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Evaluating biomedical research: the ethics committees on research

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I. THE NEED FOR AN INDEPENDENT BODY TO MONITOR ADHERENCE TO ETHICAL POSTULATES AND NORMATIVITY REGARDING BIOMEDICAL RESEARCH

1. The germ of a regulatory framework – ethical and legal– for the control of biomedical research

Research in the biomedical sector has experienced intense development, not only as a result ofmajor achievements interms of better diagnosis, prevention and treatment of many diseases, but also due to changes in their methodologies and innovative targets. Not few of many deadly diseases that were incurable or fatal only a few years ago have been positively addressed and very promising expectations have emerged in relation to other diseases. Today,genes are being investigated for new knowledge to be acquiredand applied to the treatment of diseases with bad prognosis and limited prevalence.

It is also true that over the last century some objectionable practices have been adopted that gave rise to abuse, injury and even death of people involved in this type of research. In particular, systematic aberrations recorded in concentration camps in Germany during the Second World War led to the awareness of political leaders on the one hand, and of the scientific community on the other, that clinical trials involving humans should be strictlygoverned by ethical principles and, especially, the fundamental rights of the persons involved in such studies should be respected, as well as the well-being and safety of the subjects participating in clinical trials. The incentive to generate – hypothetically–huge benefits for the whole of mankind should not justify any exceptions in terms of the respect that these people have the right to enjoy.

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The turning point was the Nuremberg process, where, as is well known, several medical doctors were tried and convicted for horrible acts against defenseless people kept in concentration camps. One of the results was the adoption of what was called the Nuremberg Code, in 1947. This pre-normative instrument, which was a milestone of great significance at the time for biomedical research in humans to incorporate principles of respect for them, was based on two main aspects: consent of the participants in trials and their scientific quality and justification.[†]

This precedent had an obvious impact on international law, as it led to some advances in the 1960s regarding the expansion of fundamental rights that could be affected by practices in medicine and human biology, which startedbecoming evident some twenty years later. As a result, the International Covenant on Civil and Political Rights of the United Nationsincluded,for the first time,a requirement for medical experimentation:

"No one shall be subjected to torture or to cruel, inhuman or degrading treatment. In particular, no one shall be subjected to medical or scientific experimentation without his or her free consent".[‡]

It is noteworthy that this Agreement clearly and correctly links abusive medical or scientific experiments to cruel, inhuman or degrading treatment, without limitingacts of aggression to the lack of consent on the part of any person subjected to experimentation.

As outlined below, despite the clear advancesbrought about by both instruments –the first one of an ethical natureand the second of a legal character– they would not provide sufficient guarantee, especially in view of abusescommitted in the 1960s in various tests involving children and adults.[§] On top of that, it was necessary to establish an additional system of control, since it was possible to avoid the consent of the subject of experimentation or secure it through pressure or based on the professional prestige of the professional requesting such consent; and there could also be cases of consented cruel, inhuman or degradingexperiments not perceived as such

[1] Romeo Casabona, C. M., "The Nuremberg Code: a milestone in the ethical postulates on human experimentation" (Editorial) in Janus, vol. LIII, No. 1220/4-11 July 1997, p.5 and seq., The same, "The influence of the Nuremberg Code: From the Helsinki Declaration to our Days" in Janus, vol. LIII, No. 1220/4-11 July 1997, p. 68 and s..

[2]Article 7. It was adopted by the General Assembly of the United Nations by Resolution 2200A (XXI) of December 16, 1966. Entered into force on March 23, 1976.

[3] AAVV (Ethical Control of Biomedical Activity, CEAB), ethical controls of biomedical activity.Situation analysis and recommendations, Madrid; Roche Institute, 2009, 13.The Willowbrookhepatitis studies are often cited as examples of objectionable research, which were carried out for five years with about seven hundred disabled children admitted to the hospital, which were eventually infected with hepatitis viruses;as well asthe experiment conducted in Tuskegee (Alabama) with four hundredafrican-american patients with syphilis, who were excluded from treatment with antibioticswithout their knowledge.

by the researcher or seen as justifiable in light of, for example, the benefits that they could allegedly bring to thousands of people due to the advances in scientific knowledge and clinical practice that they could theoretically bring about.[**]

In conclusion, especially those who are vulnerable, but not only them, need greater protection through external bodies that are independent from the people involved in the design, implementation and financing of a trial.[††]

In this regard, many years later the Oviedo Convention clearly rejected the notion that scientific progress justified any individual sacrifice:

"Primacy of the human being. The interest and well-being of human beingsmust prevail over the exclusive interest of society or science".[‡‡]

2. Research ethics committees as guarantors of the safety and fundamental rights of subjects of experimentation

Once the awareness was established in the scientific community of the need to link its research activities to respect and observance of certain ethical and legal principles, it was inferred that it was also essential that compliance with these principles should not be unilaterally checked by researchers, who are often influenced and pressured by interests that might be external butdirect, such as those of the promoters and financial sponsors of the trial; or perhaps conditioned by their own research ambitions.

The Nuremberg Code of 1947 did not refer to this, so it became urgent to search for a procedure that would satisfy these new requirements.[§§]

An increasingneed emerged to set up a body external to the trial and independent from the various participantsto take on this role. This iswhy the "Review Boards" or

[4] Beecher, H. K., "Ethics and Clinical Research," The New England Journal of Medicine, vol. 274, No. 24, 1966, 1354-1360.

[5]On the various subjects that would fall under the category of vulnerable, v. Rodriguez -Arias, D., Moutel, G.,Hervé, C. (Eds.),*Ética y experimentación con sereshumanos*, Bilbao;Desclée de Brouwer, 2008, p. 51 et seq. In particular on children, infants, pregnant women and the mentally ill and vulnerable subjects of biomedical research, v. Romeo also Casabona, C. M., "Aspectosjurídicos de la investigacióńclínica con neonatos", in "*Bioética: un diálogo plural* (Homenaje a Javier GafoFernández, S.J.", Universidad Pontificia de Comillas de Madrid, Madrid, 2002, p. 823-846 , the same, "Human Experimentation in Psychiatry: Legal Considerations", in *International Journal of Bioethics*, Volume 6, November 1995, pp.14 -20 .

[‡‡] Article 2 of the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the application of biology and medicine, made in Oviedo on 4 April 1997.Instrument of ratification of the Kingdom of Spain of October 5, 1999 (BOE of 20 October of the same year), in force since 1 January 2000. In similar terms, inspired by this Covenant, art. 2 b) of Act 14/2007, of 3 July, on biomedical research (LIB).

[§§] In thissense Rodriguez -Arias, D., Moutel, G. Herve, C. (Eds.), *Ética y experimentacióncon seres humanos*, p. 40.

"Institutional review boards" were set up in the Anglo-Saxon (especially American) regionand, later, in Europe and other countries, which were called "clinical trial committees" or "clinical ethics committees", "ethics committees of biomedical research"[***] etc., with the role of evaluating and reviewingtrial protocols, at least when humans were involved in them as subjects.[†††] It can be said that today almost all countries that have developed a policy of strongly promoting biomedical research have established such committees, despite their differences in capacities and way of operating.The first reference to them in an international document is found in the first version of the Declaration of Helsinki, issued in 1964:[‡‡‡]

"The design and carrying out of each experimental procedure involving human subjects should be clearly formulated in a protocol of the experiment to be submitted for consideration, comments and advice to a unbiased committee, which must be independent from the investigator and the sponsor, provided that such committee complies with the laws and regulations of the country where the experiment is to be performed"(Principle I.2).

In Europe, the *Rules of good clinical practice for clinical drug trials*"[§§§]include several sections on this matter.

The current legal regime of the European Community[****]also includes the requirement that each protocol must be evaluated by an independent external committee, which has led to the widespread implementation of this procedure in the European area. In the corresponding policy, specific answers are given to improve and speed up the evaluation of multi-center trials, given the frequency with which several teams and centers, both from the same country and from several others, are involved in the same test.

[8] V. on its creation, Romeo Casabona, C. M., "*Aspectos jurídicos de laexperimentación humana*" in *Homenaje al Profesor Luis Jiménez Asúa. Revista de laFacultad de Derecho de laUniversidadComplutense*, Monograph No. 11, 1986, p. 569-584.

[9] On the emergence and first steps of these committees v. AATT(Activity Control Biomedical Ethics, CEAB),*Controleséticos en la actividadbiomédica. Análisis de situación y recomendaciones*, 13 et seq.

[10]By the XVIII World Medical Assembly. The final version was approved in Seoul in 2008, which widened what was established in 1964 in connection with the operation of research ethics committees (principle 15).

[11] Identified as the CPMP/ICH/135/95 document),it has been translated, annotated and distributed by the Spanish Agency of Medicines and Health Products.

[12]Established by Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States on the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (Directive on clinical trials). It has been transposed into Spanish law by Royal Decree 223/2004 of 6 February, which regulates clinical drug trials.

Following this established line of universal control of clinical trials, Spain has incorporated into its regulations the need for any biomedical research to undergo an evaluation process:

"Investigationsshall be evaluated." (art. 2, g, LIB).[††††]

II. CHARACTERISTICS OF CLINICAL RESEARCH ETHICS COMMITTEES

As follows from the considerations above, despite the efforts made so far, only in very broad termsone can say that a final standard has been established for these committees. However, it is possible to point out some of their most important characteristics that are shared by the various systems that have been set up to this date. One of the main issues to be resolved was whether the trial assessment should be left to the profession, as apparently suggested in the beginning, or whether it should be left out of this closed area and perhaps not be involved on occasions on which its objectivity could be called into question.

2.1. Independence

Independence is the fundamental precondition for the committees to carry out their task and ensure that they effectively meet the objectives set out for them in the law. Without this guarantee, all the work of the committee is doomed to fail.

This requirement of independence and autonomy of operation is applicable, first, to the trial itself, as the committee members should not be directly or indirectly involved in any trial that they will evaluate; or they should not take part in the process of deliberations and decisions of the committee in relation to a project in which they will participate.

In addition, the independence of committee members in relation to the researchers should be ensured, meaning that they should not collaborate in such trials; and to their promoters, with whom they should not participate in other trials at the time of the evaluation and issuance of the respective report.

No less important is to safeguard this independence in relation to government, particularly to health authorities. What is meant by this is that they should not

[13]Role assigned by law to the ethics committees of investigation (Article 12 of the LIB). About the Spanish regime of clinical trials and biomedical research, v. Sanchez -Caro, J.,Abellán, F. (Coords.)*Investigación biomédica enEspaña. Aspectos bioéticos, jurídicos y científicos*, Granada; Comares, 2007, pasim ; thesame (Coords.), *EnsayosclíicosenEspaña. Aspectos científicos, bioéticos y jurídicos*, Granada; Comares, 2006, passim.

intervene in the deliberations and decisions of the committee on any trialor give orders to committee members who are employees of the hospital or health facility where the trial is carried out.

As discussed below, this independence must also prevail in relation to the decisions of other research ethics committees of the trial, including when protocols are evaluated in the light of identical or similar principles under the same research project (multi-center project).

In short, preserving this unwavering independence may require notification to the committee by one of its members of the existence of a conflict of interest in relation to a particular project and the obligation for them to refrain from participating in the information-gathering and deliberation process and in the adoption of an appropriate decision by the committee. It is true that conflicts of interest of a very diverse nature and origin can emerge, and this is why consideration should be given to the possibility of paying the committee members more than mere daily allowances andof the trials bringingextraordinary revenues for the centers in which they are carried out and/or for the researchers involved in the trial, etc.[‡‡‡‡]

2.2. Multidisciplinarity

It is known that reflecting on matters related to biomedical ethics in general requires a plural perspective or approach from the point of view of the training or expertise of those involved in such reflection in any way. It is more advisable to adopt a multidisciplinary approach in evaluating clinical trials, since the presence of peers of the researchers tends to pose the risk a biased view on the ethical issues involved, which can relegate them to the background and subordinate them to "higher" scientific achievements and their alleged benefits to society.

Much to the contrary, this plurality of training and/or "professional mentality" favors, as a first step, debate and confrontation even around matters which for some may be apparent and for others problematic according to their professional proximity to or distance from the scientific research, giving rise to more or less conflicts around them. At the same time, however, this training disparity necessarily leads, as a second step, to more thoughtful and balanced solutions, which is the spirit that should govern the decisions of these committees.

The professional profiles or basic training of the members of the committeesconstitute another matter. It is advisable that their profiles do not appear to be too restricted and also that these people are experienced in clinical practice and research, as well as in ethical and legal issues. In all cases, however, the participation of people with other

[‡‡‡‡] V. more extensively on the various conflicts emerging Loris Paul, C., "Comité de ética de la investigación (CEI)" in Romeo Casabona, C. M. (Ed.), *Encyclopedia of Biolaw and Bioethics*, volume I, Granada; Inter-University Chair in Law and the Human Genome and Editorial Comares, 2011, p. 412 and s.

profiles should not be ruled out. The former should be included in such committees, as these should not be limited, in their evaluating role, to the "external" aspects of the protocol, as on occasion, in order to accurately realize the transcendence of the research from the ethical point of view,thorough consideration of the contents, objectives and methodology of the projected trial is required.

The lattershould participate in the committees because training in ethicsis required for decisions related to ethical issues, but assuming –as has been increasingly the case – that people who are, in principle, not involved in professions related to ethics also have such training.

The presence of a jurist is also necessary, because decisions made by the committee should never contradict the legislation in force in the country concerned, especially if it is based on a democratic system that formally and materially respects human rights (constitutionally speaking, fundamental rights and civil liberties) that can be affected by trials, particularly the rights of research subjects. In addition, the existing legal regime for clinical trials and other biomedical research activities must always be complied with.

Finally, the presence of members with a different professionalbackground than that of the previously mentioned ones contributes to ensure the plurality and balance that were highlighted above.This is why the presence of a lay person or "representative" of society in these committees is usually required.

2.3. *Specialization*

The committees should restrict their role to that of evaluating and monitoring research protocols, at least when they involve human beings as subjects of experimentation. Whetherthis role should be limited to clinical trials of drugs and similar products or extended to other areas of biomedical research is another question that will be addressed below.

What we are saying here is that ethics committees for biomedical research should not address other ethical aspects that can arise in health centers or hospitals that are not related to the research in question –aspects mainly related to the clinical care of patients.

If such a need arises, it must be met through the establishment of specific committees of ethics, such as the so-called healthcare ethics committees (HECs),which have been established in many countriesalready for this purpose.[§§§§]This observation does not prevent institutional or informal communications between the two, for the purpose of facilitating the development a joint view on an ethical conflict existing in the center.

[§§§§] In Spain with Circular No. 3 of 1995,of the National Institute of Health, created by the Ethics Committees in the centers dependent on NIH at the time. Decree 143/1995, of February 7, the Department of Health of the Basque Government is similar and earlier.

The fact is that the specificity, complexity and, occasionally, the magnitude of the work involved in the research activity of a medium-sized center require this specialization, so that the committee members can attend to it with sufficient dedication and preparation, often enhanced by the experience acquired by them in this type of work. On the other hand, the excessive accumulation of issues to be addressed would probably be detrimental to the efficiency I will refer to below.

2.4. Agility

The scrupulous fulfillment of the tasks assigned to clinical ethics committees must be fully compatible with its efficiency, which translates into swift decisions and operations. This is because the evaluating function of the proposed trial should neither significantly delay its beginningnor hinder its development, which could defeat the intended goals and the hypothetical usefulness of their evaluation.

This requirement is even more important in the case of multi-center domestic or international trials, as any delays could affect the work of other research groups involved in the trialor lead the sponsor of the trial not to use the team –or even the center– in future trials. In such cases, all research groups belonging to different centers must submit their respective trials to the ethics committee that they report to, and the paradox is that it can reach conclusions and decisions that are also different from those of other committees that evaluated a similar or identical protocol.

Given the above-mentioned independence of the committees, such disparity must be respected in all cases, but it is likely that real, but perhaps not apparentdifferences have led to such divergence: how the protocol is submitted (e.g. incomplete documentation), the infrastructure of the center where the research will be carried out, the characteristics of the research team. In some cases, these faults or unsatisfactory outcomes may have occurred previously in other teams, but were corrected on their own initiative or following suggestions of the committee, but without the other research groups involved in a multi-center project being informed about such action.

In any case, achieving the goal of agility should not prevent the committee from scrupulously fulfilling its mission, even if it consists in securing additional information for the researcher or discussing with him some details of the proposed trial or completing or modifying already-filed documentation, etc. (recabar) ***

The foundations of the principles of independence, multidisciplinary and specialization –and sometimes, efficacy – pointed out above also suggest the advisability of periodicallyreplacing committee members partially whenever possible, provided that such replacement does not affect the normal activities of the committee at a given time.

III. Reconciling the duties of confidentiality and transparency

As is well-known, this is a widespread need and requirement in healthcare and medicine, which in this case is up to each and every member of the committee to

comply with, including its auxiliary staff –so it is not necessary to insist on it. Anyway, let us remember that this duty of confidentiality applies not only to the trial subjects, but also to the economic and scientific content of the protocol itself, as well as to discussions, comments, objections and decisions regarding whatcan be adopted by the committee itself.

Regarding the tasks involved in monitoring the implementation of the project, which is usually also a responsibility of these committees, it might be necessary to access information concerning the trial subjects, such as their medical history, especially if any adverse events have been detected. To begin with, access to personal information should not be hindered, as it is also subject to the duty of confidentiality that all committee members must fulfill. However, since it deals with health-related data, the subject's express consent will be required in all cases.

On the other hand, the need for transparency in any clinical trial has been more strongly emphasized in recent years for various reasons that are largely grounded, which can result in conflicts with the duty of confidentiality. Transparency and confidentiality must coexist and be reconciled with each other.[*****]

IV. HUMAN AND MATERIAL RESOURCES

The proper functioning of the committees and the agility we referred to require that the formerare provided with supporting infrastructure and other sufficient and necessary means. Therefore, an administrative secretary and other appropriate office media, physical facilities for meetings, supporting means for documentation etc., should constitute the minimum resources available to the committee; and these should even be expanded, according to the amount of work that the committee might have undertaken. This availability of resources should also cover expenses incurredby the members of the committee for carrying out their functions,particularly travel expenses to attend committee meetings.

As regards the experience of some countries –including Spain– it seems that although they usually enjoy such minimum facilities, not always specific provisions are available to cover other equally important aspects, such as the committee members' traveling expenses, facilities for communication and for meetings with other committees, organization and attendanceof meetings or training courses and refresher courses for its members, etc.

It would not be outlandish to provide allowances or controlled equivalent compensation for committee members –it should not be in any way intended as a remuneration, including a covert one– who are working altruistically, at times with

[*****]AAVV (Control Ético de laActividad Biomédica, CEAB), *Controles éticos enlaactividad biomédica. Análisis de situación y recomendaciones*, p. 22 and s.

great dedication in what constitutes an activity added to their usual professional activity, also sometimes even outside clinical activity. Such arrangements are more appealing when virtually all those involved in a research project (researchers, service providers and centers where research is conducted, benefitsof the research for promoters, and even research subjects if they suffer undesirable prejudice)are somehow compensated for their participation in the trial. Of course, provided that such arrangements are not inconsistent with their unwavering independence, which must be preserved over any other interest, for which reason such resources should not be directly or indirectlylinked to a trial or its sponsor.

V. REGULATION

In order to ensure the conditions mentioned above, it is desirable that the committees and their functions, the operating system, andthe number and composition of their membersare all normatively created, but in a flexible way that allowsfor necessary adjustments in the characteristics and dimensions of the center that they will serve and the social environment in which they will be working. And, as a projection of the principle of legality, the functions and competences of the committee should be exhaustively described and detailed to prevent – as a result of ambiguity – both excessive or abusive interference in the work of the committee, such asthat resultingfrom a researcher or sponsor influencing the committee's evaluatingrole.

VI. ROLES AND COMPETENCES OF COMMITTEES

1. The research ethics committees

The overall role of the committees is primarily one of evaluating various methodological, ethical and legal aspects of a trial under review, but italso includes the appraisal of risks feared and expected benefits. In all casesthe committee's action must be guided, above all, by the goal of ensuring the welfare and safety of trial subjects and the protection of their rights. Second, in any case subordinate to suchobjective, the committee is boundby the demand of promoting quality biomedical research, protected by the fundamental right to scientific output, which includes freedom of scientific research (article 20.1, b, CE).[†††††]

All this must be done, of course, prior to the beginning of the trial and even prior to its final approval by the appropriate granting authority, which should consider, in a binding manner, the committee's decision on the appropriateness of the proposed trial, in accordance with the evaluation. For this purpose, this should be considered as a pre-authorization with respect to which the agency granting final approval would have verified the concurring of other conditions, whose knowledge and assessment are not the responsibility of the committee, as are the burden of work imposed on the center, the existence of several research projects that may affect the operation and

[†††††] Loris Pablo, C., "Comité de ética de lainvestigación (CIS)" in Romeo Casabona, C. M. (Ed.), *Enciclopedia de Bioderecho y Bioética*, Vol I, p. 409 and s.

objectives of the center, etc., besides other aspects related to the effective development of the research,which are up to the committee to assess.

However, the committee's role should not be limited to considering the situation of the protocol as it was presented for evaluation and ruling, but should include the whole conduction of the process to completion, and it must be informed of all incidents that occur as itis carried out that can affect the subjects (adverse events), even if those befall another center, as inmulti-center trials. I believe that it must also check any possible fraudsin the investigation, either to propose the revocation of the authorization for the trial to the competent authority, if the trial is already under way, or to take them into account when assessing future trials.

As noted above, the evaluationcan also consider aspects related to the scientific nature of the test, as they can provide information of ethical or legal interest, as on the risks of the trial, the achievement of relevant and new results (e.g. concealing a treatment or the promotionof a product that is already marketed), respect for the principle of proportionality, etc. This also appliesto economic aspects related to liability insurance, compensation or remuneration to trial subjects, the allowances of researchers and their collaborators, etc.

The roles and responsibilities of these committees areoften well defined in regulations dealing with the latter,[‡‡‡‡‡]which is very correct, as indicated above. I understand that the Spanish legislation includes the most relevant of them,[§§§§§]now in a more synthetic manner than in the previous regulation (RD 561/1993 art. 42):

a) To evaluate the methodological, ethical and legal aspects of clinical trials referred to them.

b) To evaluate relevant modifications of authorized clinical trials.

c) To monitor the trial, from its beginning to the receipt of the final report.

It is advisable also –and nowadays it is also mandatory[******]– that the committees have jurisdiction over other forms of non-drug-related trials that involve human beings, whether or not they are invasive. This extension of powers includes observational studies (epidemiological research), other products, instruments or procedures, techniques and contrivances (in these cases, in a less bureaucratic manner), those which involve the managing of personal data, the use of embryos, embryonic cells and other human biological samples, as well as those related to

[‡‡‡‡‡] V. expand on the tasks and responsibilities to various legal instruments, Loris Paul, "Comité de ética de la investigación(CIS) ", p.And 410 s.

[§§§§§] RD 223/2004, art. 10 for clinical trials of drugs or medical devices, and LIB, art.12 for biomedical research in other fields (which regulates precisely said Act).

[******] V. art. 15 of the LIB.

human reproduction consisting in the use of gametes or embryos, to be permitted under domestic law, although its autonomous system will be treated below and the exclusive jurisdiction of other bodies, subject to the authorizations that this matter may require, jurisdictionally, by other bodies. For these latter cases it would be necessary to establish some more specific and flexible procedures, or at least to acknowledge competences for the reporting and monitoring of the experiment.

Finally, the committees could assume an educational or directive function in their corresponding centers, both on the various aspects related to the preparation and presentation of a protocol for evaluation by researchersand on the basic legal and ethical principles that may be involved inclinical trials.

As for the so-called humane use, when nearer to therapeutic experimentation or, better said, to the experimental therapy within clinical research, it must move in an environment of greater discretion on the part of the physician. This, within the freedom of treatment or method that must prevail in medical activity, although it is true that increased intervention and control of biomedical research has reduced the extent of that freedom. But this can only be accepted if it meets certain objective criteria:the existence of other treatments that prove to be impaired, that the new product being still in the experimental stage or with a known efficacy for other conditions other than the ones being treated offers certain reasonable expectations of healing, improvement or shows a palliative potential (weighing risks and benefits) and enjoys the patients' informed acquiescence –or, failing that, their legal representatives' or their families'. It is my opinion that these cases could be also known by the research ethics committees, preferably by the health authority,[††††††]notwithstanding that the latter is informed and revalidate the permit. This, if the urgency of the case does require its prior authorization as in any scheduled trial, while ensuring that the committee has the capacity to meet and decide as expeditiously as the case requires.

In order to streamline the procedure for issuing its ruling in multi-center trials, one of the committees involved in the evaluation, called reference committee, shall deliver its opinion, which should be binding upon all other committees (single ruling). These may refer their comments on the trial to the reference committee, but only observations on the local aspects of the trial will be binding to the reference committee. The current rules do not provide for the procedure to appoint the reference committee for acting in multi-center trials.The imposed criterion is that the promoter is to be attributed the capacity of appointing it. It does not seem to be most appropriate for a body being evaluated to elect its own evaluator. There are several alternative procedures that appear, in principle, to be more supported by objectivity and, thus, to be preferred.[‡‡‡‡‡‡]

[††††††] As stated in Art. 28 of RD 223/2004.

[‡‡‡‡‡‡] V., p. for example, proponents AAVV (Control Ético de laActividad Biomédica, CEAB), Control Ético de laActividad Biomédica, CEAB), *Controles éticos enlaactividad biomédica. Análisis de situación y recomendaciones*, p. 129 et seq.

This distribution of tasks among the committees has the advantages of facilitating the consistency and singleness of opinion, freeing other committees for other jobs, and strengthening the rationale for the survival of local committees in the Autonomous Communities where there are committees of larger geographic competency regarding multi-center trials (e.g. in the CEIC-E, of the Basque Country), since they may more intensely engage in tasks of monitoring authorized projects under implementation or already culminated.

The creation of the Coordinating Center was received with great expectations for its potential to facilitate the practice of single ruling, obtaining common criteria and consensus documentation on issues related to the evaluation and in need of clarification and harmonization. However, it is widely believed that the Centre has frustrated these expectations and has had prominent roles only in the functions assigned to it by law, and this has been at the expense of agility and coordination of the committees in performing their own functions.[§§§§§§]Nevertheless, a future modification or update of the rules on ECRs should reinforce their role and trust in the required political will for its role to be actually carried out according to theirlegal mandate.

2. Other specialized committees

It is relatively common –for evaluation and issuance of the corresponding ruling, including approval, for certain more specialized research activities that are, at the same time, more complex and sometimes more sensitive (ethically), also for public opinion–to opt for establishingspecialized and specially qualifiedcommittees that are usually unique and charged with national coverage.

This occurs, for example, in human genelab studies and perhaps also in clinical studies (e.g. the Human Genetics Commission, in the United Kingdom, with gametes and in vitro human embryos on fertility and the beginning of life (National Commission on Assisted Human Reproduction, arts. 15 and 20 of Law 14/2006), and with embryonic stem or somatic cells (or IPS) (Guarantees Commission for the Donation and Use of Human Cells and Tissues, arts. 34 ff., and 38 of Law 14/2007). The additional advantageof these bodies in relation to specific research activities that they have to rule on is that their members are more specialized and qualified, that the use of resources is optimized for activities that are usually in the minority, and that preservation of uniform standards is ensured, among other advantages.

VII. THE FUTURE: FROM THE CRISIS OF COMMITTEES TO THEIR DISAPPEARANCE?

1. The crisis of the committees: in search of other means of effective, quick and easy evaluation

§§§§§§ In thissense, too, AAVV (Control Ético de laActividad Biomédica, CEAB), *Controles éticos enlaactividad biomédica. Análisis de situación y recomendaciones*, p. 124.

European (EU) Regulation of clinical trials and of their systems and procedures for evaluation and authorization has been criticized, and some of this criticism has been far-reaching. This has served as a catalyst for the undertaking of major changes[*******] in view of the negative impact that apparently has affected the biomedical research projects conducted in the European areain recent years. This has been signaledby a relatively significant decrease in their frequency. This notable tendency of adecline in the number of trials is attributed to the loss of the appeal of the investigation when it somehow involves patients, now also including their personal health data (though not only these) and access to human biological material, sometimes from the same patients who are the trial subjects.

Several specific causes for this decrease[†††††††] have been pointed out. They are, at least partially, quite true, and therefore should be corrected though probably not as much as necessary. Let us briefly take a look at them.

1.1. Involvement of various evaluating organs for the same protocol

There have been objections to the current procedure requiring the separate submission of the projects to be evaluated, which can –and indeed does– result in diverging criteria for evaluations and for the monitoring of the implementation of projects. Each project must be approved by a different authority in each of the EU member states, and, within their borders, evaluation is referred to one or more research ethicscommittees.

It is true that disparities can be produced on the assessment of the same protocol by the various state agencies that grant approval in each country (national pharmaceutical agencies). Also, whenthe distribution or the assumption of competences among various committees of the same countryisfaulty, there may be an overlap of evaluations, which, in addition to unnecessary duplication of work, can generate new divergences in the evaluation. That happens sometimes, for example, when there is the coexistence of local and other senior committees (in the case of Spain, of autonomic rank).

It also can lead the promoter to have to submit all documentation to all bodies involved in the assessment process/authorization for each country.

To solve the problems of multi-center trials, which currently account for most of the tests carried out in health centers and are promoted by large pharmaceutical

[*******] Proposal for a Regulation of the European Parliament and the Council on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive 2001/20/EC (COM 2012) 369 final, July 17, 2012.

[†††††††] According to the Commission staff working document, *Executive summary of the impact assessment report on the review of the 'clinical trials directive' 2001/20/EC, Accompanying the document Proposal for a Regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use, and Repealing Directive* 2001/20/EC.

companies, a more coordinated procedure started to take shape in the 1990s against the then prevailing procedure, and pursuant to which each participating research group should submit the project to the committee of its own centerwithout them communicating with each other to discuss and perhaps resolve possible discrepancies between them in connection with the same project, apart from discrepancies in the nature and situation of the center itself and of the research group (local objections or observations).

With the aim of ensuring a single and common evaluation of a project involving the participation of several centers and equipment (multi-center trials), a specific procedure was adopted at the European level for evaluationsaccording to which of all committees involvedin the same country, one would be responsible for issuing the final binding report as appropriate in its case (reference committee).The other committees in other centers would restrict their focus to purely local aspects of the trial and to submitting to the evaluation committee general comments on the project to be referred to the reference committee,so that the latter could take the project into account or notin the exercise of its discretion to issue the single opinion, which would be binding forthe other committees. However, this system has replicated the previous individualistic system's decisions at European level and, for this reason, the current reform aims to provide greater geographical coverage to the evaluation and the approval process, as discussed below.

The possible disparities in the criteria for monitoring the implementation of approved projectsare also the subject of complaint in the above document.[‡‡‡‡‡‡‡] In my opinion, the regime and competencies that have been agreed upon for local committees do not seem to be the source of these inconsistencies. Monitoring focuses on preventing and detecting essential deviations of project implementation from the terms under which it was authorized and on identifying possible adverse events that the trial subjects could suffer.[§§§§§§§]Both cases, as well as actions to be carried out in each case, are sufficiently described in current regulations.

1.2. Extreme difficulty in running a clinical trial due to the inadequacy of the legal requirements in relation to practical needs

At this point it is alleged as an objection that the risk to patient safety in clinical trials may vary considerablyand depend largely on the degree of familiarity and prior

[‡‡‡‡‡‡‡] V. Commission staff working document, *Executive summary of the impact assessment report on the revision of the 'clinical trials directive' 2001/20/EC*...

[§§§§§§§] V. on the issue of adverse events in healthcare in general and specific to pharmaceutical surveillance(different from the tracking system in clinical trials, by the ethics committees on research; pharmaceutical surveillance, which has a mandatory regime, is attributed to the Spanish Agency of Medicines and Health Products; art. 54 of Law 29/2006, of 26 July, on guarantees and rational use of medicines and medical devices)), Romeo Casabona, C. M. and Urruela Mora, A.,*El establecimiento de un sistemanacional de notificación y registro de eventosadversos en el sector sanitario: Aspectoslegales*, Granada; Editorial Comares, 2010, p. 16 et seq.

experience around the active substance that is being tested. In this regard, it should be noted that it is important that the drug has already been approved in Europe or elsewhere. However, the criticism directed against the clinical trials Directive is that its requirements and restrictions apply to the same extent notwithstanding the risk to patient safety, and without considering practical aspects.

It is more questionable to accept this criticism without any further considerations. Firstly, because the safety measures that were established are of a general, that is, universal nature, as no additional conditions are distinguished regarding the harmful potential of a new drug. Therefore it is not consistent to make these requirements more flexible or to adopt completely different ones. On the contrary, the trial of a known drug for use in treating other conditions different from those that have been authorizedmay bring about new contraindications for these patients, determining the most appropriate dose for their effectiveness while reducing their potential iatrogenic effects, etc. It is true, however, that a better understanding of the process of the drug may offer more security during the trial, but without excluding other risks or unknown adverse effects. Therefore, the requirements are not understood as to which prerequisites should be excluded or reduced in these cases, as suggested by the criticism against current regulations.

1.3. Reliability of clinical trial data in a globalized research environment

It is assumed that the increasing current trend of globalization of clinical research may involve, in the same test, numerous research groups from centers located in different countries, particularly in those known as emerging economies. Although global trials entail a benefit to the participating countries, to their populations and to public health, they raise a new challenge for checking whether the trials comply with good clinical practice requirements.

It is true that the process of globalization of trials can burden the enforcement of the rules that affect them, particularly if there is the participation of countries with little substantive capacity for monitoring, and with their own evaluation bodies being composed of insufficiently qualified and non-independent members. And albeit this observation seems to suggest the giving up of strict application of the principles of good clinical practice, it must guide us in the opposite direction: precisely the globalization of clinical trials –some call it the translocation of trials– requires that reviews of methodology, ethics and the legality of trials are carried out in a more conscientious manner, particularly if performed wholly or partly in developing countries or emerging economies.

2. Forecasts of a new regulation of biomedical research, regardless of the ethics committees on research

The EU is presently engaged in a process now well underway to review the regulation of clinical trials, and this review will result in a significant modification of the current European regulatory regime (hereinafter the Proposal[********]) as well as in the explicit rejection of the current rulesembodied in Directive 2001/20/EC. This is meant to meet the demands of the pharmaceutical industry for further streamlining the evaluation process and reducing the requirements and procedures to be followed in each trialboth for the researcher and the promoter. Let us recall what was said above about the appropriateness of some of these demands and the criticisms they are based upon, but also not forgetting that there is a desire to eliminate some requirements that still seem necessary, at least for the writer of these reflections, to ensure adequate security and fundamental rights of trial subjects. The guaranteeing position that is supported in this study is not inconsistent with the assumption that the requirements and procedures should be tailored to the current needs and the evolution of biomedical research, removing anything that is unnecessarily detrimental to the agility required and the reduction of costs derived from the evaluation process itself.

In this study, I will not go into the details of most of the abundant and important developments that have been planned to be introduced,[††††††††]so I will focus on a brief explanation and on corresponding comments on the criteria and procedures for evaluation and authorization of trials carried out in more than one Member State, which are presented as one of the pillars of the reform in this area.

Indeed, one of the core aspects that the reform hinges on is, of course, the future role of ethics committees on research. The starting point to be established will affect the evaluation of multi-center trials involving several EU Member States (multistate trials, we could say in a parallel manner). The so-called "reference committee" in the intrastate field will yield, in these cases, to the "reporting State" or evaluator, which will assume responsibility for the evaluation and the binding report of a particular trial for all centers participating in it in the EU territorial space.

In this direction, the Proposal seeks to establish a procedure for evaluation and authorization that is flexible and fast, avoiding the introduction of a new centralized bureaucracy, because it will be widely controlled by the Member States. This is because all Member States where the promoter has decided to perform the test are to be involved in evaluating. To this end, it provides a mechanism for the designation of the evaluating Member State, which starts with the election by the promoter of the Member State that will assume the evaluation. This system, as applied *de facto* in the

[********] V. *Proposal for a Regulation of the European Parliament and the Council on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive* 2001/20/EC (COM 2012), 369, and cit.

[††††††††] For critical considerations in addition to those I will mention below, I refer to the European Group on Ethics in Science and New Technologies (EGE),*Statement on the Proposal for a Regulation of the European Parliament and the Council on Clinical Trials on Medicinal Products for Human Use, and Repealing Directive2001/20/EC (COM 2012), 369*.

Spanish system (with no rules backing it), is clearly inadequate, since it implies that the appraised chooses its evaluator. On the other hand, it establishes a coordinating and advisory forum, which will be responsible for resolving any problems that may arise during this process. This forum will be chaired and managed directly by the European Commission. Internal aspects of the evaluation will be in the hands of the states,[‡‡‡‡‡‡‡‡]provided that they ensure international standards for the independence of the evaluators.

This last aspect is to leave to each state the decision on the continuity of the ethics committees on research, as there is no reference to them in any of the details of the regulation; it is only a matter of creating a body whose members are independent, but not required to be multidisciplinary, some of them being completely unrelated to health systems and to the medical profession, that part of them being made up of lawyers and bioethicists. The base of the system has been consolidated over the last decades and presupposes that the evaluation must conform to legal and ethical aspects of the trials, in addition to methodological aspects, because of the importance they may have also from an ethical perspective. The fundamental ethical aspect evaluated by the state agency will be the subject's informed consent (art. 7.1, a, of the *Proposal*), which, as we saw above, was insufficient in the Nuremberg Code and also in the International Covenant for Civil and Political Rights. It seems that the European institutions have been driven by the pharmaceutical industry lobbies, leaping to the other end of the options available to improve the system.[§§§§§§§§]
On the other hand, what has also been criticized is the lack of robustness required of the arguments of a Member State to object to the report from the evaluating state,[*********] and so those arguments should be more consistent.

VIII. FINAL CONSIDERATIONS. THE DIFFICULT BALANCE AMONG COEXISTING INTERESTS

Throughout these brief reflections I wanted to highlight two fundamental ideas: research enjoys the highest recognition in our legal system; when the former consists in performing experiments using persons, the legal system has a number of direct or indirect provisions intended to ensure protection tothe rights of the latter and their

[‡‡‡‡‡‡‡‡] According to art. 7 of *The proposal*,national issues are individual competence of each state (e.g. The system of liability), ethical ones(e.g. modalities of informed consent,besides the forecasts included in this regard in Chapter V) and local ones(e.g. the characteristics of the center in which the testis to be performed).

[§§§§§§§§] Deeply critical to this provision,is the EGE,*Statement on the Proposal for a Regulation*...,becauseit supposes the failure of a universally accepted system and particularly in Europe through the Oviedo Convention and its Additional Protocol on biomedical research, in which the assessment of trials are based on the intervention of these committees.

[*********] According to art. 8.2 of the *Proposal* there only may be disagreement between a state and the evaluating state when: a) there are significant differences in normal clinical practice in the dissenting state and the evaluating state that could result in a subject being treated in a less than normal clinical practice; b) infringement of national legislation referred to in art. 86 (legislation prohibiting or limiting the use of human or animal cells).

well-being and safety, avoiding any harm to them, especially when it comes to their most precious assets.

As can be seen, this is an extremely sensitive matter that requires knowing how to ensure the smooth coexistence of various interests that can sometimes be in conflict: the requirements to protect research subjects, the proper channeling of usually expensive resources for relevant and beneficial scientific objectivesand, finally, the efficacy and freedom of scientific research.

On the other hand, we have found that some specific aspects are not sufficiently covered by sectoral regulations. The most essential guaranteeing aspects should be provided for in a law.

This opinion in favor of full regulation is justified by what is at stake: the safety and fundamental human rights of the subjects and the freedom of scientific research, sometimes with conflicting interests. Moreover, it is supported by comparative law in the countries'domestic law.

Specifically in relation to the evaluation and approval process and to the competent bodies to carry it out, it is of unanimous opinion that while the creation of a particular system formulti-center trials has been a breakthrough, it has not been able to eliminate the contradictions between the various committees, the full acquiescence of evaluations by the reference committee by other committees involved, and the reduction of the actual timing in issuing reports and the red tape involved, etc., which hinder the beginning of the trial and its smooth development. The coordinating committee has failed in what should be its main task of coordinating and harmonizing evaluation criteria and the interpretation of the applicable rules of the various committees through a consensus process, etc.

In any case, the unsatisfactory outcomes and shortcomings detected should not promote extreme alternatives leading to the marginalization or disappearance of ethics committees on biomedical research, as they have amply demonstrated their suitability to carry out accurate evaluations of several methodological, ethical and legal issues involved in trials, based on the independence, qualification and experience of its members.

On the other hand, there is an international trend towards the standardization and unification of legislation in this area –as in other fieldswith a similar prominence and incidence– both hand-in-hand with official international organizations, of which the Council of Europe is one of the best examples,[†††††††††]and with private organizations, in particularthe World Medical Association and the International Association of Penal

[†††††††††]Council of Europe,*Examination of legal problems in the medical field.Study of the legal aspects of the problems of medical research on human beings and, if necessary, legal appropriate preparation of an instrument*, 10th Meeting, Strasbourg May 1985.

Law.[‡‡‡‡‡‡‡‡‡] In European biomedical research, the EU has adopted and made regulations uniform, and at a widened scope that will still be made broader when regulation under development is approved, albeit its proposals are debatable.

[‡‡‡‡‡‡‡‡‡] V. Bassouini, Ch,ThBaffes,Th,Evrard, J. T.,*Le contrôle de l'expérimentation international sur l'homme*; Revue Internationale de DroitPénal(1980) 261-470.