarification were added in Washington 2002 and Tokyo 2004. Accessible at: http://www.wma.net/e/policy/b3.htm.

(38) From these norms, it can be deduced that under the Helsinki Declaration medical research is only deemed to be research that includes data of a personal nature. If the information used is anonymised, the ethical postulates of the Helsinki Declaration would thus not be applicable. In contrast, where the research involves personal data, informed consent is required. The Helsinki Declaration draws no distinction between experimental and observational research, but the use of the word, "experiment" in Principle 22 suggests that, in all likelihood, the Declaration's drafters are fundamentally thinking of experimental or interventionist research. Nevertheless, this is only an interpretation.

(39) Council for International Organizations of Medical Sciences (CIOIMS). "International Ethical Guidelines for Epidemiological Studies. Accesible at: http://www.cioms.ch/080221feb_2008.pdf.

Involving Human Subjects in 1993, subsequently updated in 2002.(40) Among the latter, special mention should be made of Guideline 18 on the protection of confidentiality:

Guideline 18: Protection of confidentiality

The investigator must establish secure safeguards of the confidentiality of subjects' research data. Subjects should be told the limits, legal or other, to the investigators' ability to safeguard confidentiality and the possible consequences of breaches of confidentiality.

Commentary on Guideline 18

Confidentiality between investigator and subject. Research relating to individuals and groups may involve the collection and storage of information that, if disclosed to third parties, could cause harm or distress. Investigators should arrange to protect the confidentiality of such information by, for example, omitting information that might lead to the identification of individual subjects, limiting access to the information, anonymizing data, or other means. During the process of obtaining informed consent the investigator should inform the prospective subjects about the precautions that will be taken to protect confidentiality. Prospective subjects should be informed of limits to the ability of investigators to ensure strict confidentiality and of the foreseeable adverse social consequences of breaches of confidentiality. Some jurisdictions require the reporting to appropriate agencies of, for instance, certain communicable diseases or evidence of child abuse or neglect [...].

Confidentiality between physician and patient. Patients have the right to expect that their physicians and other health-care professionals will hold all information about them in strict confidence and disclose it only to those who need, or have a legal right to, the information, such as other attending physicians, nurses, or other health-care workers who perform tasks related to the diagnosis and treatment of patients. A treating physician should not disclose any identifying information about patients to an investigator unless each patient has given consent to such disclosure and unless an ethical review committee has approved such disclosure.

Physicians and other health care professionals record the details of their observations and interventions in medical and other records. Epidemiological studies often make use of such records. For such studies it is usually impracticable to obtain the informed consent of each identifiable patient; an ethical review committee may waive the requirement for informed consent when this is consistent with the requirements of applicable law and provided that there are secure safeguards of confidentiality. In institutions in which records may be used for research purposes without the informed consent of patients, it is advisable to notify patients generally of such practices; notification is usually by means of a statement in patient-information brochures. For research limited to patients' medical records, access must be approved or cleared by an ethical review committee and must be supervised by a person who is fully aware of the confidentiality requirements.

(40) Council for International Organizations of Medical Sciences (CIOMS). *International Ethical Guidelines for Biomedical Research Involving Human Subjects* Available at: http://www.cioms.ch/frame_guidelines_nov_2002.htm.

Issues of confidentiality in genetic research. An investigator who proposes to perform genetic tests of known clinical or predictive value on biological samples that can be linked to an identifiable individual must obtain the informed consent of the individual or, when indicated, the permission of a legally authorized representative. Conversely, before performing a genetic test that is of known predictive value or gives reliable information about a known heritable condition, and individual consent or permission has not been obtained, investigators must see that biological samples are fully anonymized and unlinked; this ensures that no information about specific individuals can be derived from such research or passed back to them.

When biological samples are not fully anonymized and when it is anticipated that there may be valid clinical or research reasons for linking the results of genetic tests to research subjects, the investigator in seeking informed consent should assure prospective subjects that their identity will be protected by secure coding of their samples (encryption) and by restricted access to the database, and explain to them this process.

When it is clear that for medical or possibly research reasons the results of genetic tests will be reported to the subject or to the subject's physician, the subject should be informed that such disclosure will occur and that the samples to be tested will be clearly labelled.

Investigators should not disclose results of diagnostic genetic tests to relatives of subjects without the subjects' consent. In places where immediate family relatives would usually expect to be informed of such results, the research protocol, as approved or cleared by the ethical review committee, should indicate the precautions in place to prevent such disclosure of results without the subjects' consent; such plans should be clearly explained during the process of obtaining informed consent.

Also relevant here is the content matter of Guideline 4 concerning informed consent and the circumstances in which it could be dispensed with:

Guideline 4: Individual informed consent

For all biomedical research involving humans the investigator must obtain the voluntary informed consent of the prospective subject or, in the case of an individual who is not capable of giving informed consent, the permission of a legally authorized representative in accordance with applicable law. Waiver of informed consent is to be regarded as uncommon and exceptional, and must in all cases be approved by an ethical review committee.

Commentary on Guideline 4

[...] Waiver of the consent requirement. Investigators should not initiate research involving human subjects without first obtaining each subject's informed consent, unless they have received explicit approval to do so from an ethical review committee. However, when the research design involves no more than minimal risk and a requirement of individual informed consent would make the conduct of the research impracticable (for example, where the research involves only excerpting data from subjects' records),the ethical review committee may waive some or all of the elements of informed consent.(41)

(41) **The 2002 CIOMS Guidelines are thus very open, and leave responsibility for accepting or** not accepting a study that uses medical records containing personal data without the subject's informed consent, to deliberation by an Ethics Committee. In CIOMS 2008 for Epidemiological Studies the following commentary was added:

Categories of epidemiological research for which consent may be waived include:

a. the use of personally non-identifiable materials;

b. the use of personally identifiable materials with special justification;

c. studies performed within the scope of regulatory authority;

d. studies using health-related registries that are authorized under national regulations; and

e. cluster-randomized trials.

The rules and processes for waiver of consent apply also to situations in which permission is obtained from appropriate surrogates for research involving subjects who lack the capacity to consent for themselves (see Guidelines 14 and 15). ..

d. Studies using health-related registries. The creation and maintenance of health- related registries (e.g., cancer registries, databanks of genetic and other anomalies in newborn babies, etc.) provide a major resource for many public health activities, from disease prevention to resource allocation. Several considerations support the common practice of requiring that all practitioners submit relevant data to such registries: the importance of having comprehensive information to provide accurate information about an entire population; the scientific need to include all cases in order to avoid undetectable selection bias; and the general ethical principle that burdens and benefits should be distributed equitably across the population. Hence, registries that are established or officially recognized by governmental authorities usually involve mandatory rather than voluntary collection of data.

Studies using data from such registries (as well as studies that link data from several registries or that combine registry-data with information from publicly available sources) thus involve the use of data that have been compiled without the informed consent of the individuals involved. Such studies should be submitted to an ethical review committee and permission should also be sought from the competent authority that is legally responsible for the maintenance and use of the registry.

RECOMMENDATIONS ON THE ETHICAL ASPECTS OF COLLECTIONS OF SAMPLES AND HUMAN TISSUE BANKS FOR BIOMEDICAL RESEARCH PURPOSES

Ethics Committee of the *Instituto de Investigación de Enfermedades Raras - (CEIIER)*

Date of approval by the Committee, 27 February 2007

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1. INTRODUCTION

Filed away in hospital pathology departments are samples that have been taken from surgical procedures and stored for over a century, without this ever giving rise to dilemmas of an ethical or social nature. With the advent of new technologies that, on the one hand, enable all manner of samples to be stored, including cells that can remain alive indefinitely outside the human body, and on the other hand, enable scientific information of all types, including genetic information, to be obtained from these, a universe of possibilities for research in biomedicine has been opened up. All this has led to the emergence of complex ethical questions, not always free of controversy, and the need to address the justification for historical collections and the establishment of new collections -or human tissue banks- from a bioethical perspective.

Nowadays, collection of human biological matter and related information, as well as storage practices and use of samples in biomedical research, call for special consideration, inasmuch as there are important ethical aspects that concern both the individuals from whom the samples are taken, and the health professionals responsible for handling such samples, researchers and society in general.

Bar the occasional exception, current collections and databases suffer from a lack of definition, and most of the institutions that house them have no written guidelines or agreements governing such activity. The rules for sharing and exchanging information and biological matter are not clear, and awareness of the problems linked to the return of benefits to the research subjects or the community in general, is rather recent. Moreover, it is difficult to separate public from private research, e.g., public- and private-sector researchers might be working along the same lines, thereby giving rise to potential conflicts of interest.

The interests of researchers and society are not necessarily at odds, and development of protocols, good practice guidelines and ethical recommendations will favour society's recognition of and trust in the honesty of research and its altruistic goals.

In the collection and storage of human biological material for research purposes, the principle of autonomy must be preserved, with this being construed as the right enjoyed by every individual to accept or refuse his/her collaboration in research and the principle that no-one should be forced to contribute to such research. Similarly, guarantees are to be given to ensure that participants' rights and well-being in research are protected, and that these are to prevail over the interests of society and science. This implies protection, not only against physical risks, but also against psychological and social risks, and even any moral harm that might flow from the misuse or mismanagement of the ensuing information (e.g., el discriminatory treatment or stigmatisation, communication of the information to third parties, or use that clashes with the values held by participants), with minors and vulnerable subjects deserving special consideration.

Based on a critical review of the most relevant points, this document therefore seeks to draw up some recommendations in the hope that these may serve to guide and foster responsible debate and discussion among all parties involved.

Ethical aspects are inevitably closely linked to legal aspects. Yet, in this document the intention is to lay greater emphasis on the ethical problems that might arise from the collection and use of samples for research purposes. Furthermore, a review of the legislation governing these matters in neighbouring countries was recently published,[1] so that legal aspects will not form a specific topic area of this document. Likewise excluded from these recommendations are ethical problems arising from the use of embryo and foetal tissue, human cells or tissue and by-products, intended for application to human beings, since these are covered by specific guidelines and have their own particular ethical connotations. Similarly, use of samples for forensic purposes is also excluded.

2. BIOBANK FEATURES

Whereas the activity of collecting human matter for clinical and public health purposes is an historical fact in medicine, the concept of a biobank is a very recent development, is applied to collections of samples of widely differing types, magnitudes and purposes (albeit mainly DNA), and, moreover, entails the creation of a related database.[2,3]

Biobank origins and applications are multifold and include: banks prospectively established for a specific research project; banks of samples that are collected as part of health interventions (e.g., collections of samples remaining after neonatal screening programs) and are available for use in future biomedical research; banks set up for forensic and criminal research purposes; and banks established essentially for identification purposes (such as those set up by the armed forces in certain countries). Population banks have also been set up by government decision, with general interest goals such as searching for prevalences of specific genes and their variants in populations, simplifying the search for disease-predisposition biomarkers, examining interactions between environmental genes and factors, improving the discovery of treatment targets, refining disease-prevention strategies or furnishing the necessary data for evidence-based decision-making vis-à-vis individuals, families and populations.

Some of the uses of bio banks were inconceivable just a few years ago, and technological advances have followed upon one another with such speed that it is difficult to forecast all their future research potential.

Tissue or cells (haematic cells, fibroblasts, osteoblasts, etc.) contain DNA and are thus a direct source of information and genetic research. These plus other matter, such as body fluids, serum and urine, are likewise useful for obtaining information on genetic characteristics, for research into genomics, proteomics, metabonomics, cytomics, etc., and also constitute valuable reference material for development of diagnostic and healthcare applications in general.

A good part of the scientific interest in such samples currently centres on genetic information, and a considerable proportion of biobank bibliography refers to banks of DNA already extracted from some biological material.

There is a perception on the part of society that genetic information corresponds to personal information of a more sensitive type, in that, on the one hand, it may contain characteristics that identify the source subject, and on the other, it contains data pertaining to the family (and, sometimes, even the community or population) setting, thereby conceivably giving rise to a sense of apprehensiveness with regard to any possible misuse. As a result, it is claimed that such genetic information calls for exceptional legal treatment and protection measures, a stance that has been dubbed “genetic exceptionalism”. Yet, genetic information forms part of the complete spectrum of health information and does not per se constitute a separate category, i.e., all medical, including genetic, data require quality levels and confidentiality

safeguards of the same calibre as those recently indicated by the European Commission.[4]

From the viewpoint of the relevant ethical principles in biomedicine (justice, non-maleficence, autonomy and beneficence), there are no arguments that would justify a range of differentiated treatment as between DNA banks or the matter they contain and other types of human material biobanks (even though these may not contain DNA) having healthcare, research or public health purposes. The ideas and recommendations contained in this document are, thus, equally applicable to all.

3. RECOMMENDATIONS

1. BIOBANK ORGANISATION AND OPERATION

Recommendation 1. A biobank must have institutional support. The institution that houses the biobank is responsible for its custody and should provide it with a structure, an organisation and a set of written internal rules that regulate its operation and define responsibilities, quality policy and health and/or scientific goals.

It is necessary for a biobank to have a delimited physical space, structure, organisation, scientific management, and an operations rulebook, with allocation of responsibilities, both as regards ensuring bank quality and data protection, and as regards the protocols for incorporation and withdrawal of samples, and for release of samples to researchers at external institutions, be they public non-profit or private-sector institutions. The latter includes release of samples to researchers from other countries, in accordance with any possible international regulations (where these exist) and general biobank policy.

Researchers must request authorisation for the establishment of the biobank, and institutional support for maintenance of the security of the samples and databases in line with prevailing legal requirements. Authorisation must imply the availability of adequate finance.

In the interests of quality, and before embarking upon the collection of samples, Standardised Work Procedures must be established for: 1) obtaining samples; 2) obtaining and recording data associated with such samples, including the system for collecting and filing informed consent records; 3) storage conditions, including the safety mechanisms to guarantee these, temperature monitoring and recording, and safety devices to ensure that the conditions are maintained uninterruptedly; and 4 conditions for the dispatch of samples and accompanying shipping documentation.[5]

Likewise, safety mechanisms must be put in place to ensure the confidentiality and long-term maintenance of the database in accordance with prevailing legislation, with the relevant protocol being duly drawn up.[6,7]

The institution housing the collection or biobank is liable for its custody. Custody implies responsibility for the security and safety of the samples stored, safeguarding donors' interests, and ensuring control over the use and availability of both samples and results. Accordingly, more stringent safeguards and protection can be offered with respect to source subjects' rights, and provision made for attending to the necessary formalities in the event of a change of researchers.

Recommendation 2. Enhanced access to and exchange of information and samples for research should be ensured, provided that confidentiality is protected.

Various international organisations have recommended that samples should be available for the scientific community, and have highlighted the beneficial value of

such collaboration.[8-11] The value of any given collection is proportional to the amount and quality of its samples and related information, and the greatest benefits are to be had from high-quality cooperative research. Hence, provided that confidentiality is protected, fostering access to and exchange of information becomes an ethical imperative. Such activity includes the issue and availability of catalogues listing the samples contained in the biobank.[12] The drawing-up of an annual report of the bank's activities and the research to which it has contributed is a way of formally placing the collection's value, usefulness and ensuing health benefits on record.

Recommendation 3. A biobank should seek the advice of an Ethics Committee, which will ensure compliance with the ethical principles applicable both to biomedical research undertaken in projects that serve to add samples of human origin to the biobank, and to any use that may be made of these.

Both the collection of biological samples for research and the creation of a biobank must be supervised by an independent, multidisciplinary Ethics Committee. Its goal will be to protect the dignity, rights, safety and well-being of the participant subjects, specifically with respect to consent, confidentiality, assessment of the balance between the benefit and risk of the research, and any use to which the material and related data may be put.

The Ethics Committee is to issue reasoned reports of its assessments. Furthermore, the Ethics Committee will be able to advise the institution or researchers on changes in regulations and legislation relating to the topic, and on any possible ethical conflicts that might arise as a result of advances in science and technology applied to human beings and the reconciliation of researchers' and participants' interests.

Recommendation 4. The biobank must avail itself of the services of a scientific committee, which will advise the director on the biobank's management and scientific goals, and draw up the pertinent operating standards. Similarly, the committee will advise on any research activities to be undertaken that are of strategic importance to the optimal use of the biobank, approve any transfer of samples to third parties, and provide guidance on the prioritisation of release of samples.

The institution could consider the possibility of ethical and scientific evaluation being undertaken by a single committee that assisted the biobank's director. Through the actions of an independent body, the ultimate goal would be to ensure respect for ethical rules and responsible management of the samples of human biological material and related databases that go to make up the biobank.

2. DEGREE OF IDENTIFICATION OF SAMPLES

Recommendation 5: When it comes to considering the need to establish a newly-created biobank, the degree of identification of the samples must be defined and justified in terms of the collection's designated goals, purposes and end-use. All these aspects should be submitted the Ethics Committee for review.

Samples can be stored with identifiers, using different degrees of identification, or alternatively, without identifiers. Such samples are deemed identifiable in the former and non-identifiable in the latter case.

2.1. Identifiable

— *Identified:* The samples retain a personal identifier, e.g., name, ID number, or social security number. The researcher has access to same and can link the database and research information directly to the source subject.

— *Identifiable/ coded/ reversibly disassociated/ pseudoanonymised.* These are terms used in the bibliography for samples that retain a code linked to identifiable personal information. In those cases where the researcher does not have access to the code but this is instead under a third party's control, the material is termed, "linked anonymised", which confers enhanced confidentiality protection.

2.2. Non-identifiable

— *Irreversibly anonymised/ irreversibly disassociated*. These are terms used for samples in which -whether per se or in combination with other related data- it has been rendered impossible for the source subject to be identified as a result of a reasonable effort. Such samples are also termed, "unlinked anonymised".

— *Anonymous.* These are samples that are initially collected without personal identifiers and thus retain no link with the subject's identity.

Although biobanks with anonymous data and non-identifiable samples are more manageable and, in principle, pose fewer ethical problems, for certain types of research, such as epidemiological research or the study of given hereditary diseases, the retention of personal identifiers may nonetheless be necessary or convenient. Keeping samples with links to personal, medical or lifestyle data for research purposes may require identifiers to be retained in order to make biomedical research more effective, since this would enable source subjects to be contacted, not only to gather new information but also to link such information to other records. Furthermore, subjects could benefit from research results, where these lead to new therapeutic or preventive options. In such a situation, the storage of samples linked to personal health data makes it essential for maximum protection to be ensured, so as to safeguard the confidentiality of source subjects.

Hence, any decision to remove identifiers irreversibly calls for careful consideration of the benefit-risk relationship because, while there are demographic and clinical data that may accompany an anonymised sample, future research proposals may nevertheless be rendered unviable due to the absence of sample identifiers. Should the decision be taken to anonymise the sample irreversibly, the procedure must then be standardised and protocolised. Both the anonymisation process and the use of non-identifiable samples should also be subjected to an ethical review, since research with non-identifiable samples is not exempt from a bioethical dimension. Moreover, if such samples were to belong to a group or community that was identifiable as such, this would be particularly relevant in view of the harm that could ensue from their use.

3. SAFEGUARDS FOR BIOBANK INFORMATION MANAGEMENT

Recommendation 6: Biobanks must organise an information system and relevant security protocol which ensure that source subjects' personal data, health data and

data drawn from research results are protected in accordance with the prevailing legal regulations, with the confidentiality of the data being guaranteed at all times.

Before embarking upon sample collection, the information to be gathered and the format (manual and computerised) used to store sample-related information must be defined. Both must be guided by respect for the subject's autonomy, right to privacy and confidentiality of data envisaged under the legal regulations currently in force.[7,8] It is therefore necessary for the biobank to draw up a protocol outlining the appropriate measures for ensuring compliance, and laying down the chain of custody of the samples and related database, and any restrictions on access to same. Similarly, provision must be made for measures to ensure compliance with the rights of objection, rectification and cancellation.

4. CONSENT TO PARTICIPATE IN RESEARCH AND HAVE SAMPLES INCORPORATED INTO A BIOBANK

Recommendation 7: Incorporation of prospectively collected biological samples into a biobank and their use for research require the subject's informed consent. Omission of informed consent must be an exception and must, in all cases, be approved by an Ethics Committee. Subjects must be made to understand that their samples are to be used for research purposes.

Informed consent is necessary for participation in research, incorporation of samples into a biobank and their subsequent use in research.

Researchers must in all cases ensure that source subjects receive the appropriate information and understand that the sample collected is to be used for research and not therapeutic purposes, so that no personal benefit will be had from its donation. Source subjects must also be informed that they retain their rights over their samples and data, that confidentiality in the handling of same is guaranteed, and that the projects in which their samples are involved will be evaluated and approved by an independent Ethics Committee.

In exceptional circumstances, e.g., when historical samples are incorporated into a bank, these can be used without the subject's prior consent, though always under the supervision of an Ethics Committee (also see recommendation 16 on post-mortem samples).

Recommendation 8: Once granted, informed consent may be extendable for use of samples and related data in subsequent research, for purposes compatible with those of the project for which they were collected. Nevertheless, researchers would have to offer subjects the opportunity of choice with respect to any subsequent use of their samples.

Stored samples may be used in research conducted at a later date, provided that the aims pursued are compatible with those originally designated. To this end, it is essential that source subjects be able to choose with respect to any such subsequent use. The researcher can offer subjects diverse possibilities, such as: a) having the option to refuse consent for secondary uses; b) permitting any use, but only in cases where the sample is irreversibly anonymised; c) permitting research relating exclusively to a given disease or diseases; d) consenting to the sample being kept, subject to the

condition that, if it were to be used in another project, specific consent would be sought; and, e) having the option to grant blanket consent for the use of samples.

Although blanket or generic consent for future research use of prospectively collected samples that retained their identifiers might be inappropriate, it could nonetheless be sought in special circumstances (e.g., in cases of reuse of samples kept for diagnostic confirmation, where subsequent use for research purposes would represent a benefit for society, yet recontacting source subjects would entail an excessive workload or additional funding).

Recommendation 9: The process of obtaining informed consent requires: complete, specific and suitably adapted information; comprehension of the information; and a freely given, voluntary, express, specific and documented grant of consent by the participant.

The creation of the biobank, as well as its possible uses for future research, must be undertaken with the participants' free, voluntary, express, specific, informed and documented -normally, written- consent.[13] Only in given exceptional situations can this be done without the subject's prior consent.

Source subjects or their legal representatives (see recommendation 10 addressing research on vulnerable subjects) must be informed about the samples to be stored and the data to be recorded, and this information must be supplied individually, be specific to each research project, and be suitably adapted to the individual subject's comprehension ability and cultural characteristics.

Researchers must ensure that, before giving consent, the source subject has understood the information furnished to him/her.

Members of staff who access the data in the performance of their professional functions are subject to the duty to respect confidentiality.[3,14] The researcher or institution responsible must ensure that all such staff members are conversant with these obligations.

The source subject must receive a copy of the briefing documents used and a signed copy of the consent given.

Recommendation 10. Research may be conducted on vulnerable subjects (in particular, minors or those lacking capacity to give consent) provided that: the research results are likely to be of direct benefit to the participants' health; such research may not be conducted on other subjects capable of giving their consent; and, the legal representatives of the intended participant have given their written consent. Where the person lacking capacity is an adult, he/shall participate in the consent procedure to the extent that this is possible. Likewise, account is to be taken of the opinion of minors, in accordance with their age and degree of maturity.

Prospective samples are to taken from children or other vulnerable subjects only where the results of the research are likely to yield a direct benefit vis-à-vis the participant's health, because in such cases the duty of protection must take precedence over the possibility of obtaining valuable knowledge.

The general criterion to be followed is that of "minimum risk", with this being construed as the risk that anyone would assume in his/her daily life and activities. This in turn means that any research which exceeds this minimum level of risk, may only be undertaken if the benefits to be obtained can be expected to offset the risk,

and if such benefits will be for the source subjects. This minimum risk must be evaluated by an Ethics Committee, having reference to all the information available and weighing up the circumstances.

In exceptional cases, where it is not foreseeable that the research results will have a direct benefit on the participant's health, a research project could be authorised when it is aimed at contributing to the enhancement of scientific knowledge about the individual's disease and obtaining results that might afford benefits for other persons who are of the same age or suffer from the same disease, provided that such knowledge cannot be obtained through other subjects capable of giving consent.

The informed written consent of the legal representatives is required. Where the person not having capacity is an adult (over 16 years of age), he/she is to participate in the authorisation process to the extent that this is possible. Similarly, account is to be taken of the opinion of minors, in accordance with their age and degree of maturity.[7,13]

Recommendation 11: The informed consent document must be drawn up. This is to include the consent form and information sheet, both of which must be submitted to an independent Ethics Committee for discussion and approval.

In line with the nature of the information (see recommendation number 8 on blanket consent and subsequent use of samples), the informed consent process is to be set out in a document that must include the form and information sheet on consecutively numbered pages. At minimum, this document must include the following aspects:

1) the purpose and goals of the research project;
2) the potential that the material provides for research;
3) the purpose and goals of the biobank;
4) the procedure and risks associated with the taking of samples;
5) the duration of storage and availability of the sample, once the agreed storage period has expired or in the event of the source subject's death;
6) the institution entrusted with the custody of the biobank;
7) the identity of the researcher and biobank director;
8) the variables to be recorded in the related database;
9) the individuals' right to express their wishes as regards consent for future use of the samples or data for research. Subjects would be entitled to stipulate restrictions for the use of their samples;
10) possible release of the samples and data to other researchers and, where applicable, the conditions for such release;
11) the safeguards for maintenance of confidentiality of any information obtained. Source subject are to be informed regarding any persons who will have access to personal data (e.g., researchers, health professionals, etc.);
12) the right to revoke consent at any time;
13) the right to be informed about the possible elimination or irreversible anonymisation of the samples and data;
14) the individuals' right to decide whether or not they wish to receive information on such research results that concern them and, if so, who, when and how they are to be informed;

15) the possibility that commercial use will be made of material and data, including the results of such research[15] and that the source subject will not receive any financial benefit;
16) should it not be possible for research results to be published without identifying the person who participated in or furnished biological samples for such research, the results shall only be published where there has been prior consent thereto;[3]
17) the expected benefits, if any, for source subjects and their families from their participation in the research, and the risks;
18) the benefits for science and their possible healthcare repercussions;
19) subjects' rights of objection, rectification and cancellation with respect to their data in accordance with prevailing legislation, as well as their right to request the sample's removal or destruction; and,
20) the guarantee that the project has been duly evaluated and approved by an Ethics Committee.

Recommendation 12: Source subjects have the right to withhold their consent to participate and to revoke consent given at any time, without giving explanations of the reasons, and without incurring penalisation of any type.

To withhold or withdraw consent to participate in research or have a sample included in a biobank is the every source subject's right and, thus, may in no case give rise to any form of discrimination against him/her and, in particular, against his/her right to healthcare.

In those cases in which there may be justification for scientifically analysing the reasons for not participating, any request for information about such reasons must be made subsequently, so as to avoid influencing the decision.

Revocation by a patient of informed consent in respect of a sample included in a biobank will lead either to the destruction of same or, alternatively, to the elimination of any identifying element, thereby anonymising the sample, without prejudice to the preservation of data resulting from any research that may have been previously conducted.[3] The question of which of the above two criteria is the more suitable in the circumstances will be for an independent Ethics Committee to decide.

Recommendation 13. In the case of samples obtained for healthcare purposes (whether for diagnostic ends or via other health interventions), their incorporation into a biobank and possible future use in research require the necessary informed consent. This can be sought simultaneously, albeit in a specific and differentiated manner, with consent for the performance of tests or interventions.

Biological samples obtained for healthcare purposes, such as those obtained for genetic testing of different types (invariably DNA, live cells, whether cultivated skin fibroblasts or immortalised lymphoblast cell lines) or those obtained from population screening, such as samples left over from neonatal screening, are very valuable scientific material, and destroying them on conclusion of the healthcare process may entail a considerable loss.

The individuals from whom the samples/data have been obtained must be informed of the latter's possible storage and subsequent use in research, and their consent to and the conditions upon which these two goals may be attained must be

sought and agreed[16,17] (see recommendation 7 on the requirements for obtaining informed consent).

This recommendation refers to biobanks that have been prospectively built up. For management of historical collections, kindly also see recommendation 16 on post-mortem samples.

5. RIGHT TO KNOW AND RIGHT NOT TO KNOW

Recommendation 14. Source subjects must be informed of the results of the research and also, where applicable, of the possibility that unexpected findings may be made in the course of research. Subjects must be offered the possibility of deciding whether or not they wish to receive this information.

The fostering of patient autonomy, a factor that underlies obligations relating to information and informed consent in all research on human beings, includes: on the one hand, the patient's right to know the research results (both expected and unexpected), which in turn entails the researcher's duty to offer such information[18] (see point 14 of the explanatory part of Recommendation 11 on the wording of the informed consent document) and, on the other, consideration of the subject's possible legitimate interest in not wishing to know certain information, such as genetic information obtained from research (ranging from information on discordant paternities to advance knowledge of incurable diseases). An instance of this would be to prevent adverse psychological and major undesirable consequences, particularly where the information were not associated with the ability to alter the circumstances or failed to represent a possible direct advantage for the subject, or alternatively, where the information obtained in the research might be somewhat inconclusive or less than 100% predictive. This consideration has come to be termed the "right not to know".[3]

There is no automatic presumption of this "right not to know". Instead, the affected party must expressly choose to "activate" it. In view of the fact that information which affects an individual, may not do so exclusively and may thus be of potential interest to third parties (family or friends) who have not participated in the study, this right is not absolute and can be restricted where the aim is to avoid a relevant risk to third parties. In this respect, the "right not to know" is not equivalent to the "right to know".

The disclosure of results of genetic research is paradigmatic of such situations.[18] In addition to the above, the often 'translational' nature of research, the development of pharmacogenetics, as well as retrospective research on samples drawn from historical banks, which can produce results of interest to the families many years after being collected, may be a source of ethical problems.

Accordingly, all these considerations must be systematically evaluated, not only by biobank management, but also by researchers and Ethics Committees, when it comes to drawing up the protocols, work procedures and pertinent informed consent procedures. A good solution is for researchers to adopt an *a priori* criterion as to whether or not unexpected discoveries are to be disclosed, regardless of whether such discoveries may or may not have a direct bearing on the source subject's health, and submit this to the Ethics Committee for consideration, particularly insofar as the principle of non-maleficence is concerned.

Should it prove possible to foresee or predict the type of discoveries that may be made in a prospective research project, it would be advisable for this matter to be agreed with the subject beforehand. In retrospective research, the criteria to be followed must be established previously and submitted to the Ethics Committee for review.

As in routine healthcare procedures, in any case where research might include genetic testing, the information and disclosure processes should be take place within a genetic counselling context.

6. CONSENT FOR RELEASE OF SAMPLES TO THIRD PARTIES

Recommendation 15. Where applicable, release of samples to third parties should take into account the conditions agreed in the informed consent. In all cases, release of samples for other research is to be evaluated by an Ethics Committee, which will consider the project's scientific validity, as well as the need, if any, for renewal of consent to be sought.

The criteria for release of samples to third parties are to be stipulated in the procedure for obtaining informed consent. The principal researcher and the institution are responsible for custody of samples and for safeguarding the interests of source subjects. Hence, they should draw up a global policy for release of samples, considering that:

1) samples are only to be released when the applicant researcher submits a research project approved by an Ethics Committee;
2) the Ethics Committee of the institution housing the biobank is to evaluate such projects for which release of samples (and related data) is sought, and shall, where applicable, approve the release of the samples and demand compliance with the conditions agreed upon in the informed consent document or renewal thereof (see recommendation 7 and explanatory text); and,
3) a balance is to be sought between development of research and maintenance of the biobank's scientific value. In this respect, the scientific committee may advise on release priorities in the event of any conflict.

7. TAKING OF POST-MORTEM SAMPLES

Recommendation 16. For extraction of biological matter from a deceased person for research purposes, account is to be taken of appropriate previous consent given by the subject or, where this is lacking, by his/her relatives or legal representatives. No samples are to be taken from a deceased person for research if the deceased person is known to have objected to it. [2]

Under Spanish law, body organs or other anatomical specimens may be extracted from deceased persons for therapeutic or scientific purposes, in any case where such persons have failed to leave an express objection thereto on record.[19,20] Nevertheless, a good practice from an ethical standpoint is to seek informed consent from relatives or legal representatives to biological samples being obtained from deceased persons and preserved for research purposes.

Furthermore, relatives should be apprised of and consulted on the possible implications for their interests of any research done on identifiable samples. They must also be informed of what type of sample is to be preserved, who is to safeguard it, where it is to be stored and in what type of research it could be used.

8. MANAGEMENT OF HISTORICAL COLLECTIONS OF BIOLOGICAL SAMPLES

Recommendation 17. Historical collections of biological samples obtained for healthcare or research purposes must meet the established requirements and recommendations for setting up a new biobank, with the new samples being incorporated subject to the necessary request for informed consent. Conditions laid down for retrospective use of samples require evaluation by the Ethics Committee.

When identified or identifiable sample are to be used, researchers must recontact the source subject in order to seek new consent, except where the Ethics Committee deems that there are special circumstances for exemption, with the necessary precautionary measures being taken.

Post-mortem samples are to receive the same consideration.

It is commonplace for hospital diagnostic departments to house a great number of stored human biological samples which were collected for healthcare or research purposes and stored without informed consent being sought. In such cases, the advisability or inadvisability of preserving these historical samples will have to be assessed, taking into account their scientific value and the difficulties of bringing together collections in some cases (e.g., rare diseases), provided that the terms of use are regulated and the relevant ethical and legal aspects are borne in mind.

Collections of anonymous or irreversibly anonymised samples do not pose special problems of use, since they could hardly harm source subject if they are unidentifiable.

In the case of existing non-anonymous or non-irreversibly anonymised collections, researchers should make a reasonable effort to contact the source subjects, in order to obtain new consent for the projected study. However, this measure may be impracticable, either because it calls for a disproportionate effort or invalidates the study as a result of selection biases being introduced, or because it could cause psychological harm to the extent that the subject is made to relive a painful personal or familial situation. In such cases, an Ethics Committee could evaluate and, where applicable, approve the use of biological samples without specific consent, on condition that the following requirements were met, namely: that the proposed research is of relevant scientific interest; that the samples are necessary for the attainment of the research goals; that there is no evidence to show the source subject would have raised any objection to the sample being used for research; and, finally, that the research will in no way prejudice the source subject's interests.

In collections of historical samples, it is possible that some of the source subjects may have died. This fact cannot justify a policy of unrestricted access on the grounds that there is no longer any risk or harm for the individual, for the simple reason that, if research on post-mortem samples were to involve relevant information about live relatives, this could prove harmful to them.

If an individual restricted the use of his/her samples for research when he/she was alive, these restrictions will continue in force after his/her death.

9. OWNERSHIP AND MARKETING OF SAMPLES AND RESEARCH RESULTS

Recommendation 18. Surrender of samples by source subjects must be without financial consideration. Neither source subjects nor their family or friends are to obtain financial benefit from the surrender of the sample, or any commercial benefits that might flow from the results of the research.

There are two reasons to justify why surrender of samples should be disinterested: the first of these is the conviction, present within our cultural context, that organs and tissue, including blood, should neither be bought nor sold,[21] since it is thought that the human body should not be the source of financial gain, since this would mean treating persons as objects and so violating respect for their dignity.

The second reason is as follows: source subjects give their sample voluntarily and retain certain rights with respect to the sample and its destination. The act of surrender is not exactly the same as the act of donation, yet the principle governing surrender of samples is the same as that relating to donation of organs, i.e., disinterested and altruistic solidarity. The source subject offers a valuable asset for science and society, in most cases without seeking to obtain personal therapeutic benefit. No financial benefits are to be had, since this would nullify the act of surrender-donation. Yet, this is no bar to the person from whom the sample has been extracted being entitled to receive compensation for any expenses he/she may have incurred or any losses that he/she may have suffered, provided that such compensation does not constitute remuneration.

In contrast, technical tasks such as the taking of samples, storage, etc., may indeed give rise to a legitimate and reasonable remuneration for the biobank. In this respect, it would also be licit for the biobank to receive compensation for the costs of collection, storage and dispatch of samples where these are requested by third parties (release to other researchers, pharmaceutical companies, etc). However, to delimit this practice in a satisfactory manner is difficult and so, with the aim of achieving a balance that would be fair for source subjects and any possible benefits that third parties might obtain, it would be desirable if consideration were instead given to the avenue of shared enjoyment of benefits (see recommendation 19 on return of benefits to the community).

Insofar as the results obtained from research are concerned, the ensuing benefits (stemming from the marketing of a drug or its by-products) are deemed to correspond to those who promote or conduct the research. The source subject of the sample used in the research should neither receive any financial benefit nor have any legal right over such research.[3,22] It is advisable for source subjects to be informed of this aspect in the context of procuring informed consent (see recommendation 11 on the information to be given in the process of obtaining consent).

10. RETURN OF BENEFITS TO THE COMMUNITY

Recommendation 19. The ultimate aim of any benefits yielded by the results of research based on biological samples is the improvement of the community and shared enjoyment of such benefits should thus be sought. Return of benefits to the community is a response to the principles of equity and justice.

In order to achieve an equitable balance between source subjects and third parties (pharmaceutical, biotechnological and other companies), and as the key to the moral legitimacy of research, the most appropriate thing would be to endeavour to ensure shared enjoyment of the benefits,[11,23] which may take any of the following forms:

— special assistance to the persons and groups that have taken part in the research;
— access to medical care;
— provision of new diagnostics, facilities for new treatments or drugs stemming from the research;
— support for health services;
— capacity-building facilities for research purposes;
— preferential access to therapies developed as a result of their contributions to the biobank; and also,
— participation in therapies in line with the principle laid down by the Human Genome Organisation (HUGO) Ethics Committee[23] in its Statement of Benefit-Sharing, which requires investment of 1% to 3 % of net research earnings in public foundations, e.g., in the expansion of medical or humanitarian aid infrastructures.

Knowledge obtained through research is a benefit for the community and an asset that, in all justice, should be shared and should contribute to humanity as a whole. Hence, the results should be published without any undue delay, disseminated critically and supported by the appropriate documentation. It is advisable for the principal results to be published in a way that ensures they reach the study participants and other interested members in the community in which the study was conducted.[24]

4. REFERENCES

1. MARTÍN URANGA A, MARTÍN ARRIBAS MC, DI DONATO JH, POSADA DE LA PAZ M. *Las cuestiones jurídicas más relevant en relación con los biobanks. Una visión a la legislation de los países miembros del project Eurobiobank.* Instituto de Salud Carlos III. Madrid 2006.
2. COUNCIL OF EUROPE. *Recommendation Rec (2006)4 on Research on biological materials of human origin.* Council of Europe; 15 March 2006.
3. BOLETÍN DE LAS CORTES. *Proyecto de Ley de Investigación Biomédica 121/104,* BOCE núm. 104, 22/9/2006. [Biomedical Research Bill. Parliament Gazette]
4. EUROPEAN COMMISSION. *25 recommendations on the ethical, legal and social repercussions of genetic testing.* European Commission; 2004.
5. BOLETÍN OFICIAL DEL ESTADO. *Real Decreto 65/2006 por el que se establecen requisitos para la importación y exportación de muestras biológicas.* BOE núm 32, 7/2/2006. [Royal Decree laying down requirements for the import and export of biological samples. Government Gazette]
6. BOLETÍN OFICIAL DEL ESTADO. *Ley Orgánica 15/1999, de Protección de Datos de Carácter Personal.* BOE núm 298, 13/12/1999. [Personal Data Protection Act]
7. BOLETÍN OFICIAL DEL ESTADO. *Real Decreto 994/1999, por el que se aprueba el reglamento de medidas de seguridad de los ficheros automatizadas que contengan datos de carácter personal.* BOE núm 151, 11/6/1999. [Royal Decree governing the regulation of security measures for automated personal-data files]
8. HUMAN GENOME ORGANIZATION (HUGO): *Statement on the Principled Conduct of Genetic Research.* Genome Digest 1996;32: 2.
9. WORLD HEALTH ORGANIZATION (WHO): *Proposed international guidelines on ethical issues in medical genetics and genetic services.* Geneva: WHO; 1997.
10. COUNCIL OF EUROPE. *Recommendation No. R (89) 4 on Collection of Epidemiological data on Primary* Health Care. Int Dig Health Leg 1990; 41: 148.
11. UNESCO – *International Bioethics Committee: Universal declaration on the human genome and human rights.* Paris; 11 November 1997.
12. EUROPEAN SOCIETY OF HUMAN GENETICS. *Data storage and DNA banking for biomedical research: technical, social and ethical issues.* Recommendations of the European Society of Human Genetics. Eur J Hum Genet 2003; 11 (Suppl 2): S8-S10.
13. COUNCIL OF EUROPE. *Additional protocol to the convention on human rights and biomedicine concerning biomedical research.* Article 19. Council of Europe. Strasbourg; 2005.
14. BOLETÍN OFICIAL DEL ESTADO. *Ley Orgánica 10/1995, del Código Penal: artículo 199; sobre el deber de revelar.* BOE no. 281, 24/11/1995. [Penal Code: Disclosure of professional secrets]
15. OFFICIAL JOURNAL OF THE EUROPEAN UNION. *Directive 98/44/CE of the European Parliament and of the Council of 6 July 1998, on the legal protection of biotechnological inventions.* Considerando 26. OJCE L 213, 30/7/98.
16. LABERGE C, KHARABOYAN L, AVARD D. NEWBORN SCREENING, *Banking and Consent.* Gen Edit 2004 Vol II (3). [cited 12 March 2007] www.humgen.umontreal.ca.
17. SOCIEDAD ESPAÑOLA DE BIOQUÍMICA CLÍNICA Y PATOLOGÍA MOLECULAR (SEQC). COMISIÓN DE ERRORES METABÓLICOS CONGÉNITOS. COMITÉ CIENTÍFICO. PÀMPOLS ROS T, CORTÉS CASTELL E Y DULÍN IÑIGUEZ E. *Protocol para la retención, almacenamiento y usos posteriores de las muestras residuales de sangre seca recogida sobre papel adsorbente en los programas de cribado neonatal.* Química Clínica 2006; 25 (2) 97-103. [Protocol for the retention, storage and subsequent uses of residual dry blood samples collected on adsorbent paper in neonatal screening programmes. Proposal for regulation from a professional perspective: Spanish Clinical Biochemistry & Molecular Pathology Society. Scientific Committee. Committee for Congenital Errors of Metabolism]
18. KNOPPERS BM, JOLY Y, SIMARD J, DUROCHER F. *The emergence of an ethical duty to disclose genetic research results: international perspectives.* Eur J Hum Genet. 2006 Dec;14(12):1322.

19. BOLETÍN OFICIAL DEL ESTADO *Ley 30/1979, de 27 de octubre sobre extracción y trasplante de órganos.* Artículo 5.2. BOE núm. 266, 6/11/1979.[Organ Transplant and Extraction Act]

20. BOLETÍN OFICIAL DEL ESTADO. *Real Decreto 411/1996 por el que se regulan las actividades relativas a la utilización de tejidos humanos.* Artículo 8. BOE núm. 72, 23/3/1996. [Royal Decree governing activities relating to the use of human tissue]

21. COUNCIL OF EUROPE. *Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine.* Article 21. Council of Europe. 1997.

22. GODARD B, SCHMIDTKE J, CASSIMAN J-J AND AYMÉ S. *Data storage and DNA banking for biomedical research: informed consent, confidentiality, quality issues, ownership, return of benefits. A professional perspective.* Eur J of Hum Genet 2003; (Suppl 2): S88-S112.

23. THE HUMAN GENOME ORGANISATION (HUGO) *Ethics Committe.* Statement on Benefit-Sharing, April 9 2000. [cited 12 March 2007]. www.hugo-international.org/Statement_on_Benefit_Sharing.htm

24. EUROPEAN FEDERATION OF THE INTERNATIONAL EPIDEMIOLOGICAL ASSOCIATION (IEA): *Good epidemiological practice (GEP) proper conduct in epidemiological research.* Berne: European Federation of the International Epidemiological Association; 2002 (updated June 2004).