

Original article

Ethical Review of Research Protocols: Experience of a Research Ethics Committee

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ABSTRACT

Introduction and objectives: Since the passing of the Law on Biomedical Research it has been the task of research ethics committees to assess the methodological, ethical and legal aspects of all research carried out on humans or human biological samples. The aim of the study is to analyze the experience of the Research Ethics Committee for the Carlos III Health Institute in the ethical assessment of research proposals involving human subjects.

Methods: A descriptive study of the observations made on research projects registered between June 1, 2009 and June 30, 2010.

Results: About two thirds of the projects evaluated in this period needed some type of amendment. Most of the comments were aimed at improving informed consent and procedures to ensure confidentiality (153 observations, 57.6%). Fifty (18.9%) observations related to the principles of beneficence and nonmaleficence. The remaining observations involved incomplete or incorrect documentation, or requests for additional information.

Conclusions: The largest number of observations related to the autonomy of research participants. It is important for researchers to be aware of the principle of autonomy in their interaction with study participants. Research ethics committees should therefore promote greater understanding of ethical issues on biomedical research.

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Revisión ética de proyectos. Experiencia de un comité de ética de la investigación

RESUMEN

Introducción y objetivos: Desde la aprobación de la Ley de Investigación Biomédica, se incorpora al ámbito de actuación de los comités de ética de la investigación la evaluación de los aspectos metodológicos, éticos y legales de toda investigación que se realice en seres humanos o con muestras biológicas humanas. El objetivo de este estudio es plasmar la experiencia del Comité de Ética de la Investigación del Instituto de Salud Carlos III en la evaluación ética de los proyectos de investigación en seres humanos.

Métodos: Estudio descriptivo de las observaciones realizadas a los proyectos de investigación registrados desde el 1 de junio de 2009 al 30 de junio de 2010.

Resultados: Aproximadamente dos tercios de los proyectos evaluados en este periodo necesitaron algún tipo de enmienda. La mayor parte de las observaciones se dirigieron a la mejora del consentimiento informado y de los procedimientos de garantía de confidencialidad (153 observaciones, el 57,6%). Las observaciones relacionadas con los principios de beneficencia y no maleficencia fueron 50 (18,9%) y el resto, con deficiencias de la información aportada sobre aspectos concretos del estudio o de carácter administrativo.

Conclusiones: El ejercicio de la autonomía de los participantes en las investigaciones ha supuesto la mayor parte de las observaciones realizadas. Es necesario que los profesionales sanitarios se sensibilicen con las implicaciones del respeto al derecho de autonomía de los participantes. Los comités de ética de la investigación, por lo tanto, deben promover la toma de conciencia sobre las cuestiones éticas de la investigación biomédica.

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Palabras clave:

Bioética

Comité de ética de la investigación

Consentimiento informado

Muestras biológicas

Protección de datos

Revisión ética

INTRODUCTION

Since the Spanish Law on Biomedical Research (LBR) was approved in 2007 (Law 14/2007, issued on July 3, 2007), there have been substantial changes to the processes used to evaluate the

ethical acceptability of research involving human subjects. All studies must now have been approved by a research ethics committee (REC), and prior consent must be obtained from all individuals to participate in the study. The RECs have a mission to protect the dignity, rights, safety, and well-being of subjects who participate in biomedical research and to offer public accountability through the publication of their decisions.¹

Although existing guidelines had established the principles to be applied in the ethical approval of clinical trial protocols,^{2,3} the

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Abbreviations

LBR: Law on Biomedical Research
 REAWC: Research Ethics and Animal Welfare Committee
 REC: research ethics committee

LBR extended those principles to all studies involving human subjects. Thus, evaluation of the methodological, ethical, and legal considerations associated with all research involving human subjects now falls within the purview of RECs. Such research includes the collection, donation, and use of cells, tissues, and organs for research purposes.

The increasing complexity of biomedical research in human subjects can generate a variety of ethical conflicts, which can be further compounded by the difficulties of complying with the new legislation. The RECs must therefore be in a position to help identify appropriate ways in which to balance the interests of research against the need to protect the rights of study participants, and ultimately to work towards meaningful advances in science that remain adapted to the needs of society.

The Research Ethics and Animal Welfare Committee (REAWC) of the Carlos III Health Institute was established in 2006 as a reference REC for the Institute and its constituent foundations: the Spanish National Cancer Research Center (*Centro Nacional de Investigaciones Oncológicas*), the Spanish National Cardiovascular Research Center (*Centro Nacional de Investigaciones Cardiovasculares*), and the Center for Research on Neurological Diseases (*Centro de Investigación de Enfermedades Neurológicas*). Its mission is to evaluate research involving human subjects, including samples or data obtained from them, as well as the appropriateness of animal procedures. In 2009, in order to adapt to the LBR and to improve some aspects of its functioning, changes were made in relation to the nature, functions, composition, and working procedures of the committee. The committee for the evaluation of research involving human subjects is currently made up of 9 members from a range of specialties: medicine, bioethics, nursing, epidemiology, and philosophy, as well as social work (as a lay member of the committee).

Due to the nature of the institute as a public research organization, and to the number of foundations it supports, the committee receives a large number of studies involving the use of biological samples, many of which were stored and collected prior to the introduction of the LBR or that have been obtained from other centers.

Now that 2 years have passed since the LBR was introduced, the committee can reasonably be expected to have gained sufficient experience to develop stable working practices. The aim of this study was to describe the experience of the committee over a 1-year period. To this end, all of the research projects submitted to the committee for approval during that period were analyzed.

METHODS

Data were collected on all of the protocols submitted to the REAWC for evaluation between June 1, 2009 and June 30, 2010. All observations made regarding either ethical or administrative issues associated with each protocol were recorded. The number of versions presented for each protocol was recorded along with the mean time taken until approval.

The observations were initially grouped into 3 blocks according to their relationship with:

1. The principles of bioethics (principle of autonomy, beneficence, nonmaleficence, and justice).⁴
2. Defects in the supporting documentation.
3. Requests for more information on a specific aspect of the project.

The principle of autonomy recognizes the capacity of the individual to take personal decisions. In the observations related to this principle, we included those linked to information provided in the process of obtaining informed consent as well as others that are of particular importance for biomedical research. These included protection of privacy and confidentiality; information on rights to access, correct, cancel, or oppose personal data, and the procedures to exercise those rights; and the right to know the results of the research and to consent to the donation of biological samples and data.

The principles of beneficence and nonmaleficence are linked to the moral obligation to maximize possible benefit and minimize potential harm associated with research. According to this aspect, we considered: *a*) observations aimed at minimizing risks and potential harm to participating subjects and maximizing potential benefits, specifically in research involving subjects unable to provide consent and in vulnerable populations; *b*) those in which care of the subject could be jeopardized by research interests; *c*) those related to inadequate classification of samples (coded/anonymized samples), and *d*) protection against harm.

In relation to the principle of justice, which encompasses impartiality and equity, we took into account the concept of distributive justice, which has particular implications in the selection of research subjects, as well as in appropriate distribution of risk and burden on the one hand, and potential benefit on the other.⁵

Procedures for the Evaluation of Projects

Submission, consideration, evaluation, and communication of findings mainly took place via e-mail. Once the documentation (application, research protocol, patient information leaflet and informed consent form, and any other supporting documentation) had been received, it was given a record number that could be used to follow the documents throughout all stages of the evaluation process. The complete documentation was sent to all members of the committee. To ensure adequate and rigorous ethical evaluation, 2 members of the REAWC were designated as taking primary responsibility for evaluation of the project. They were responsible for presenting a detailed review to the full committee as a basis for discussion. When disagreements occurred, the committee secretary indicated those points of disagreement and facilitated discussion in order to reach agreement on the response to be given to the investigator.

If the research project met all of the ethical and legal requirements, a favorable report was made and sent to the principal investigator, including a copy of the original report by mail and a PDF copy by e-mail. If observations were made on the project, a response to the investigator containing proposals for improvement was prepared.

In the case of projects involving a committee member, that member does not participate in the deliberation process, as is standard practice. The same procedure is followed when an investigator has a direct relationship with a member of the committee.

The committee has access to a web page containing documents and guidelines for investigators.⁶

Analysis

A descriptive analysis of the results was undertaken. Discrete variables were expressed as percentages or, when the spread of the data was large, as median (interquartile range).

RESULTS

During the period analyzed, 66 projects were registered: 32 during 2009 and 34 during 2010. In 22 (33%) of those, no observations were made. A total of 265 observations were recorded. These were classified as follows: 203 (76.5%) related to the principles of bioethics; 41 (15.6%) due to incomplete or incorrect documentation; and 21 (7.9%) to request additional information regarding an aspect of the project.

The median number of observations per project was 4 (mode, 0; range, 0–17). A median of 2 versions were presented (1; 1–4), and the process of evaluation approval lasted a median of 13.5 days (13; 1–95).

Observations relating to the principle of autonomy accounted for 57.6% of the total. Of those, observations related to information provided in the process of obtaining informed consent accounted for 62%; the remaining 38% were related to other types of problems affecting the principle of autonomy. Observations relating to the principle of nonmaleficence accounted for 18.9% of observations. Incomplete or incorrect documentation accounted for 15.6% of observations, and requests for additional information on projects for 7.9% (Table 1).

The main problems relating to informed consent forms were the absence of a consent form (6 projects), a lack of specificity in the requested consent (17 observations), and the absence of information on the involvement of the participants in the study (14 observations). The lack of a form to provide authorization for storage (and information on the storage location of samples), the subsequent use of samples, or the provision of samples to third parties, as well as permission for the subject to be contacted again in the future should additional information be required, accounted for 50 observations (52.6%) (Table 2).

A total of 19 observations were made regarding the measures taken by the investigator to protect the privacy and confidentiality of the information collected.

In terms of information on the rights of the participants, 9 documents were observed not to contain information on the right to be informed of the results of the study, either individually or generally, or the manner in which the participant would be informed. In terms of rights to access, correct, cancel, or oppose—which, in general, is included in all such documents—requests were made for specification of the procedures to follow in order to exercise those rights on 27 occasions. Of note are the observations made regarding the requirement for specific consent to donate samples to third parties from nonaccredited biobanks (3 projects) (Table 3).

Fifty observations (18.9%) were made in relation to the principles of beneficence and nonmaleficence. Only 5 studies (9 observations) were evaluated in which the study population involved children or vulnerable subjects. The observations made in this group were aimed at guaranteeing compliance with article 20 of the LBR regarding the protection of persons who are unable to provide express consent and to prevent potential harm when children reach the age of consent.^{7,8}

On 26 occasions, clarifications were requested regarding inadequate classification of the samples or data (coding/anonymization). Thirteen observations were made regarding the requirements to protect against potential harm in projects involving invasive interventions. Finally, in 2 studies the care of

Table 1

Classification Frequency, and Percentages of Observations on Research Projects Submitted for Evaluation

<i>I. Relating to the principle of autonomy</i>	153 (57.6)
Informed consent	95 (62)
Other issues relating to the principle of autonomy	58 (38)
<i>II. Relating to the principles of beneficence and nonmaleficence</i>	50 (18.9)
Research involving subjects unable to provide consent or vulnerable groups	9 (18)
Priority of patient care over the interests of research	2 (4)
Management of coded/anonymized samples	26 (52)
Insurance against harm	13 (26)
<i>III. Incomplete documentation</i>	41 (15.6)
<i>IV. Request for additional information regarding a specific aspect of the project</i>	21 (7.9)
Total	265 (100)

Table 2

Observations Relating to the Principle of Autonomy. Informed Consent

<i>I. Absence of informed consent form</i>	6 (6.3)
<i>II. Lack of specificity in the informed consent form</i>	17 (17.9)
<i>III. Lack of information relating to participation of the subject in the study</i>	14 (14.7)
<i>IV. Absence of consent for storage and final destination of the samples/data</i>	50 (52.6)
<i>V. Clarification regarding the type of samples, their consequences, and provision of genetic counseling</i>	8 (8.5)
Total	95 (100)

Table 3

Other Observations Relating to the Principle Of Autonomy

<i>I. Guarantees of confidentiality</i>	19 (32.8)
<i>II. Failure to indicate the participant's right to know the results and the procedure to follow to receive that information</i>	9 (15.4)
<i>III. Description of the procedures to follow to exercise the rights of access, correction, cancellation, and opposition</i>	27 (46.6)
<i>IV. Provision of samples to third parties by unaccredited biobanks</i>	3 (5.2)
Total	58 (100)

the patients could have been adversely affected by research interests; in these cases the investigators were reminded of their responsibility in this area.

DISCUSSION

The LBR serves as a reference point for all types of research, not only that involving clinical trials of drugs. Furthermore, it led to the establishment of RECs to evaluate the methodological, legal, and ethical appropriateness of the study protocols and protect the rights, safety, and well-being of all subjects who participate in biomedical research. Independent evaluation of the scientific merit of a research project, its compliance with state legislation, and its ethical acceptability are essential to guarantee that these principles are respected.

The LBR takes into consideration legal requirements and international treaties such as the Declaration of Helsinki,⁹ the Convention on Human Rights and Biomedicine (the Oviedo Convention),¹⁰ along with its Additional Protocol Concerning

Biomedical Research from the European Council.¹¹ It therefore offers strong guarantees regarding the protection of the rights of individuals who participate in a biomedical research study. Nevertheless, research involving human subjects often presents moral conflicts. The RECs must therefore evaluate and discuss each application carefully and endeavor to achieve consensus based upon commonly accepted ethical principles relating to research: the principles of autonomy, beneficence, nonmaleficence, and justice. In practical terms, these principles are applied by assessing the risk-benefit ratio, informed consent procedure, selection of samples, and protection of confidentiality.

This study analyzed the experience of a REC in the evaluation of research projects following the introduction of the LBR. Although a large number of articles have been published on the activity of RECs in approving clinical trials of drugs,^{12,13} few have addressed their activity in evaluating other types of project. The steering committee on bioethics has also undertaken self-evaluation of its work and working practices in an effort to identify areas for improvement.¹⁴

The results of our study indicate that approximately two thirds of the projects presented to a REC contain some sort of ethical or administrative defect. Most of the observations made by the REC were related to the principle of autonomy, mainly the provision of informed consent, but also regarding the principles of beneficence and nonmaleficence.

It is important that the rights and well-being of participants in biomedical research is guaranteed. This implies protection not only against physical risks but also against the inappropriate use or management of the resulting information¹⁵ (eg, discriminatory or stigmatizing use, communication of information to third parties, or uses inconsistent with the values of the participating subjects). This is of particular importance in research involving children or vulnerable adults.

In our study, very few of the applications involved research that included children; nevertheless, recommendations have been made that in the process of obtaining informed consent, the legal guardian should be advised of the need to inform the child. Consequently, once the child has reached the age of consent, he or she should be informed about samples that have been donated and information held from the proposed study, as well as the results of the study in which he or she participated. These considerations are of particular importance in cohort studies and studies of genetic disorders.^{7,8}

Vulnerable individuals also include students or workers linked to the investigator or promoter of the study, as was the case in 2 of the projects. Because these individuals are closely linked to the investigators, there is pressure on them to participate in research, and this can lead to an imbalance between burden and benefits. When such individuals agree to participate, whether it is justified or not, they may be inappropriately influenced by the possibility of preferential treatment or by fear of disapproval or reprisals if they refuse. In these situations, RECs must demand special justification for the invitation of vulnerable individuals to participate in a research study, and if those individuals are selected, the appropriate measures to protect their rights and well-being must be strictly applied.¹⁶

Protection of personal data and maintenance of confidentiality are fundamental requirements in biomedical research involving human subjects.^{17,18} Although most institutions have well-established procedures to declare databases containing personal information to the relevant data protection agencies, researchers are often unaware of them. The RECs must ensure that personal information collected in the course of biomedical research is considered confidential and therefore protected. The investigators must justify the nature and level of identifiability of the data, as well as the corresponding measures to maintain confidentiality.

Samples and personal data must be held separately (coded or anonymized and unlinked) according to the proposed needs of a specific study. Nevertheless, there can be confusion over the difference between coded data (reversibly disassociated data that retains the capacity to be identified with its owner) and anonymized data (irreversibly disassociated), as well as over the implications of that distinction. This occurred in 26 of the observations included in our study. If coded data are used, the participants must be informed and given clear information regarding who will have access to the identifying information; they must also consent to the use of their data in this manner. If irreversibly disassociated (anonymized) data are used, the participants should be informed of this and the implication that the information will no longer be identifiable in the future explained; again, they must consent to this use.

A notable observation in our study was the lack of specificity related to informed consent. Seventeen observations related to a lack of information regarding the involvement of the participants in the study and 14 to a failure to adequately explain the reason that consent was being sought. In general, misconceptions exist about the nature of informed consent. There is a tendency for investigators to simply copy sections directly from guidelines on preparation of informed consent forms,⁶ without understanding the aims of obtaining informed consent (none other than to indicate an agreement between the investigator and the participant that an independent decision has been made to participate in the study having first understood the objectives of the study and the nature of the involvement). This explains, for instance, why participants may be informed of all of the rights of the donor without providing details on how to exercise those rights or who to contact in order to withdraw their samples, or the finding that the consent form does not provide options or checkboxes in which to indicate decisions.

When samples are collected prospectively and their future use is envisaged, it is recommended that in the process of obtaining initial consent the different options regarding the future destination and use of the samples or data (storage in a biobank, inclusion in a collection or destruction after completion of the project, and restrictions on their use in certain types of research) should be explained to the participant. In this way, participants will be in a position to make informed decisions and indicate their chosen options in the consent form. In all cases, unconditional consent or a lack of direct indication on the form would be unacceptable.

The REAWC receives a large number of applications for approval of studies involving biological samples, and many of these samples were collected prior to introduction of the LBR or have been obtained from other centers. A large proportion of the observations made in relation to informed consent were due to the lack of consent for the use of "historical" samples stored with identifiable personal information. The recommendations of the REC in these cases have been for the investigator to take reasonable measures to obtain consent from the donors to use their samples and data for research purposes. Nevertheless, the LBR recognizes the possibility of use without consent if samples have previously been anonymized (second transitory disposition of the LBR), and this option has therefore also been offered to investigators.

Another issue that has generated extensive discussion is the donation of samples from "biobanks" to third parties. On this point, the LBR establishes that accredited biobanks can provide samples and associated data for use in research projects that have been approved by the ethics committee of the biobank. Given that the royal decree establishing the minimum requirements for authorization and registration of biobanks has not yet been approved, centers that donate samples must act in accordance with the general criteria indicated in the LBR. In other words, provision of samples requires approval of the specific project or line of research

for which the samples are requested by the ethics committee of the center in which the samples were obtained.

It would not be sufficient to obtain approval from the REC of the biobank (which has not yet been authorized) until the special regimen for provision of samples by biobanks is approved.

As mentioned, consent to storage of samples in a biobank must be clearly separated from consent to participation in the study, and it must be possible to provide consent independently (eg, by marking separate checkboxes). It should be specified where the samples will be stored, who is responsible for the “biobank” or the collection of samples, and the use to which the samples will be put in future studies (specifying, if relevant, possible lines of investigation). Study participants must receive guarantees that the samples will be handled and used responsibly and confidentially.

Evaluation of research projects has centered mainly on the assessment of those ethical and legal considerations related to the information given to the patient and the provision of informed consent. The evaluation is mainly carried out electronically, thereby reducing the mean time from receipt of the application to provision of a final report.

CONCLUSIONS

Our experience shows that healthcare professionals need to have greater awareness of the rights of individuals who participate in biomedical research. In particular, they need to be active in protecting the right to autonomy. Therefore ethics committees have an important role to play in promoting ethical practices in biomedical research and in identifying solutions to ensure that the interests of researchers and society do not take precedence over the rights of the participants.

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CONFLICTS OF INTEREST

None declared.

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