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SPECIAL ARTICLE

Research ethics: From principles to practical aspects

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Abstract Any research conducted on human beings or human biological samples requires a prior ethical assessment to avoid risks and problems for all involved parties. The legislation in this regard is very broad and emphasizes the safeguarding of patient rights in relation to the universal principles of autonomy, beneficence and justice. The present article reviews the regulations applicable to clinical trials, observational studies with drugs, biobank projects or any other type of study that may be conducted in the health care field. It also addresses the role of research ethics committees, data protection and the foundations of scientific integrity.

PALABRAS CLAVE
Ética;
Investigación;
Legislación;
Protección de datos

Ética en investigación: de los principios a los aspectos prácticos

Resumen La realización de cualquier investigación con seres humanos o sus muestras biológicas requiere una valoración ética previa con el fin de evitar riesgos y problemas a todos los actores del proceso. La legislación al respecto es muy amplia y hace hincapié en la preservación de los derechos de los pacientes en relación con los principios universales de autonomía, beneficencia y justicia. En este manuscrito se revisan las normativas sobre ensayos clínicos, estudios observacionales con medicamentos, proyectos de biobanco o cualquier otro tipo de estudio que se pueda realizar en el ámbito de la salud. Así mismo se analiza el papel de los comités de ética en Investigación, la protección de datos y las bases de la integridad científica.

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Introduction

Biomedical research must be conducted in adherence to universally recognised ethical principles that ensure the advancement of knowledge, the improvement of the human condition and the progress of society, always safeguarding the dignity and autonomy of human beings. More recently, these principles have addressed aspects such as the protection of personal data, animal welfare and environmental conservation.[1]

We do not need to go far back in history to understand the need for ethics in research. Articles like the one published by Beecher[2] in 1966, or experiments like the Tuskegee study conducted through 1972 in Alabama, in the United States,[3] evince the need to be uncompromising in this regard. In the field of paediatrics, as would be expected, research has also not been free of ethical problems. The example of the scandal of experiments at the Willowbrook State School[4] and the role of Saul Krugman[5] in this controversy are studied in every course in bioethics, and they are but a sample of a myriad instances that could be cited.

Although there have been radical changes in our world since the publication of the ethical principles of the Declaration of Helsinki of the World Medical Association in 1964[6] or the Belmont Report in 1978,[7] today it is still necessary to ensure strict controls in any research project, however small and banal it may seem, if we are to avoid repeating errors of the past. For this reason, we thought it would be relevant to publish an article summarising theoretical and practical aspects concerning research ethics and, to some extent, scientific integrity in our society.

Spanish legislation on the subject

The Spanish legislation on the subject is extensive and varied, although some aspects still require further elaboration (Table 1). Although the Spanish Constitution already mentions the right to privacy, it is Law 41/2002 on the Autonomy of the Patient[8] that heralded a series of legal texts that have been momentous in shaping research ethics in Spain. This law recognises the right to the confidentiality of personal health data for every individual, and denies everyone the right to access personal health care data without the prior authorization of the individual in question, thus setting the foundations of the concept of informed consent that has since become indispensable in biomedical research.

The second fundamental law on the subject is Law 14/2007 on Biomedical Research,[9] which, in addition to stating in its preamble that health care research is crucial with the aim of improving the lives of the citizens, mandates that a research ethics committee (REC) evaluate any biomedical research project involving interventions on human beings or the use of biological samples. Thus, the scope of the ethical oversight assigned to RECs in the legislation on clinical trials was expanded to apply to all biomedical research. This law dictates that research in humans can only be conducted if there is no experimental alternative of comparable efficacy, must not entail risks or discomfort that are disproportionate in relation to the potential benefits to the subject and, if it does not offer potential direct benefits for its subjects, can only be undertaken if the REC responsible for evaluating the project considers that it poses a minimum risk to them.

A Royal Decree (RD) that is key in biomedical research is RD 1716/2011 regulating biobanks.[10] This RD regulates all aspects pertaining to the handling, storage and circulation of biological samples. It establishes that biological samples of human origin collected for research may be stored in private collections, gathered for specific projects or custodied in biobanks. Each type of collection must be managed differently, and biobanks require an external ethics committee to evaluate sample procurement requests from an ethics standpoint, in addition to an external scientific committee to evaluate the research projects.

But it is unquestionably RD 1090/2015, which regulates randomised controlled trials (RCTs) with medicines, specific ethics committees for the evaluation of research involving medicines (REC-M) and the Registro Español de Estudios Clínicos (REec, Spanish Register of Clinical Trials),[11] that has had the greatest impact on the functioning of RECs. It was to fulfil the requirements of Regulation EU No 536/2014 and resulted in a significant overhaul in the work of the committees and the imposition of the single opinion directive. This RD specifies in detail the role of REC-Ms in the evaluation of methodological aspects, the appropriateness of the facilities, the qualifications of the principal investigators, information documents and informed consent as well as aspects pertaining to data protection, securing insurance and the collection of evaluation fees.

Continuing in chronological order, it is important to now mention Order SSI/81/2017[12] regarding the right to privacy of the patients in relation to students and residents in medical and health sciences, which establishes that students will not be allowed access to patient data that has not been anonymised unless the patient provides informed consent first.

Organic Law 3/2018 of 5 December on the Protection of Personal Data and Guarantee of Digital Rights (OLPD-GDD), written for the application of Regulation (EU) 2016/679 on the protection of personal data at the European level, regulates the handling of data in medical and health research in its additional provision 17.[13,14] This law establishes the role of RECs in the evaluation of studies that use health-related data, whether personally identifiable, pseudonymised or anonymised, imposing new requirements regarding the composition of these committees, such as the need to have a data protection delegate or, failing that, an expert on the subject.

On the other hand, RD 957/2020 on Observational Studies with Medicines (OSMs) used in humans[15] replaced Order SAS/3470/2009[16] regulating observational postmarketing studies (PMSs) with medicines (EPA). This RD not only changed the term PMS to OSM, but also modified and simplified the steps required to approve postmarketing surveillance studies, which are needed to ensure the effectiveness and safety of drugs in real world clinical practice, eliminating the requirement of obtaining the classification as such a study from the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS, Spanish Agency of Medicines and Medical Devices) as an initial step.

We end this review with the recently approved statutes of the Comité Español de Ética de la Investigación (Spanish Committee of Research Ethics),[17] an organization instituted

Table 1 Spanish legislation on the subject of research ethics.

Legislation	Key points
Spanish Constitution of 1978	– Right to honour, personal and family privacy and control of one's own image
Law 41/2002 on the Autonomy of the Patient	– Confidentiality of health care data – Need of authorization to access data – Foundations of informed consent
Law 14/2007 on Biomedical Research	– Mandates evaluation by a REC of any study involving human beings or human biological samples
Royal Decree 1716/2011 regulating biobanks	– Specifies the functions and operation of biobanks
Royal Decree 1090/2015 regulating clinical trials with medicines	– Regulates RCTs according to European directives – Single opinion directive – Introduces REC-Ms
Order SSI/81/2017 on the right to privacy of patients in relation to medical and health science students and residents	– Prohibits access to patient data to students, unless the data are dissociated or the patient provides informed consent
Law 3/2018 on the Protection of Personal Data and Guarantee of Digital Rights	– Provision 17 refers to health-related data – Establishes the legal definition of anonymised and pseudonymised data – RECs must have an expert on data
Royal Decree 957/2020 on Observational Studies with Medicines used in humans	– Replaces the concept of postmarketing surveillance studies by the concept of observational study with drugs, modifying applicable regulations

RCT, randomised control trial; REC, research ethics committee; REC-M, ethics committee for the evaluation of research involving medicines.

in 2011[18] and dependent on the Consejo de Política Científica, Tecnológica y de Innovación (Council of Scientific, Technological and Innovation Policy), an official, independent and advisory body on matters related to research ethics and scientific integrity. The functions of this committee, among others, are to establish the general principles for the development of good practice guidelines in research, including recommendations to prevent, detect, address, avoid and resolve conflicts of interest.

Documents of a non-legal nature/ethical guidelines

The Prussian regulation of 1900, developed in response to the Neisser case, is considered the first modern document of research ethics in the West.[19,20] Later on, the Nuremberg code of 1947 was the first to clearly and concisely specify the essential principles in research: voluntary consent, good to society, previous results justifying the experiment, avoidance of unnecessary physical or psychological suffering, a favourable risk-benefit assessment, protection of the patient, qualification of researchers, right to drop out of the study and possibility of stopping the study if needed.[21] Still, there were limitations to the Nuremberg code, chief among them that it applied only to experimentation on healthy voluntary participants, prioritised the interests of society, placed limitations on the conditions under which participants could drop the study and did not contemplate external ethics reviews. It provided general recommendations that had no legal weight.

The World Medical Association issued the ethical principles of the Declaration of Helsinki in 1964, which has since been updated in successive editions, the latest approved in Fortaleza (Brazil) in 2013. The purpose of the Declaration was to safeguard the dignity of the individual and the privacy of patients in research. It established several requirements for an experimental study to be considered appropriate, among which were the prior development of a full experimental protocol, reviewed and approved by an independent ethics committee, with subsequent oversight and monitoring of the study. It also required that studies be led by qualified professionals and that the benefits of the study outweigh its risks. Before agreeing to participate, subjects had to be informed in detail about the procedures involved in the experiment, any risks and any circumstances that may affect the outcomes. Participants had to give their consent freely, and could not be subject to coercion, pressure or deception. In the case of individuals not fully able to provide it, consent has to be provided by the legal guardian. Lastly, the Declaration states the obligation of researchers to publish complete and accurate results, whether they are favourable or not.

In 1978, the Belmont Report (ethical principles and guidelines for the protection of human subjects in research) was published in response to the infamous Tuskegee

Table 2 Chief non-legal documents on research ethics.

Document	Key points
Prussian Regulation(1900)	– First modern document on the subject
Nuremberg Code (1947)	– Establishes the core principles of research ethics
Declaration of Helsinki of the World Medical Association (1964)	– Establishes requirement of a study protocol and evaluation by a REC – Qualified professionals – Risk/benefit assessment – Information and free consent of participants – Allows consent by a legally authorised representative – Commitment to publication of results
Belmont Report (ethical principles and guidelines for the protection of human subjects in research) (1978)	– Essential principles of bioethics: autonomy, beneficence and justice
International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS-WHO) (1982)	– Ethical issues in developing countries – Core principles and commentary on their interpretation
Good Clinical Practice (GCP) guidelines (1995)	– International guidance (Europe, Japan and USA) for performance of RCTs –Duties and responsibilities of the different involved parties –Standard procedures for designing, conducting, recording and reporting RCTs
Universal Declaration on Bioethics and Human Rights of the UNESCO (2005)	– Expanded the scope to include research ethics

CIOMS, Council For International Organizations Of Medical Sciences; GCP, Good Clinical Practice; RCT, randomised clinical trial; REC, research ethics committee; UNESCO United Nations Educational, Scientific and Cultural Organization; WHO, World Health Organization.

syphilis study, conducted in African Americans, which was denounced by the press in the United States. The report established the 3 core principles of bioethics: respect for persons (autonomy), beneficence and justice.[7,22]

The principle of autonomy stands for the right of all persons to be treated as autonomous individuals and those who cannot be autonomous to be protected, and contemplates autonomy as changing throughout the lifespan and potentially requiring re-evaluation. Autonomy is the core principle underlying the need to provide information about the study and obtain informed consent. The principle of beneficence, and its subsequent elaboration in the principle of nonmaleficence, refers to the obligation to assess the risk and benefits in every instance and to maximise the latter. This principle is the reason that RECs always assess the study design and methods. Lastly, the principle of justice calls for equitable selection of study participants with an equitable distribution of the expected risks and benefits.[23,24]

In 1982, the Council for International Organizations of Medical Sciences (CIOMS) published the International Ethical Guidelines for Biomedical Research Involving Human Subjects in collaboration with the World Health Organization (WHO). These guidelines, whose fourth edition was published in 2016, addressed research ethics issues particular to developing countries, comprising 25 core guidelines with commentaries.[25,26]

Another essential document was the Universal Declaration on Bioethics and Human Rights of the United Nations Educational, Scientific and Cultural Organization (UNESCO) of 2005, which addressed the safeguarding of human dignity and rights, autonomy, vulnerability and integrity, privacy and confidentiality, justice and equity, the respect for diversity, social responsibility, solidarity and cooperation, the protection of future generations and the protection of the environment.[27]

To conclude, we ought to mention the Good Clinical Practice (GCP) guideline of the de la International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). It is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Adherence to it ensures the protection of the rights, safety and wellbeing of trial participants and the reliability of results. Among the ICH guidelines for the performance of clinical trials, it is worth highlighting the E11 document, which focuses on the paediatric population.[28,29]

Table 2 presents a succinct summary of the most important non-legal documents on the subject.

Research ethics committees

The origin of RECs in Spain goes back to the second half of the past century. Although in some hospitals there were already groups that assessed ethical aspects in some manner, the earliest reference to their existence in Spain in a legal context is found in a royal decree from 1978 (RD 944/1978),[38] since followed by several royal decree and ministerial orders that have been specifying their functions and structure, related legislation and definitions. But it was the Law on Biomedical Research of 2007[9] that established the

Table 3 Research ethics committees (RECs and REC-Ms) in Spain (register of the Agencia Española del Medicamento y Productos Sanitarios).

Autonomous Community	Scope of REC-M	REC-M	REC
Andalusia	Province/autonomous community	8	4
Aragón	Autonomous community	1	
Asturias	Autonomous community	1	
Cantabria	Autonomous community	1	
Castilla León	Local/province	9	
Castilla-La Mancha	Local	6	1
Catalonia	Local	24	5
Valencia	Local	12	9
Extremadura	Autonomous community	1	1
Galicia	Autonomous community	1	3
Balearic Islands	Autonomous community	1	
Canary Islands	Province/local	2	
La Rioja	Autonomous community	1	
Madrid	Local/regional	18	1
Murcia	Local	2	2
Navarre	Autonomous community	1	
Basque Country	Autonomous community	1	5
Total		90	31

REC, research ethics committee; REC-M, ethics committee for the evaluation of research involving medicines.

requirement of approval by a REC for any study involving research in human beings or human biological samples.

Royal Decree 1090/2015 defines RECs as independent bodies with a multidisciplinary composition whose main purpose is to safeguard the rights, safety and wellbeings of participants in biomedical research and to provide a guarantee of ethical treatment by ruling on the research proposal, taking into account the perspective of laypersons, and particularly of patients or patient organizations.

This decree (RD 1090/2015) defined the role of REC-Ms (RECs with the authority to authorise RCTs with pharmaceuticals), in addition to their structure and functioning, stipulating that they need to be accredited by the competent health authorities and that neither the REC-M as a whole or any of its members can receive any direct or indirect remuneration from trial sponsors. Furthermore, in relation to the evaluation of RCTs conducted in minors, it established that REC-Ms had to include members who were experts in paediatrics or seek consultation regarding clinical, ethical and psychosocial issues specific to the field of paediatrics.

The duty of these committees (RECs or REC-Ms) is to uphold scientific and methodological rigour, verify adherence to current regulations and ethical principles and guarantee the wellbeing and safety of research participants. It is also responsible for evaluating any relevant modifications to authorised studies and to monitor them until the final report is produced. Although initially this only applied to the evaluation of RCTs, the scope of these committees currently includes the evaluation of any study involving human participants, patient data or human biological samples, regardless of its methodological design and/or complexity.

According to the AEMPS register for 2021, there are 90 accredited REC-Ms in Spain[39] (Table 3). The scope of REC-Ms is very broad, for instance, there are committees of regional or provincial scope, and committees that operate at the hospital or institutional level. The only committees accredited to evaluate studies involving drugs or medical products and devices are REC-Ms, while RECs can evaluate all other types of projects.

In 2011, the Asociación Nacional de Comités de Ética en Investigación (ANCEI, National Association of Research Ethics Committee)[40] was created in Spain, which has since carried out relevant activity in the promotion of institutional collaboration, representation and education. The association collaborates with RECs/REC-Ms in the development of their activity, promoting teamwork and developing guidance materials that are published periodically.

Handling of personal data

The protection of the privacy of individuals subject to research (their image, personal information and dignity) and the confidentiality in the management of personal data by researchers are two key aspects in conducting research in the field of health.

The Law on the Autonomy of the Patient[8] restricts the use of data documented in health care records, and consent must be obtained from patients to use this information for any other purpose, including research. Thus, informed consent is essential in research ethics as a means to guarantee adherence to the principle of autonomy.

However, as we will discuss further down, the conditions to access to health care records with research purposes have been modified with the enactment of the OLPD-GDD, including the specific research scenarios contemplated in the law as exceptions in which access to health records is permitted without consent.

Regulation (EU) 2016/679 on data protection (REUDP) establishes the principles that apply to the handling of health-related data, generally allowing their use for sci-

Table 4 Requirements imposed by Organic Law on the Protection of Personal Data and Guarantee of Digital Rights (OLPD-GDD 2018) to the handling of health-related data i biomedical research.

1. Consent	The pertinent parties (or legal guardians) can provide consent for the use of their personal data for the purposes of medical or health care research.
2. Waiver of informed consent in exceptional situations	Health care authorities involved in public health surveillance can carry out scientific studies without the consent of the involved parties if the research in the event of a public health threat in which the research is of exceptional relevance.
3. Reuse of data	The reuse of personal data for health research is considered lawful and compatible with ethical standards if the data are used for purposes or in fields of research related to the original study.
4. Pseudonymization	–The team responsible for performing the pseudonymization and the research team must be technically and functionally separate – The pseudonymization of data entails a commitment to confidentiality and to prevent reidentification. – Access to third parties must be denied. – Reidentification will only be allowed in the event of a health problem or threat to the safety of the subject, a serious threat to the subject's rights, or to guarantee provision of health care.

entific purposes. However, although this use is allowed, it must be proportionate to the intended purpose, comply with data protection rights and be subject to the measures necessary to protect the rights and interests of research subjects.

The OLDP-GDD[13] adopts the principles of the REUPD, referring for the need of transparency and adherence to the law in data handling, limits to the use of data based on its purposes, the minimization and accuracy of data processing, limitations to the amount of time data can be stored and the integrity and confidentiality of the data. The second section of additional provision 17 is devoted to data handling in health and medical research, specifying that it requires prior approval by a REC and establishing certain requirements (Table 4).

A recent novelty, the pseudonymization of data allows access to health records for research purposes without requiring consent from the subjects. The rationale for requesting a waiver of informed consent must be presented to the competent committee, which must determine in each case whether the established conditions are met. Committees can also waive the need for consent in retrospective studies in which the effort involved in obtaining consent is excessive for the purposes of the study (deaths, changes in address) if loss of that data could be a source of bias in the results, and only if anonymization or pseudonymization of the data are not possible.

When it comes to clinical trials in the paediatric age group, it is important to take into account the need to obtain information supported by evidence to prevent the use of unapproved drugs or of approved drugs for indications not approved in the summary of product characteristics.[41–43] In this regard, we ought to highlight the directive of the Law on Biomedical Research that establishes that ''consent by proxy may be acceptable when the individual is not legally competent on account of disability, impairment or being a minor, and only if there are no other alternatives for research'' and that ''individuals with disability and minors will participate to the extent possible and depending on their age and capacities in decision-making throughout the research process.''

Scientific integrity and codes of good scientific practice

The National Declaration on Scientific Integrity signed by the Confederación de Sociedades Científicas de España (COSCE, Alliance of Scientific Societies of Spain), the Comisión de Rectores de Universidades Españolas (CRUE, Committee of Spanish University Rectors) and the Centro Superior de Investigación Científica (CSIC, Spanish National Research Council) in 2015 states that scientific integrity is directly associated with the scientific rigour, excellence and quality of research in addition to ethical and responsible conduct in scientific work.[30] Therefore, we speak of scientific integrity when we discuss the principles, values and responsibilities that are the basis of good scientific practice. The Singapore Statement of 2010[31] established 4 core principles: honesty in all aspects of research, accountability in the conduct of research, professional courtesy and fairness in working with others and good stewardship of research on behalf of others.

Scientific integrity must be maintained at every step of the research process, from the formulation of questions to the communication of results, through the methodological design, execution and analysis of the findings, without forgetting that it also applies to the work setting, both in the interaction between professionals and in their qualifications. Integrity is a moral imperative that is shared by every party involved in research, including investigators, administrators, institutions, funding agencies, publishers and scientific societies.

The pursuit of scientific integrity has led to the development of what is known as good scientific practice guidelines, which, while not replacing legislation, offer directives to reinforce ethical standards, promote research quality and prevent misconduct. Nearly all societies or institutions related to research have a good scientific practice code,

of which the Code of Conduct for Research Integrity the All European Academies (ALLEA)[32] is the most salient.

As regards good practices, we ought to highlight the need to maintain the strictest policy in relation to the disclosure of conflicts of interest by all involved parties. Conflicts of interest are situations in which the judgment of a professional in relation to a primary interest (integrity) may be unduly influenced by a secondary interest. These conflicts must be disclosed and are not considered misconduct if they are identified and taken into account. There are many types of conflicts of interest, not only financial, and transparency must be exercised. Not only researchers, but also academics, journal editors, evaluators, administrators and committee members have the duty to disclose their interests to the public so that there are no concerns regarding their independence and integrity.[33,34]

Poor scientific practice is not limited to the classic triad of plagiarism, fabrication and falsification, but can affect any rung in the chain of scientific output. One example is the integrity of the members of the editorial teams of scientific journals, who play an essential role in the dissemination and publication of results.[35–37]

Although the functions assigned explicitly to RECs concern the evaluation, along with the subsequent approval or refusal, of research proposals and the monitoring of the studies underway, we must not forget their role in education and in guaranteeing the scientific integrity of research, as reflected by the Law on Biomedical Research. In this regard, we ought to highlight the work of committees in the dissemination of knowledge related to ethical and legal aspects of biomedical research aimed at researchers with the purpose of ensuring adherence to ethical standards in research.

Some practical conclusions

Any study in human beings or using human biological samples must be approved by a REC/REC-M. This applies both to studies of large scope or importance (clinical trials, observational drug studies, studies with biological samples and/or medical devices or products) and to any project that involves handling patient data, whatever its type, significance or purpose, ranging from student theses to retrospective observational studies intended for publication or whose results are to be presented in any other form.

Prior approval of these studies by a committee is indispensable, as it guarantees adherence to ethical principles and the legal rights of participants, in addition to their methodological quality and safety, with the premise that if a study is not methodologically correct it cannot be considered ethically acceptable.

Obtaining informed consent from patients should be standard practice for any research project. The confidentiality of patient data must be protected throughout the entire process and, while there are situations in which a waiver may be requested, informed consent is an essential component of guaranteeing adherence to the ethical principle of autonomy. In any case, the request for exemption from informed consent must be evaluated by a REC/REC-M, which will decide on the matter after investigating the particular circumstances of the study.

Research ethics committees and REC-Ms play a key role in the advancement and implementation of ethical and legal aspects aimed at guaranteeing the scientific integrity of research by promoting values such as objectivity, independence, impartiality or transparency. Health care professionals, researchers and research ethics committees must ensure that scientific progress unfolds in adherence with ethical and legal principles, rigorously upholding the rights of research participants.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Consejo Superior de Investigaciones Científicas (CSIC). Éticaen la investigación. [Accessed 18 March 2023]. Available from: http://www.csic.es/es/el-csic/etica/etica-en-la-investigacion.
2. Beecher HK. Ethics and clinical research. N Engl J Med. 1966;274:1354–60.
3. Curran WJ. The Tuskegee syphilis study. N Engl J Med. 1973;289:730–1.
4. Goldby S. Experiments at the Willowbrook State School. Lancet. 1971;1:749.
5. Krugman S. The Willowbrook hepatitis studies revisited: ethical aspects. Rev Infect Dis. 1986;8:157–62.
6. Asociación Médica Mundial. Declaración de Helsinki de la AMM. Principios éticos para las investigaciones médicas en seres humanos. [Accessed 18 March 2023]. Available from: http://www.wma.net/policy/.
7. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report. [Accessed 18 March 2023]. Available from: http://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/index.html.
8. Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica. [Accessed 28 June 2023]. Available from: http://www.boe.es/buscar/act.php?id=BOE-A-2002-22188.
9. Ley 14/2007, de 3 de julio, de Investigación biomédica. [Accessed 28 June 2023]. Available from: http://www.boe.es/buscar/act.php?id=BOE-A-2007-12945.
10. Real Decreto 1716/2011, de 18 de noviembre, por el que se establecen los requisitos básicos de autorización y funcionamiento de los biobancos con fines de investigación biomédica y del tratamiento de las muestras biológicas de origen humano, y se regula el funcionamiento y organización del Registro Nacional de Biobancos para investigación biomédica (+ Orden ECC/1404/2013 – modificación). [Accessed 28 June 2023]. Available from: http://www.boe.es/buscar/doc.php?id=BOE-A-2011-18919.
11. Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos. [Accessed 28 June 2023]. Available from: http://www.boe.es/buscar/doc.php?id=BOE-A-2015-14082.
12. Orden SSI/81/2017, de 19 de enero, por la que se publica el Acuerdo de la Comisión de Recursos Humanos del Sistema Nacional de Salud, por el que se aprueba el protocolo mediante el que se determinan pautas básicas destinadas a asegurar y proteger el derecho a la intimidad del paciente por los alumnos y residentes en Ciencias de la Salud. [Accessed 28 June 2023]. Available from: http://www.boe.es/eli/es/o/2017/01/19/ssi81.

13. Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales. [Accessed 28 June 2023]. Available from: http://www.boe.es/buscar/doc.php?id=BOE-A-2018-16673.
14. Reglamento (UE) 2016/679 del Parlamento Europeo y del Consejo, de 27 de abril de 2016, relativo a la protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de estos datos y por el que se deroga la Directiva 95/46/CE (Reglamento General de Protección de datos). [Accessed 28 June 2023]. Available from: http://www.boe.es/buscar/doc.php?id=DOUE-L-2016-80807.
15. Real Decreto 957/2020, de 3 de noviembre, por el que se regulan los estudios observacionales con medicamentos de uso humano. [Accessed 28 June 2023]. Available from: http://www.boe.es/eli/es/rd/2020/11/03/957.
16. Orden SAS/3470/2009, de 16 de diciembre, por la que se publican las directrices sobre estudios posautorización de tipo observacional para medicamentos de uso humano. [Accessed 28 June 2023]. Available from: http://www.boe.es/eli/es/o/2009/12/16/sas3470.
17. Real Decreto 53/2023, de 31 de enero, por el que se aprueba el Reglamento del Comité Español de Ética de la Investigación. [Accessed 28 June 2023]. Available from: http://www.boe.es/eli/es/rd/2023/01/31/53.
18. Ley 14/2011, de 1 de junio, de la Ciencia, la Tecnología y la Innovación. [Accessed 28 June 2023]. Available from: http://www.boe.es/eli/es/l/2011/06/01/14/con.
19. Patuzzo S, Goracci G, Ciliberti R. Thomas Percival. Discussing the foundation of medical ethics. Acta Biomed. 2018;89:343–8.
20. Vollmann J, Winau R. The Prussian regulation of 1900: early ethical standards for human experimentation in Germany. IRB. 1996;18:9–11.
21. Vollmann J, Winau R. Informed consent in human experimentation before the Nuremberg code. BMJ. 1996;313:1445–9.
22. Carroll TW, Gutmann MP. The limits of autonomy: the Belmont Report and the history of childhood. J Hist Med Allied Sci. 2011;66:82–115.
23. Adashi EY, Walters LB, Menikoff JA. The Belmont Report at 40: reckoning with time. Am J Public Health. 2018;108:1345–8.
24. Sánchez López JD, Cambil Martín J, Luque Martínez F. Informe Belmont. Una crítica teórica y práctica actualizada. J Healthc Qual Res. 2021;36:179–80.
25. Organización Panamericana de la Salud y Consejo de Organizaciones Internacionales de las Ciencias Médica. Pautas éticas internacionales para la investigación relacionada con la salud con seres humanos, Cuarta Edición. Ginebra: Consejo de Organizaciones Internacionales de las Ciencias Médicas (CIOMS); 2016.
26. Macrae DJ. The Council for International Organizations and Medical Sciences (CIOMS) guidelines on ethics of clinical trials. Proc Am Thorac Soc. 2007;4:176–8.
27. Declaración Universal sobre Bioética y Derechos Humanos de la Organización de las Naciones Unidas para la Educación, la Ciencia y la Cultura (UNESCO) de 2005. [Accessed 28 June 2023]. Available from: https://unesdoc.unesco.org/ark:/48223/pf0000146180_spa.locale=es.
28. European Medicines Agency. ICH E6 (R2) Good clinical practice - Scientific guideline. [Accessed 28 June 2023]. Available from: http://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice-scientific-guideline.
29. Kaur S, Choy CY. Ethical considerations in clinical trials: a critique of the ICH-GCP guideline. Dev World Bioeth. 2014;14:20–8.
30. Consejo Superior de Investigaciones Científicas (CSIC), la Confederación de Sociedades Científicas de España (COSCE) y Crue Universidades Españolas. Declaración Nacional sobre Integridad Científica. [Accessed 28 June 2023]. Available from: http://www.csic.es/es/actualidad-del-csic/se-presenta-la-declaracion-nacional-sobre-integridad-cientifica.
31. Second World Conference on Research Integrity. Singapore Statement on Research Integrity. [Accessed 28 June 2023]. Available from: http://www.wcrif.org/guidance/singapore-statement.
32. All European Academies. The European code of conduct for research integrity. [Accessed 28 June 2023]. Available from: http://www.allea.org/code-of-conduct/.
33. Institute of Medicine (US) Committee on Conflict of Interest in Medical Research, Education, and Practice. In: Lo B, Field MJ, editors. Conflict of interest in medical research, education, and practice. Washington (DC): National Academies Press (US); 2009.
34. Torgerson T, Wayant C, Cosgrove L, Akl EA, Checketts J, Dal Re R, et al. Ten years later: a review of the US 2009 institute of medicine report on conflicts of interest and solutions for further reform. BMJ Evid Based Med. 2022;27:46–54.
35. Abad-García MF. El plagio y las revistas depredadoras como amenaza a la integridad científica. An Pediatr. 2019;90:57.e1–8.
36. Solís Sánchez G, Cano Garcinuño A, Antón Gamero M, Alsina Manrique de Lara L, Rey Galán C. Plagio y ética en las publicaciones científicas. An Pediatr. 2019;90:1–2.
37. Armond ACV, Gordijn B, Lewis J, Hosseini M, Bodnár JK, Holm S, et al. A scoping review of the literature featuring research ethics and research integrity cases. BMC Med Ethics. 2021;22:50.
38. Real Decreto 944/1978, de 14 de abril, por el que se regulan los ensayos clínicos de productos farmacéuticos y preparados medicinales. [Accessed 28 June 2023]. Available from: http://www.boe.es/buscar/doc.php?id=BOE-A-1978-12157.
39. Agencia Española del Medicamentos y Productos Sanitarios. Información relativa a los Comités de Ética de la Investigación con medicamentos (CEIm). [Accessed 28 June 2023]. Available from: http://www.aemps.gob.es/medicamentos-de-uso-humano/investigacionclinica_ceim/.
40. Asociación Nacional de Comités de Ética de la Investigación. [Accessed 28 June 2023]. Available from: https://ancei.es.
41. Meek Lange M, Rogers W, Dodds S. Vulnerability in research ethics: a way forward. Bioethics. 2013;27:333–40.
42. González-Duarte A, Zambrano-González E, Medina-Franco H, Alberú-Gómez J, Durand-Carbajal M, Hinojosa CA, et al. The research ethics involving vulnerable groups. Rev Invest Clin. 2019;71:217–25.
43. Bradbury-Jones C, Isham L, Taylor J. The complexities and contradictions in participatory research with vulnerable children and young people: A qualitative systematic review. Soc Sci Med. 2018;215:80–91.