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Research ethics committees in Europe: trials and tribulations

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Abstract *Introduction:* Ethics committees have been an integral part of clinical research since 1975, when they were introduced through the amendment of the Declaration of Helsinki. Every proposal for clinical research on human subjects has to be submitted to an independent ethics committee for review and approval. The European Clinical Trials Directive 2001/20/EC was implemented in 2004 to harmonise the legislative framework for clinical research in Europe in order to make Europe more competitive in clinical research while at the same time improving the protection of research participants. *Results:* We have evaluated the situation of ethics committees in Europe five years after the implementation of the new law with special consideration of the number of Ethics Committees per European Member State and the number of members within the specific committees, including the selection of members, also in regard to gender aspects and training requirements, the remuneration or compensation of members in regard of their review obligations, and also issues of conflicts of interest. *Conclusion:* Inadequate remuneration for professional services and gender imbalance are universal concerns across Europe. As the position of ethics committees changes continuously towards greater responsibility, further guidance is needed to uniformly adapt their structures to those needs.

Keywords Ethics committees · EU Clinical Trials Directive · Clinical research · Ethics committee members · Conflict of interest · Compensation · Gender aspects · Training requirements

Introduction

It is now more than 30 years since ethics committees were institutionalized as integral part of clinical research through the first amendment of the Declaration of Helsinki, adopted in Tokyo 1975.[1] Ethics committees are established to review clinical research protocols. Their decision was originally just an opinion, or advice given by the peers of the investigator, without any legal consequences; now—many years later—they have a defined legal status regarding drug trials. Today, no clinical

[1]World Medical Association (2002) World Medical Association Declaration of Helsinki: Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects. Adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964. Amended by the 29th World Medical assembly, Tokyo, Japan, October 1975; 35th World Medical Assembly, Venice, Italy, October 1983; 41st World Medical Assembly, Hongkong; 48th General Assembly, September 1989, Somerset West, Republic of South Africa, October 1996 and the 52nd General Assembly, Edinburgh, Scotland, October 2000 and the Note of Clarification on Paragraph 29 added by the World Medical Association General Assembly, Washington 2002.

research project can be started or published in a biomedical journal without the positive vote of an ethics committee. However, this is not a legal obligation, but a requisite imposed by editors of scientific journals. Furthermore it needs to be emphasized that the obligation of submitting a research project to an ethics committee is not harmonised within Europe regarding the nature of the research (observational study, retrospective evaluation of data, etc.).

Research ethics committees in Europe are typically composed of scientists and lay members; of physicians, members from the nursing profession, members with legal expertise, a pharmacist, somebody with ethical expertise, a statistician, at least one representative of a patient organisation, and others. Their main obligation is to review research protocols for clinical trials within a certain time frame. Although the European Clinical Trials Directive 2001/20/EC[2] was only aimed at research projects of medicinal products, some countries have—while transforming it into their national law—legislated in such a way that it applies also to other types of clinical studies, for example studies with medical devices, studies involving physical interventions, psychological manipulations, use of human biological material, and research on sensitive data.[3] Ethics committees have to evaluate, among other things, the relevance of the trial, the design of the trial in terms of its aims, scientific validity and risk/benefit ratio; the suitability of the researcher, available facilities and supporting staff, recruitment of trial subjects and methods of obtaining informed consent. Unfortunately the field of competence of ethics committees still lacks harmonization throughout the different European member states and in comparison with US ethics committees, which might lead to problems with editors of scientific journals when submitting a manuscript.

In the year 2004 the European Clinical Trials Directive came into force; the objective was to "simplify and harmonize" European research including the ethical review of clinical research. Since 2004 specific legal requirements have been foreseen in the European member states, among those the so-called "single opinion" procedure for multi-centre clinical research projects. The objective of the European Directive was to enhance the competitiveness of European research, especially in comparison with clinical research in the US. However, because ethical issues are at the European member states' own discretion, the systems still differ greatly throughout Europe. Member states such as France, where a specific system of provision of "one single opinion" was already in existence before the European Directive came into force, had little problem complying with the law compared with member states where ethical review has been a predominantly local issue. There the ethics committees did not like the idea of giving up influence and power and argued that they needed to "protect their patients".

The functions of ethics committees are very important. They were established to prevent misconduct in clinical research, and their prime obligation is to protect patients and healthy volunteers in this research. But other, very important, objectives are support of the investigator and his investigational plan, and, third, to give public assurance that clinical research is conducted in a transparent and ethical way.

But, are European ethics committees fit to serve all those purposes? How do representatives of ethics committees judge the current situation? The European project ICREL—Impact on Clinical Research of European Legislation,[4] the objective of which was to measure and analyse the direct and indirect impact of the Clinical Trials Directive and related legislation in the European Union on all categories of clinical research and on the different stakeholders (commercial and non-commercial sponsors, ethics committees, and competent authorities) has demonstrated in its survey that further guidance is needed.[5]

Number of ethics committees within European member states

Ethics committees are very heterogenous in Europe. This applies also to the number of ethics committees which are institutionalized in the different European member states (see Table 1, which shows the relationship between the number of inhabitants and the number of ethics committees disregarding the actual number of research projects per country) [1].

Number of members of ethics committees

Another issue of diversity is the number of members: Whereas France requires 14 members with permanent status—seven experts and seven lay members—and 14 substitute members, the number of members required in Germany is 7–15 depending on states legislation or university policy. In Poland, where there are 55 ethics committees and one appeal committee at the Ministry of

[2]Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

[3]Sweden: The act on ethics review of research involving humans (2003:460).

[4]http://www.efgcp.be/icrel.

[5]ICREL final report, http://efgcp.be/ICREL/#report.

Table 1 Number of ethics committees and inhabitants in European Union member states

Country	Inhabitants in 1,000[a]	Number of ethics committees[b]	Number of ethics committees (including local ethics committees)	Ethics committees per million inhabitants
Austria	8,356.7	27		3.23
Belgium	10,741.0	35	215	3.26
Bulgaria	7,602.1	103		13.55
Czech Republic	10,474.6	9	>100	0.86
Cyprus	801.6	1		1.25
Denmark	5,519.3	8		1.45
Estonia	1,340.3	2		1.49
Finland	5,325.1	25		4.69
France	64,105.1	40		0.62
Germany	82,062.2	53		0.65
Greece	11,262.5	1		0.09
Hungary	10,029.9	1		0.10
Ireland	4,517.8	13	40	2.88
Italy	60,090.4	264	>900	4.39
Latvia	2,261.1	5		2.21
Lithuania	3,350.4	2		0.60
Luxembourg	491.7	1		2.03
Malta	412.6	1		2.42
Netherlands	16,481.1	31		1.88
Poland	38,130.3	55		1.44
Portugal	10,631.8	1		0.09
Romania	21,496.7	1		0.05
Slovakia	5,411.1	9	89	1.66
Slovenia	2,053.4	1		0.49
Spain	45,853.0	136		2.97
Sweden	9,259.0	8		0.86
UK	61,612.3	126		2.05

[a] Source: Eurostat. News release 179/2008—15 December 2008 (http://epp.eurostat.ec.europa.eu/pls/portal/docs)
[b] Source: Ref. [1]

Health, the required number of members is 11–15. In Sweden 16 members are required, including the chairperson who has to be or have been a judge. Five members have to represent public interests. In Denmark the number of members is 7–15, among those four have to be lay members. In Portugal there are research ethics committees in every health-care institution with a minimum of seven members, and one national research ethics committee which is responsible for the issue of the "single opinion" and has 35 members. In Austria there is a minimum number of ten members with the specific requirement that for each application a physician in that specific medical field has to be involved, in addition to a physician who is not associated in any way with the trial and is not medical director of the institution where the trial is to take place. Next to the patient representative a member of an organised group of handicapped representatives is mandatory.

Training requirements for ethics committee members

There is no formal requirement for initial and ongoing training and education for ethics committees members across Europe. Training is necessary with regard to ethics and laws of clinical research, methods of clinical research, and the current standard operating procedures of the specific ethics committees related to the meetings and to the obligations ethics committee members have to fulfil. Members are selected for their specific expertise in a certain field, for example nursing, or law, or being a physician. But the other qualifications regarding clinical research are neither required nor taught. There are practically only rudimentary requirements for training in the individual EU member states. Only the UK has introduced regulations [2].

Selection of ethics committee members

Furthermore, there is practically no guidance regarding the selection process or application procedures to become a member of an ethics committee. Members are usually nominated by the institution which is responsible for the implementation of an ethics committee. The requirements for adherence of members to a specific group (physician, nurse, lawyer, ethicist, etc.) are given in the ICH-GCP Guidelines or in the various laws, but there are no

prerequisites for further qualifications, or transparent public application procedures. The relevant expertise in clinical research, in methodologies, and in clinical practice is not required.

Conflict of interest of ethics committee members

There is only very brief consideration of conflict of interest in the pertinent law in so far as members are required to announce a conflict of interest and to refrain from voting in such situations. But there is no active demand for the ethics committee to search for such conflicts on a regular basis. This is a problem, as increasingly start-up companies are founded from within the university hospitals and investigators might hold shares of companies and do thus have financial and academic conflicts of interests. If such physicians are also ethics committee members, the result is a multitude of possible conflicts, also with competing applications and applicants.

Compensation for ethics committee members

Except for some ethics committees where the members are compensated with a small attendance fee, members are generally working on an honorary basis. This means that they are not paid for their work, a situation which was acceptable 30 years ago, when the submission of clinical research projects was scarce and thus the time spent reviewing was limited. But now, in 2009, the workload is heavy and ethics committees usually meet monthly and have to review, discuss, and vote on many protocols; it is no longer prudent to ask for "free" assessment of the submitted applications. For example the ethics committee of the Medical University of Vienna handled 753 projects, 436 of which were interventional. The median time for a positive vote was 65 days after filing the project. If one counts the preparation time for a meeting, reading the protocols, the external reviews, the informed consent documents, and all the other relevant documents, many hours of uncompensated work are spent by highly qualified professionals. The ethics committee of the Medical University of Vienna was established 1978; it is one of the largest in Europe and has 12 regular meetings per year and another 12 sub-meetings regarding expedited review [3, 4] of research protocols with minor risk and minor burden. The regular meetings generally last a minimum of 8 h, the expedited review meetings take half a day. All together this adds up to approximately—not counting the preparation time of reading the protocols, external reviews and other documents—150 h. 150 h are the equivalent of approximately four weeks of regular work. The often encountered argument, "in order to avoid any conflicts of interests, the contribution of members of ethics committees cannot be compensated financially" is false and has to be repudiated. On the contrary, it is not acceptable to expect unremunerated work in this field as this leads to irreverence of the task, although one might argue that the participation in an institutional ethics committee is part of the multifaceted job of hospital doctors or physicians in university hospitals for which they are paid. The future of ethics committees can only be the small but professionalized committee of highly qualified and trained experts who are adequately paid for their contribution as an integral part of clinical research.

Ethics committees and gender

Another issue of importance is the gender issue: This issue applies in two ways—the representation of women among the members of an ethics committee (the members are constituted from "men and women" but there are no quotas for gender representation [5]) and the recommendation for the inclusion of women in clinical research projects. Guidance and regulations are needed to strengthen attention to gender equality in representation on ethics committees. Furthermore reasons for excluding women from clinical research projects should be investigated. Ethics committees should specifically address this issue and formulate rules for the observance of gender issues and the inclusion of women in research protocols.[6]

Future aspects

Needless to say, much has been achieved in the last 30 years, Ethics committees have not only been established in Europe and the US, but also in other countries where clinical research is being conducted. Next to the World Medical Associations Declaration of Helsinki other worldwide operating organisations, for example the World Health Organisation (WHO), the United Nations Educational, Scientific, and Cultural Organisation (UNESCO), The Council for International Organizations of Medical Sciences (CIOMS), and others have issued guidelines to structure and regulate clinical research also in those countries where no specific laws are in place, so that research projects can be conducted there in a standardized way and investigators and ethics committee members can be trained. This is important, because in developing countries facilitation and promotion of clinical

[6]Recommendations with Gender Reference for Ethics committees and Clinical Studies; Opinion of the Bioethics Commission at the Federal Chancellery, Austria (15 Nov 2008) http://www.bundeskanzleramt.at/DocView.axd?CobId=33153.

research projects are also necessary for the population to obtain healthcare for many diseases and conditions, which otherwise they would not receive, and it is also important because many research projects are collaborations with the developed countries and ethical review in a standardized and accepted manner avoids exploitation of poorer populations.

Ethics committees play an important role in guaranteeing transparency in clinical research. They are stakeholders for the conduct of clinical research according to good clinical practice. In the future, they will play an even greater role in regard to scientific integrity and will re-evaluate clinical research projects and the way the research project was conducted from its submission to publishing of the final report [6]. In order to carry out all these functions, it is necessary that the structures are adapted to these needs. Ethics committees have to strive for excellence to fulfil their obligations and to live up to the high expectation of the public.

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