

Clinical Research Ethics in Respiratory Medicine

E. Fernández de Uzquiano^a and R. Álvarez-Sala^b

^aSecretaría Técnica del CEIC, Hospital Universitario La Paz, Madrid, Spain.

^bServicio de Neumología, Vocal del CEIC, Hospital Universitario La Paz, Madrid, Spain.

Clinical research plays an increasingly strong role in the development of respiratory medicine. Familiarity with issues that affect research on human subjects is therefore essential, particularly so with regard to the conduct of clinical trials of medical interventions.

This paper begins with a brief introduction to the ethics of clinical research. We highlight the importance of directives on ethics and the need to understand and comply with them when any type of experiment is conducted on humans. There follows a brief description of historical codes of bioethics and an account of their underlying principles, origins, and consequences. Finally, we discuss Spanish Royal Decree 23/2004 of February 6, 2004 which came into force on May 1 that year; we outline its general principles and analyze 2 types of problem that have emerged: those that result from the article requiring a "single opinion" and those of investigators who act independently of the pharmaceuticals industry.

The situation of clinical research in respiratory medicine at our hospital is then described. Finally, the 7 requirements of ethical research listed by Emanuel and colleagues are proposed as a tool pneumologists can use to analyze and assess whether or not a specific trial meets minimum ethical requirements.

Key words: *Clinical trial. Ethics committees. Informed consent. Pneumology.*

Aspectos éticos de la investigación clínica en neumología

La investigación clínica en neumología desempeña un papel cada vez más relevante en el desarrollo de la especialidad. Por ello se hace necesario el conocimiento de los aspectos éticos en investigación con seres humanos y, en concreto, en ensayos clínicos con medicamentos.

Se comienza la revisión con una breve introducción a los aspectos éticos en investigación clínica resaltando su importancia y obligado conocimiento y cumplimiento a la hora de llevar a cabo cualquier tipo de experimentación en seres humanos. Posteriormente, se realiza una breve descripción de los códigos éticos históricos y de los principios de la bioética mencionando su origen, así como las consecuencias que de ellos se derivan. Nos detenemos en el reciente Real Decreto 223/2004, de 6 de febrero, que entró en vigor en España el pasado 1 de mayo de 2004, para destacar sus principios generales y analizar los principales problemas que de él se derivan, fundamentalmente 2: los que son consecuencia de la exigencia del "dictamen único", y los relativos a los investigadores cuando actúan como promotores independientes de la industria farmacéutica. Se describe el papel de la neumología dentro de la investigación clínica con medicamentos en nuestro hospital, para posteriormente proponer los 7 requisitos del grupo de Emanuel como guía práctica para ayudar a los investigadores en neumología a analizar y valorar si un determinado ensayo cumple las mínimas exigencias de la ética clínica.

Palabras clave: *Ensayo clínico. Comité ético de investigación clínica. Hoja de información/consentimiento informado para los participantes. Neumología.*

Introduction

The protection of the subjects of investigation is the fundamental aim of clinical research ethics.¹ Controlled clinical trials are unarguably the gold standard for assessing the efficacy and safety of new medications and they belong, in general, to the final phase of biomedical pharmaceuticals research. We should always

bear in mind that involving subjects in a clinical trial puts them in a situation in which their fundamental rights can easily be violated. Trials of treatments must therefore be carried out in accordance with ethical guidelines and legal requirements that govern research on human subjects.²

A pneumologist who designs a clinical trial is obliged to specify and adequately control a range of aspects that vary in function of the disease setting. That must be remembered if a trial is to achieve the necessary scientific rigor, be ethically justified and, therefore, yield useful results for its participants and for society. The objective of a clinical trial is to answer specific questions that must be formulated previously.³

Correspondence: Dr. R. Álvarez-Sala.
Servicio de Neumología (planta 12). Hospital Universitario La Paz.
Paseo de la Castellana, 261. 28046 Madrid. España.
E-mail: ralvarezw.hulp@salud.madrid.org

Manuscript received February 15, 2005. Accepted for publication March 1, 2005.

On the other hand, we must not lose sight of the fact that, although an ethical decision is handed down in relation to a concrete clinical trial, the pharmaceutical industry that promotes it and the agencies that regulate it are well aware of a plan for developing the drug and that they take a broader view. In that view, a specific clinical trial is only a step toward a final objective: approval to market the drug and apply it properly in clinical practice. Those ends are achieved after a series of successful phases through which various questions are posed and answered.⁴

The tacit agreement among the members of the International Committee of Medical Journal Editors to refuse to publish original articles arising from research projects that are not approved by a clinical research ethics committee has increased the need to understand the requirements for such approval.⁵

We provide a brief historical review to show how codes, declarations, and ethical guidelines relative to clinical investigation arose after World War II and were initially a consequence of what happened in Nazi concentration camps, where prisoners were subjected to cruel experiments against their will. The codes, declarations, and ethical guidelines exist as a result of certain events and in order to prevent future wrongdoing.

The Nuremberg Code of 1947⁶ grew out of the judicial sentences that condemned the atrocities committed by the Nazis. The code focused on the need to obtain a subject's consent and a favorable balance between benefit and risk. However, the code does not treat the question of fair selection of subjects or the evaluation of trials by an independent body. The World Medical Association later drafted the Declaration of Helsinki (1964), which underwent subsequent revisions in Tokyo in 1975, Venice in 1983, Hong Kong in 1989, South Africa in 1996, and Edinburgh in 2000.⁷ The revisions sought to make up for deficiencies in the

original Nuremberg Code, dealing for the first time with the ethical principles a physician should follow when undertaking research on human subjects. The code came to include a distinction between medical research related to clinical care and other nontherapeutic biomedical investigation on human beings. In practice, that distinction is often difficult to establish, just as it is difficult to draw the line between giving medical care and doing research. The Belmont Report⁸ of 1979, on the other hand, established a continuum between care and research and named certain basic principles applicable to both situations. Those principles focus on informed consent, on a favorable risk-benefit balance, and on the need to protect vulnerable populations from being subject to research that puts them at risk. Finally, the ethical guidelines on biomedical research on humans of the Council for International Organizations of Medical Sciences that were drafted in 1982, revised in 1993 and 1999, and finally published in 2002 also include a section on compensation for subjects in case they suffer injury as a result of investigation.⁹ Table 1 shows a selection of ethical guidelines for carrying out research on humans.

The first to provide an analytical structure that could serve to guide our thinking about the ethical problems posed by human research was the Belmont Report,⁸ which established the basic principles of bioethics. Those principles are still valid today.¹⁰

The first principle is autonomy, which encompasses 2 ethical premises: *a*) individuals should be treated as autonomous agents and *b*) persons with diminished autonomy are entitled to protection. In practice, the end result of this first principle is the need to obtain informed consent before initiating investigation. The key issues to discuss with a patient honestly and without deception are the benefits and risks that might derive from participating in a particular trial.

TABLE 1
Basic Ethical Guidelines for Conducting Biomedical Research on Humans

	Year Drafted or Revised	Source
Nuremberg Code	1947	Nuremberg International Military Tribunal, decision in the United States of America
Declaration of Helsinki	1964, 1975, 1983, 1989, 1996	World Medical Association
Belmont Report	1979	National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research
International Ethical Guidelines for Biomedical Research Involving Human Subjects	Drafted in 1982, revised in 1993, and approved in 2002	Council for International Organizations of Medical Sciences, collaborating with the World Health Organization
Good Clinical Practice: Consolidated Guidance	1996	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
Convention for the Protection of Human Rights and Dignity of the Human Being With Regard to the Application of Biology and Medicine (Oviedo Convention)	1997	Council of Europe

The second and third basic principles involve beneficence and, consequently, avoidance of doing harm—concepts that dictate nearly absolute obligations that are only limited by the concurrent need for the investigator to respect autonomy. These principles suppose that a clinical trial is justifiable only when possible risks are reduced to a minimum and the possible benefits are maximized for all participants.¹¹

The fourth principle is justice. The practical expression comes from answering the following question: Who ought to receive the benefits of research and bear its burdens? There should be equal distribution of benefits between the class of subjects who participate in research and those who will receive its possible benefits. The theoretical benefit to society of research as opposed to the risks a specific subject should face is difficult to assess and doing so requires careful analysis by all parties involved: promotor, evaluator, investigator, the ethics committee, and the participating subject. Participation as a subject in a trial is an altruistic act in favor of society, in benefit of others, and that should be properly assessed.¹¹

To enable the relationships among these principles to be established and to seek a situation of balance, Gracia¹² established a 2-tiered approach. The first level encompasses the principles of justice and doing no harm. Failing to comply with these principles should lead to refusal to approve the proposed research. Trials that should be disallowed are those in which a subject is going to suffer gratuitous injury, whether because of selection based on belonging to a vulnerable population or because the study is badly designed and can not produce benefits for anyone. The second level involves the principles of beneficence and autonomy, to which absolute values can not be given. For example, there might be a case in which a patient wants to participate in a trial but the investigator is convinced that doing so would be harmful: in such case it would be impossible to give absolute consideration to the principle of autonomy without undermining application of the principle of beneficence. On the other hand, if an investigator is completely sure that the best option for a patient is to participate in a trial, but said patient does not desire to do so, we have a situation in which it is impossible to give absolute consideration to the principle of beneficence without violating that of autonomy.

Rules of good clinical practice also point to the need to guarantee the quality of investigation and protect the rights of subjects in trials, with the purpose of controlling permission to market new medications. Those rules were established by the Food and Drug Administration of the United States of America in 1977¹³ and were later implemented in Europe, where they became obligatory in 1991.^{14,15}

Legal Requirements in Spain

The highest law in Spain is the constitution and any other laws enacted must respect it. The values outlined in the constitution provide a positive judicial

framework of fundamental rights and clinical trials must be evaluated and organized in keeping with them. Should there arise inconsistency or contradiction between constitutional rights and values and other values of any type, those of the constitution must prevail.²

Law 25/1990 of December 20, which deals with medications,¹⁶ marked the start of a new era for clinical investigation, which must be undertaken in Spain in accordance with current technical requirements and ethical principles. Later, Royal Decree 561/1993 of April 16 established the specific functions and responsibilities of those who take part in clinical trials and stipulated the requirements for approval. That decree mentions the need to follow good clinical practice guidelines and it covers the minimum ethical obligations for carrying out trials of medications (articles 10 and 12, on ethical postulates).¹⁷

The new Royal Decree 223/2004 of February 6 (RCL 2004, 325)¹⁸ incorporates Directive 2001/20/EU (GCP) of April 4 passed by the European Parliament and the Council of Ministers.¹⁹ That Directive harmonizes the legislative initiatives of member states in the European Union with regard to clinical trials of medicines. RCL 2004, 325 takes into consideration the Declaration of Helsinki, the Oviedo Convention²⁰ on human rights and biomedicine, and the rules for adequate protection of personal information established by Spain's Organic Law for the Protection of Personal Data 15/1999, of December 13.²¹ It also covers the obligation to apply good clinical practice guidelines in the planning, execution, registration, and reporting of results of trials carried out in Spain and stipulates a set of internationally recognized ethical and scientific quality requirements that guarantee the rights, safety, and well-being of participants in research as well as the reliability of results.²²

We wish to emphasize the general principles that this new Royal Decree establishes for clinical trials in Spain²³:

1. No clinical trial can be undertaken in Spain without the approval of the appropriate ethics committee and the authorization of the Spanish Agency for Medicines and Health Care Products (AEMPS).
2. The good clinical practice guidelines of the European Union will be applied in the conduct of all clinical trials in Spain.
3. No participant can be enrolled in a clinical trial if consent has not been given, following an explanation of possible risks. Particular attention will be given to safeguarding vulnerable populations such as minors and adults with disabilities.
4. All clinical trials of medications except those that use approved agents should have an insurance policy that covers injury and damages that might derive from participation in the trial.
5. The research promotor must report to the competent authorities, and to the institutional review

board or ethics committee charged with monitoring the trial, all information pertinent to the safety of the medication being tested.

The enactment of this Royal Decree has also necessitated considerable change in how ethics committees evaluate trials in Spain. Putting into practice the required “single opinion” for each country participating in multicenter studies has enormously complicated procedures and created a great deal of work for Spanish review boards, which for the moment do not receive sufficient support for their efforts from the health care agencies.²⁴ The new Royal Decree has increased the traditional problems of ethical review boards (lack of resources and incentives) and demotivated their members, who find themselves unable to combine committee work with heavy clinical workloads. At this time ethics committees and review boards face difficult problems, such as finding volunteers willing to work without compensation and with sufficient ethical, legal, and procedural knowledge to evaluate studies adequately.

We should remember that ethics committees are bodies that in practice guarantee that guidelines, regulations, and laws are complied with. Such committees are defined by Spanish Royal Decree 223/2004 to be “independent, composed of health care professionals and lay members of the community, charged with protecting the rights, safety and well-being of participants in clinical trials and offering public assurance of the same by way of a ruling on the protocol for the trial, the qualifications of the researchers, and the sufficiency of the research facilities as well as judging the methods and documents that will be used to inform subjects about the nature of the trial with a view to obtaining informed consent.”

Many organizational issues remain to be resolved in relation to the new ways that ethics committees review clinical trials. The inefficiency of the central coordinator for such review boards and in many cases the scarce support from Spanish autonomous communities have meant that ethics committees have applied principles in an idiosyncratic and uncoordinated way. In our opinion it would be highly desirable to resolve these practical problems as soon as possible because the role of these committees is mainly to protect patient rights and, in many cases, they are promoters of good clinical research practice.

Another problem brought about by the new Royal Decree relates to the difficulties researchers encounter when they act as promoters of trials not financed by the industry. The first main difficulty involves payment of the insurance policy or assurance of payment to cover possible injuries to participants. The second is related to coverage of the cost of administering the drugs involved in the research. We might also add that there is a profound lack of awareness of obligations and responsibilities involved when the researcher also acts as promotor.

TABLE 2
Clinical Trials in Respiratory Medicine Conducted at a Tertiary Care Hospital, 2000-2003*

Year	No. of Trials Started	Disease	No. of Trials/ Disease
2000	6	Asthma	2
		COPD	2
		Cystic fibrosis	1
		Respiratory distress	1
2001	8	Asthma	4
		COPD	2
		Respiratory distress	1
		Sleep apnea-hypopnea syndrome	1
2002	5	Asthma	3
		COPD	2
2003	8	Asthma	3
		Cystic fibrosis	2
		COPD	2
		Pneumonia	1

*COPD indicates chronic obstructive pulmonary disease.

Role of the Respiratory Medicine Department in Clinical Research on Medicines at Hospital Universitario La Paz

We analyzed all proposed clinical trial protocols evaluated by our hospital’s review board in the years 2000 through 2003 to determine the departments responsible for each one. Of a total of 639 trials reviewed (156 in 2000, 140 in 2001, 165 in 2002, and 178 in 2003), 56% (n=359) were in medical specialties and 7.5% (n=27) were specifically in respiratory medicine. Pneumology ranks sixth among our hospital’s departments that undertake trials on medications. The great majority of trials (93%) have been promoted by the pharmaceuticals industry and only 7% are independent, promoted by clinical researchers or scientific societies.

Table 2 shows the diseases that have provided the contexts for those trials. Thus, 74% of respiratory medicine trials involve 2 diseases: asthma (44%) and chronic obstructive pulmonary disease (29.6%). We also saw that clinical trials in the context of pneumonia are only rarely carried out by the pneumology department; rather, they are undertaken by internal medicine or emergency departments.

Ethical Aspects to Consider in Clinical Trials in Respiratory Medicine

To have a strong position, research in pneumology must be done by investigators who are familiar with and put into practice the ethical and legal guidelines that regulate such practice. It is not enough to be experts in specific procedures, statistical analysis, outcome measures, and other scientific aspects of a trial.

As a starting point for evaluating the ethical aspects of clinical trials, it will be useful to consider each of the 7 ethical requirements proposed by Emanuel et al²⁵

TABLE 3
**Ethical Requirements for Clinical Research According
 to Emanuel et al²⁵**

- | |
|--|
| <ol style="list-style-type: none"> 1. Intrinsic value of the research 2. Scientific validity of the trial 3. Fair subject selection 4. Favorable risk-benefit ratio 5. Independent review of the trial 6. Informed consent 7. Respect for enrolled subjects |
|--|

(Table 3). Those requirements represent an attempt to provide universal principles and they must all be fulfilled, although adapted to the specific circumstances of a proposed protocol in consideration of the characteristics of the participating subjects, the research team, and the hospital—all within the framework of current Spanish law.

We will take the time to analyze the ethical issues to consider in clinical trials needed for the development of new drugs in respiratory medicine in the light of each of those requirements.

Intrinsic Value of the Research

The results that can be foreseen from a trial must be of value to the participants and/or society in the short or long term. This means there should be therapeutic or diagnostic improvements in a specific disease setting. Only if this is so will it be fair to subject participants to possible risks and to use limited resources. The results, moreover, must be published regardless of whether they are positive or negative.

A clinical trial is not ethical if its results can not be generalized, if the starting hypothesis is inconsistent, if its design is faulty, or if the results have already been demonstrated.

Clinical practice normally involves deciding which of available treatments is the most appropriate or if it is better to prescribe a treatment for a patient or to refrain from doing so, and these are the questions that should guide the choice of a control treatment in clinical trials. Evidently, improper selection of a control group can invalidate a trial.

Scientific Validity of a Clinical Trial

All research should be methodologically rigorous. A clinical trial might have lofty aims, but if it is not properly conducted it will not be able to answer the research question posed and will therefore be intrinsically unethical. It will expose participants to risk for no purpose and use limited resources in the process. Nor would it be ethical if the answer sought has already been found for the same clinical setting. A clinical trial that compares treatments must have an appropriate and valid null hypothesis. Herein lies the importance of the concept of equipoise for justifying the start of a clinical trial. Equipoise applies strictly when the ratio of benefit

to risk is similar for 2 or more interventions, with the ethical requirement that there should be a reasonable doubt about the superiority of one treatment over another, including over placebo treatment. This situation rarely exists in clinical investigation, however. The benefits and risks are different for each of the interventions and both are studied at the same time.¹¹ Still, if there were consensus on what the best treatment was, there would be no null hypothesis and the research would be invalidated, as the results would not tell us more about the best treatment to prescribe or about the most favorable balance between benefit and risk.

Fair Subject Selection

Fair selection of patient subjects encompasses decisions that range from the stipulation of inclusion and exclusion criteria to strategies for recruitment.

The objectives of a trial should be the basis for deciding who can be enrolled, not factors related to vulnerability, ease of recruitment, or others unrelated to the purpose. Nor would it be ethical to deny a group of patients the right to participate in a trial without having a scientific reason for doing so or without information that justifies their exclusion because they are more liable to suffer injury.

It is best to conduct research in a patient population that reflects those who can later benefit from the results. If a product under investigation is intended for use in women or children, it must be trialed in those groups in order to obtain information about how it might affect them. Although it is not necessary for all phases of product development to be carried out in children, it would be appropriate to enroll them in late phases after safety has been tested in adults.

Nor should it be forgotten that the risk-benefit ratio of a trial can vary depending on what study population is enrolled. In keeping with a trial's aims, participants should be selected with a view to minimizing risks but not with the idea of increasing positive outcomes.

Favorable Risk-Benefit Ratio

A clinical trial will be justified only provided that *a*) potential risks to participants are kept to a minimum, *b*) the participants are likely to benefit, and *c*) the potential benefits for participants and/or society are proportional to or outweigh the risks. This requirement of a favorable risk-benefit ratio covers the basic bioethical principle of beneficence and avoidance of harm.

Methodological reflections on design (hypothesis, control treatment) that affect a trial's sample size have a direct bearing on the risk-benefit ratio for individual patients who take part.

The use of a placebo in the control group is one of the most controversial issues in clinical research. The ethical question is whether it is acceptable to give placebo to a control group in a clinical trial if there exists an effective treatment for the disease. Article 29

of the October 2000 Edinburgh revision of the Declaration of Helsinki,⁷ established that the use of a placebo is only permissible when no proven therapy exists. That provision gave rise to great controversy, which was finally resolved with the publication of a note of clarification issued by the World Medical Association General Assembly in Washington, DC in 2002.²⁶ The note stipulated that placebo-controlled trials may be ethically acceptable even in the event that a proven treatment exists if there are strong and convincing methodological reasons that make a placebo control necessary or if the clinical setting for research is a benign disease such that the participants run no added risk that might cause severe or irreversible injury.

Independent Review Process for Trials

In Spain, the institutional review boards, ethics committees and the AEMPS guarantee that the requirement for independent review is met and they have the authority to approve, modify, or deny approval for a clinical trial. Clinical research puts individual humans at risk in benefit of society. Evaluation by these independent bodies assures society that research participants are treated ethically and prevents a part of society from exploiting another. Moreover, these bodies certify for participants that the design is ethical and that the risk-benefit ratio is favorable. Currently there exist for some international trials independent committees that have the power to carry out mid-trial inspection of data relating to efficacy and safety. Those committees can modify the protocol or halt the trial altogether if they consider it necessary.

Public administrations and institutions should give stronger support to the work of these independent bodies that protect the welfare and rights of individual subjects.

Informed Consent

Informed consent is given through a document that is the basis for guaranteeing the principle of autonomy and the right of patient privacy in research. By signing the form, competent subjects freely choose to participate in the trial and authorize the processing and analysis of data recorded in clinical charts.¹⁵

Informed consent is a process that starts when the researcher provides a potential participant with details about the trial by way of an information sheet. The researcher also has the ethical obligation to ascertain that the subject has the capacity to give consent. When a subject is deprived of autonomy, legal guardians must give consent.

For clinical trials involving minors, the consent form should be addressed to parents or legal guardians, whose consent to the child's participation is sought. In addition, for mature child participants (older than 12 years but younger than 18) a special information sheet should be provided if the minor is able to understand it.

The sheet should summarize general information about the study in a way that is adapted to the mature child's level of comprehension so that consent can be given.

The information sheet should be carefully reviewed and validated by the ethics committee before the trial is approved. In fact, most requests for clarification and changes issued by the ethics committee at our hospital involve the information sheet for obtaining consent.

Respect for Enrolled Subjects

Ethical obligations do not end with informed consent. Participating subjects must continue to receive treatment that respects their rights throughout the course of a trial, even if they decide to withdraw for any reason. From the beginning of a trial until its closure, the following rights must be respected:

1. Right to withdraw, or to revoke consent, without negative consequences
2. Right to be informed of any relevant event that arises during the trial that might influence the decision to remain in the trial
3. Right to confidentiality, mentioned expressly in the Spanish Law for Protection of Personal Data 15/1999, and to protection of privacy
4. Right to close monitoring of the trial, to assure that the registered protocol is being followed and all is in accordance with bioethical principles and good clinical practice guidelines

One of the functions of ethics committees established by Spanish Royal Decree 223/2004 (article 10, chapter III) is the continuous oversight of clinical trials, from their initiation until the reception of final reports.¹⁸ This task is currently the weak point of review board activities. Strict, effective monitoring of trials in a hospital like Hospital Universitario La Paz would require human resources assigned exclusively to that task.

Regulatory agencies should also be alert to whether high standards of design and conduct of trials are maintained as previously established by the promoters, researchers, and auditors, as approved by the ethics committees. Researchers who are familiar with good practice guidelines and who apply them to research should have no problems with the audits stipulated by these bodies. To perform audits, most pharmaceutical companies have their own quality control units made up of independent professionals. The deficiencies most often detected by clinical trial auditors affect informed consent, inadequate data recording, incorrect following of the protocol, and poor accounting for drug stocks.¹

Conclusions

Clinical research in pneumology plays an increasingly important role in the development of the specialty. Understanding the ethical implications of

research with human subjects is therefore essential, particularly in clinical drug trials.

Protecting subjects participating in research is a responsibility shared by various persons and groups, but it is essential for the researcher who conducts the study to recognize, as soon as possible, any circumstance that can affect patients' safety or rights.²⁷

New ways to further our understanding of various respiratory diseases are currently opening up and clinical trials are an essential tool for progress. Respiratory pharmacology will be proposing agents and devices or systems that are increasingly useful and have fewer side effects. Clinical trials have a sure future, therefore, in pneumology. Their importance and their number will certainly grow in the coming years and it is to be expected that patients will be the ultimate beneficiaries.

This makes it all the more important for clinical trials in our specialty to be rigorous and fulfill requirements for ethical research conduct at all times, to protect our patients to the greatest extent possible.

Acknowledgments

We thank the members of the clinical research ethics committee of Hospital Universitario La Paz for their cooperation.

REFERENCES

1. Gil Aguado A, Lavilla P, García Puig J. El investigador clínico ante las auditorías. *Farmacoterapia*. 1996;13:231-6.
2. Bakke OM, Carné X, García Alonso F. La regulación legal de la investigación clínica. In: Bakke OM, Carné X, García Alonso F, editors. *Ensayos clínicos con medicamentos. Fundamentos básicos, metodología y práctica*. Barcelona: Doyma; 1994. p. 13-22.
3. Álvarez-Sala Walter JL, Calle Rubio M. Generalidades del ensayo clínico en asma. In: Picado C, Prieto Andrés L, editors. *El ensayo clínico en el asma*. Majadahonda: ERGON; 1999. p. 1-9.
4. Gracia D, Lahuerta J, Carné X, Dal-Ré R. ¿Es ético realizar ensayos clínicos controlados con placebo en el desarrollo de un nuevo fármaco para el trastorno depresivo mayor? (I). Consideraciones sobre el valor intrínseco y validez científica del estudio. *Med Clin (Barc)*. 2004;123:546-50.
5. Amdur RJ, Biddle C. Institutional review board approval and publication of human research results. *JAMA*. 1997;277:909-14.
6. Katz J. The Nuremberg Code and the Nuremberg trial. A reappraisal. *JAMA*. 1996;276:1662-6.
7. World Medical Association. Declaration of Helsinki, adopted by the 18th World Medical Association, Helsinki, Finland, 1964, and attended in Tokyo in 1975, in Venice in 1993, in Hong-Kong in 1989, in South Africa in 1996, and in Edinburgh, Scotland, in October 2000. Available from: www.wits.ac.za/bioethics/helsinki.htm
8. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report*. Washington, DC: US Government Printing Office; 1979.
9. Council for International Organizations of Medical Sciences. *International ethical guidelines for biomedical research involving human subjects*. Geneva: CIOMS; 2002.
10. Gracia D. *Fundamentos de bioética*. Madrid: EUEDEMA; 1989.
11. Lahuerta J, Gracia D, Casas M, Baca E. ¿Es ético realizar ensayos clínicos controlados con placebo en el desarrollo de un fármaco para el trastorno depresivo mayor? (y II). Relación beneficio/riesgo y consentimiento informado. *Conclusiones*. *Med Clin (Barc)*. 2004;123:585-90.
12. Gracia D. *Procedimientos de decisión en ética clínica*. Madrid: EUEDEMA; 1991.
13. Food and Drug Administration. *Clinical investigations: proposed establishment of regulations on obligations of sponsors and monitors*. *Fed Reg*. 1977;42:49612-30.
14. CPMP Working Party of Efficacy of Medicinal Products. *EEC Note for guidance: good clinical practice for trials on medicinal products in the European Community*. *Pharmacol Toxicol*. 1990; 67:361-72.
15. Gil A, Lavilla P, Fernández de Uzquiano E. El consentimiento informado en la investigación clínica. *An Pediatr Contin*. 2003;1: 109-18.
16. Ley 25/1990, de 20 de diciembre, del Medicamento. *BOE* no. 306, de 22 de diciembre de 1990, 2643.
17. Real Decreto 561/1993, de 16 de abril, por el que se establecen los requisitos para la realización de ensayos clínicos con medicamentos. Madrid: Ministerio de Sanidad y Consumo. *BOE* no. 114, de 13 de mayo de 1993, 1476.
18. Real Decreto 223/2004, de 6 de febrero, por el que se regulan los ensayos clínicos con medicamentos. *BOE* n.º 33, de 7 de febrero de 2004. p. 5429-43.
19. Directiva 2001/20/CE del Parlamento Europeo y del Consejo de 4 de abril de 2001, relativa a la aproximación de las disposiciones legales, reglamentarias y administrativas de los Estados Miembro sobre la aplicación de buenas prácticas clínicas en la realización de ensayos clínicos de medicamentos de uso humano. *DOCE* no. L121, de 1 de mayo de 2001. p. 33-4.
20. Consejo de Europa. *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)*, Oviedo 4 de abril de 1997. *BOE* no. 251, de 20 de octubre de 1999, 36825-30.
21. Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal. *BOE*, de 14 de diciembre de 1999, 43088-99.
22. EMEA Workshop on "Ethical considerations in clinical trials." 2001. Available from: www.emea.eu.int
23. Millán Rusillo T. El Real Decreto 223/2004 de ensayos clínicos y su aplicación. *Inv Clin Farm*. 2004;1:19-20.
24. Lavilla P, Fernández de Uzquiano E, Gil Aguado A, Frías J. Investigación en ensayos clínicos en la Comunidad Europea: luces y sombras del nuevo RD 223/2004. *Inv Clin Farm*. 2004;1:21-4.
25. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA*. 2000;283:2701-11.
26. Note of clarification on paragraph 29 of the WHA Declaration of Helsinki. 2002. Available from: wwma.net/e/policy/b3.htm
27. Steinbrook R. Protecting research subjects—The crisis at Johns Hopkins. *N Engl J Med*. 2002;346:716-20.