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Research Ethics Committees: Can They Contribute to the Improvement of Clinical Research in Europe?

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Abstract: There is an increasing crisis of credibility in the world of clinical and epidemiological research because of lack of transparency in the identification of research priorities, increasing dominance of commercial interests over patients' problems, limited funds for independent research, and lack of awareness that clinical research is integral to the duties of clinicians as patients' agents. Research Ethics Committees (RECs) are an important component of the research world and since their institution there are expectations at their ability to protect patients and improve clinico-epidemiological research. To many people, however, the task of RECs is still essentially that of safeguarding the ethical/informed consent issues related to research protocols without a role in the core content (scientific and clinical) of the research projects themselves. Others argue that the duties of RECs should be broader because scientifically invalid research is in itself unethical. The remits of RECs, therefore, should embrace a full range of issues, from assessment of the core content of research (objectives, nonredundancy, clinical relevance, and likelihood of reaching the stated goals) to the protection of publication and dissemination rights of researchers from the intrusiveness of commercial sponsors. This debate is further complicated by current arrangements in countries where RECs' decentralization has made their operation less homogeneous and reproducible, with a diffuse discontent about the end results of their activities. In the first part of the article I discuss the evolution of the concept of the ethics of clinical research and the main differences in the arrangements of RECs across Europe. In the second part, after a brief discussion of the new European Directive on Clinical Trials and its potential problematic impact on publicly-funded trials, I propose a series of actions that should be taken to improve the functioning of RECs and outline the cultural changes needed for research of better methodological quality and of greater relevance to patients. **Key words:** *bioethics*, *ethics committees – clinical*, *ethics committees – research*, *scientific misconduct*, *therapeutic human experimentation*

DIMINISHING trust in the world of clinical and epidemiologic research has recently led to various and authoritative appeals (Angell, 2002; Davidoff et al., 2001). Several issues have been singled out as being responsible for this situation, including (*a*) limited or no autonomy of clinical investigators vis-à-vis their sponsors; (*b*) lack of transparency in the identification of priorities; (*c*) undue influence of commercial interests over patients' problems; (*d*) limited or no funds for independent—ie, investigator-initiated—research; and (*e*) lack of awareness that clinical and epidemiological research is integral to the duties of physicians as patients' agents whenever they can contribute to a decrease in the uncertainties about the effectiveness of medical interventions. Most of these problems are due to the limited public investment in research and could be alleviated by a

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profound shift in health policies and societal investment worldwide (Garattini & Liberati, 2000).

Research Ethics Committees (RECs)—Institutional Review Boards (IRBs) in the United States—are an important component of the research world. Since they were established it has been assumed that they would protect patients and individuals by ensuring informed participation in research and by appraising the methodological quality and relevance of clinical and epidemiological research. There is however a worrying lack of empirical evidence that RECs have actually been effective, even in ensuring that truly informed consent is granted by research participants (Oxman et al., 2001). The task of RECs is still seen by many to be restricted to safeguarding ethical/informed consent issues related to research protocols, without a role in assessing the core scientific and clinical content of research projects. Recently, a different view has been emerging, indicating that RECs should have a broader remits, ranging from the assessment of the core content of research (objectives, nonredundancy, clinical relevance, and likelihood of reaching stated goals) and the protection of publication and dissemination rights of researchers from the intrusiveness of commercial sponsors (Emanuel et al., 2000; Federman et al., 2003; World Medical Association Declaration of Helsinki, 2000).

In this article, after reviewing the evolution of the concept of research ethics, I discuss differences in arrangements of RECs in Europe and the issues raised by implementation of the new European Clinical Trials Directive. Moreover, I propose some actions that should be taken to enable RECs to become agents of a research that is

a. *relevant* (in terms of patients and society, and justified on the basis of systematic reviews of all relevant prior evidence);
b. *valid* (in terms of application of the most reliable research methods);
c. *nonharmful to patients* (including the guarantee of a truly informed participation); and
d. *free of interference* (in terms of diffusion and dissemination of its results).

I will not discuss the role of RECs as advisors of local health organizations and healthcare professionals on broader ethical issues or on questions arising from grey areas of scientific knowledge. Nor will I discuss the role of Data and Safety Monitoring Boards (DSMBs) of individual trials even though exploration of how DSMBs and RECs could interact, especially in the monitoring phase of clinical trials, would be worthwhile.

THE EVOLVING CONCEPT OF RESEARCH ETHICS

While there is general consensus about some of the essential features of an ethical clinical and epidemiologic research, today's challenges require an integrated framework in which the ethical and scientific dimensions of research are seen as continuous rather than discrete.

Recognizing the need for local adaptation and reassessment concerning the health-related, economic, sociocultural, and technological conditions at stake in different settings, Emanuel and colleagues (2000) have recently proposed 7 essential requirements defining a general framework when evaluating the ethics of clinical and epidemiological research: (*a*) social or scientific value; (*b*) scientific validity; (*c*) fair subject selection; favorable risk/benefit ratio; (*d*) independent review; (*e*) informed consent; and (*f*) respect for potential and enrolled subjects. Emanuel and coworkers' analysis starts from the recognition that to most researchers, bioethicists, policy makers, and other members of RECs informed consent is still seen as the key indicator of the ethics of research protocol. This has historical origins as most of the codes developed over the last 50 years or so (the Nuremberg Code, the Declaration of Helsinki, etc) were written in response to specific events and with a view to avoid the repetition of scandalous tragedies. Although these codes reflect part of the picture that needs to be monitored in order to protect individuals and the community, they are insufficient to

capture everything that makes research ethical, especially in terms of avoidance of undue risks for the patients, duplication of unnecessary research, use of inappropriate comparator(s) aimed at favoring the experimental interventions, etc (Emanuel, 2000).

The taxonomy of Emanuel and colleagues (2000) stresses that informed consent is only one component of the ethical evaluation of clinical research, and introduces the idea that the ethics of a research project goes beyond formal adherence to methodological principles in designing a research protocol. It introduces as essential components of the ethical judgement the *social value* of the proposed research and a *favorable risk/benefit ratio* of the interventions to be tested. The latter, however, needs qualification, as understanding the risk/benefit profile of a new experimental intervention means 3 separate things: (*a*) assessing whether the way the new study is designed is appropriate vis-à-vis its stated objectives; (*b*) deciding whether the study is necessary at all, given the knowledge and information already available; and (*c*) evaluating whether the new information gathered will provide truly useful information for the care of patients. As I discuss in the final section of this article, only (*a*) and (*b*) can be assessed by RECs at the level of research appraisal while (*c*) can be completely understood only a posteriori, once the new information has been incorporated into the existing one (a systematic review of other relevant information). Distinguishing these aspects is clearly important; one of the most worrying negative consequences of the increasing dominance of commercial interests in clinical research is the performance of research in which the benefits to individual and future patients are likely to be negligible, or research addresses an already answered question replicated only for marketing or commercial reasons.

To be sure, thorough evaluation of these aspects is far more complex (Federman et al., 2003) than formally evaluating adherence to the key principles of trial methodology (such as assessing whether appropriate end points and the mechanisms for patient selection and treatment assignment have been specified, etc) or checking that legal and insurance aspects have been correctly handled. Moreover, RECs today face other more important and subtle challenges that patients and the public expect them to meet (Federman et al., 2003; Garattini et al., 2003). For an extensive discussion of these issues readers may consult the recent Institute of Medicine's report "Responsible research: A system approach to protecting research patients" (Emanuel et al., 2000).

Research on the reasons that patients agree to participate in clinical trials (Jenkins & Fallowfield), shows that they are motivated essentially by 3 factors: anticipation of personal health-related benefits; perception that the invitation to enroll is a guarantee by a trusted medical advisor that the best available care will be delivered; and expectation that the results of the research may help future patients in situations similar to theirs. It seems logical to assume that an ethical imperative is that these expectations should be fulfilled.

Since the late 70s the upsurge of clinical epidemiology (Sackett, 2002) and, later, evidence-based medicine has challenged the status quo of medical knowledge by documenting a substantial lack of internal validity and clinical relevance of research information produced, both in drug (Born & Collins, 1997; Nicolucci et al., 1989; Rossetti et al., 1993) and nondrug (Assendelft, 1995) interventions. Similarly, there is increased awareness that the research agenda is distorted by the lack of explicit mechanisms to identify and prioritize research questions according to patients' needs (Garattini & Liberati, 2000). Data from the Italian registry of clinical trials – Osservatorio Nazionale Sperimentazione Clinica (Ministero della Salute, 2003) – confirm this situation. Of the 1659 studies approved by RECs in Italy between 2000 and 2002, 64% were phase III or IV trials. Over two thirds of the total (1260/1659, 77%) were sponsored by pharmaceutical companies, 19% by independent research groups, and only 3% by universities. Finally 82% (1309/1605) were multicenter and 59% (667/1129) international. There are legitimate concerns that the situation may become increasingly more unbalanced because of the decrease of public funds

for independent research at national level and the lack of European funds for clinical and epidemiological research.

RESEARCH ETHICS COMMITTEES: ORIGIN AND DIVERSITY

The Declaration of Helsinki and other international regulations should make it obvious to all those involved in human research that ethical principles should be followed and that review of a study protocol by RECs is a compulsory step for clinical trial. Nonetheless, examples of unethical research are still reported, with researchers dazzled by the potential scientific and financial rewards, forgetting the moral and humane principles to which they should adhere (Geraci, 1992; Hoston & Peterson, 2001; Lurie & Wolfe, 1997; Rothman & Michels, 1994; Salit, 1992; Sutherland et al., 1993; Varmus & Satcher, 1997). Because of the lack of clear evidence that RECs have been able to fulfil their safeguard role, they continue to be both highly valued as well as strongly criticized (Alberti, 2000; Blunt et al., 1998; Savulescu et al., 1996).

Published reports on the activities of RECs in different countries indicate that there is large variation in their practice. This reflects differences in their general mission, different organization, lack of specific guidance, heterogeneity in their membership, etc (Dal Re et al., 1999; Italian Cochrane Centre, 2002). Of course, evaluation of research protocols and clinical trials is only part of the overall duties of RECs to provide advice to healthcare institutions and providers on ethical issues arising in daily clinical practice and from potential application of research findings to patient care. The reality is, however, that RECs are becoming overloaded by the increasing number of trials carried out in hospitals and healthcare institutions, and that they often spend most of their time appraising research protocols without having either the necessary skills to do it effectively, or the infrastructure and resources to monitor trials efficiently.

Assessments of the quality of research protocols before and after they have been reviewed by the same RECs, and across different RECs, as well as analyses of what contributes to approval or rejection by RECs, are rare and unsystematic and mostly hampered by the lack of explicit criteria and documentation. RECs are thus part of the problem, together with the misleading confidentiality rules set by commercial sponsors and uncritically accepted by regulatory agencies and the scientific community (Ashcroft & Pfeffer, 2001). Systematic analyses of how RECs operate are not only necessary but also key to improving the current and widening gap between patients' interests and the research currently done.

COMMON ISSUES FOR EUROPEAN RECs

The literature on the organization and functioning of RECs in Europe is scanty, and the legislative and organizational arrangements are evolving continuously (see Table 1). One is therefore left with occasional reports that either come from individual RECs or represent the informed opinion of individual researchers/clinicians or policy makers (Blunt et al., 1998; Dal Re et al., 1999; Italian Cochrane Centre, 2002; Varmus & Satcher, 1997). In many European countries the number of RECs has been increasing over the last few years in response to an increased awareness of the ethical problems in relation to human experimentation, the growing number of research protocols carried out at hospital and health services level, and the increased regulatory requirements of national and international bodies.

The main differences that exist today among European countries in the legislation and functioning of RECs have to do with (Italian Cochrane Centre, 2002) (*a*) *their general scope and duties*; (*b*) *the degree of centralization/decentralization* of their functions (especially as far as research protocol evaluation is concerned); (*c*) *the type of expertise* required for those serving on them; (*d*) *the resources* (budget and infrastructure) that should be made available to ensure that RECs can operate effectively; and (*e*) *requirements*

Table 1. Development and essential features of RECs in some European countries*

Germany	The first independent ethics committee was established in Germany in 1972 and the first one to assess clinical studies in 1978. As of 2002, the number of RECs was 52 (35 in university hospitals and 17 linked to regional medical associations). All are centrally certified and independent. Existing RECs review about 10,000 projects per year with an average of 200 per REC. There is no central registry (although discussion is ongoing in this respect).
Spain	Since 1982 no experimental study can be carried out without authorization from the regulatory authority. Since 1982 a database called *Base de Datos Espanola de Ensajos Clinicos* has been progressively enriched with new data. Since 1999 the registry has been under the control of the Agencia Espanola de Medicamentos. Since 1993 (Real Decreto 561/1993) all experimental studies need to be approved by local RECs. The law also defines RECs, and the number and profile of their members. The number of RECs has reached 150. In recent years there has been a tendency to reduce their number and to create regional committees, which operate under more explicit criteria.
The Netherlands	In 1999, with the *Medical Research Involving Human Subjects Act*, the whole system of ethical and scientific review was reorganized and local RECs were launched. A Central Committee (with 13 members from different backgrounds and nominated by the Ministry of Health) exists to review particularly complex research projects, to accredit local RECs, and oversee the collection of all data about ongoing trials in a central national registry. Local REC membership include at least 1 medical doctor, a pharmacologist, a clinical researcher, a bioethicist, and a lay member. Every year, each REC submits a detailed report of its activities to the Central Committee. At the beginning of 2002, the number of RECs was 77, became 55 in mid 2003, and is likely to be further reduced.
Italy	Up to 1998, all experimental studies had to be reviewed and authorized by the Central Drug Committee (*Commissione Unica per il Farmaco, CUF*). In 1998, local RECs were established with the aim of decentralizing and speeding up the approval process. As of December 2002, there were 248 registered RECs. All experimental studies have to be authorized by local RECs. There is no preliminary assessment by the Central National Bioethics Committee (*Comitato Nazionale di Bioetica*), which is a government-appointed body that provides general advice on broad ethical issues and is not involved with the assessment of research protocols, nor with the monitoring of REC activities. A national registry (*Osservatorio Nazionale per la Sperimentazione Clinica*) has existed since 2002 and an annual report on REC activities has been regularly published since 2001. RECs must report the results of their assessments to the central registry, but compliance with this is still variable. Data have not been initially accessible to the public but only to individual RECs. Public accessibility to an essential set of information is going to be implemented starting in 2004. For more information see http://oss-sper-clin.sanita.it/dati_pubblicazioni.htm

(*Continues*)

Table 1. (Continued)

Norway	The system is made up of a National Commitee for Medical Research (NEM) and 5 regional RECs (established in 1985). NEM is a coordinating and advisory body for regional RECs (with a referral population ranging from 600,000 to 1.2 million people). NEM has the duty to inform researchers, policy makers, and the public of current and potential questions concerning research ethics. Regional RECs have 8 members with a multidisciplinary background (2 from the medical profession, 1 nurse, 1 policy maker, 1 ethicist, 1 lawyer, 1 psychologist, and 1 lay representative) and are responsible for scientific and ethical assessment of all medical research in their respective geographic areas. Results of the deliberations of RECs are not publicly accessible. Multicenter studies are reviewed by the REC where the project leader is located. Recommendations made by each REC are final and there is no central court of appeal. For more information see http://www.ethikkom.no/REK/english/RREC
Denmark	For 20 years there has been a Central Committee (with 2 members of each regional committee, 1 lay member, and 1 scientific member). Besides the Central Committee there are 8 regional RECs responsible for all research activities in a given geographic area. REC statutes and laws were launched in 1997. Since 1992 REC membership has envisaged a lay majority. A workload of about 3000 protocols is estimated per year. All transactions of RECs are open for public inspection. For more information see http://www.forsk.dk/eng/CVK/publ/jub2001_uk/chap2.htm
Sweden	The basis for Ethics Committees is the Declaration of Helsinki. Ten regional RECs are linked to the universities. They cover all medical research in their respective regions. There is no central court of appeal.
United Kingdom	The number of local RECs has been increasing over time. In 1991 a more centralized system was introduced and since 1997 a system of Multicentre Research Ethics Committees (MRECs) was set up—one per region plus Northern Ireland, Wales, and Scotland—but there are still 255 active local RECs. MRECs have responsibility for multicenter clinical trials: MRECs are independent advisory bodies providing advices on the science and general ethics of multicenter research proposals and each multicenter project is assessed by 1 MREC only. After MREC assessment local RECs are still expected to make their own evaluation. RECs are funded locally in a quite variable way, and members' work is essentially voluntary. MRECs have paid administrative staff. MREC and REC membership is multidisciplinary with an average of 12 people. Since 2001, in preparation of the European Directive, a series of documents/guidance have been produced to harmonize and coordinate REC functions. For more information see http://www.corec.nhs.uk

*For more information about RECs in Europe see http://www.COE.INT/legal-affairs/legal_co-operation/bioethics/COMETH/2-links.asp#topOfpage.

in terms of explicit criteria and rules for the assessment process.

Interestingly, available information also shows that, in many countries, there have been shifts from one extreme—a unique National Committee as it was in Italy up to 1998—to the other—with over 280 local RECs now operating in Italy, many local

RECs in Spain, Germany, the Netherlands, and United Kingdom, and a regional arrangement in Denmark and Norway (see Table 1).

Moreover differences exist in terms of the level of coordination required, type of expertise, etc, with regulatory decisions seemingly taken in the absence of good empirical evidence that one model is better than any other. One suspects that the unacknowledged confounding factor is the conflict between the economic implications of a quick *green light* to drug companies for conducting the studies needed to support the registration of a drug and what is really relevant for patients' health and welfare, and for knowledge advancement (Cave & Holm, 2002).

All in all, we are left with the reality that it is increasingly difficult to agree on what makes a research project ethical. Even if consensus exists about some components of this judgement (Emanuel et al., 2000; Federman et al., 2003) wide disagreement often continues to emerge in specific cases (Geraci, 1992; Hoston & Peterson, 2001; Lurie & Wolfe, 1997; Rothman & Michels, 1994; Salit, 1992; Sutherland et al., 1993; Varmus & Satcher, 1997).

Moreover, there are other important questions that need to be answered: (*a*) how many RECs are needed in a given country? (*b*) should functions be separated/harmonized when it comes to approving a research protocol? (*c*) what should be the relationship between the REC and DSMB for individual multicenter studies? (*d*) are special rules needed for multicenter studies? and (*e*) will RECs in a given country, and soon at European level, ever be enabled to become part of a harmonized network, so that information can be easily and quickly socialized and procedures made more consistent?

THE EUROPEAN CLINICAL TRIALS DIRECTIVE

On April 2001, a European Directive on Clinical Trials was approved, concluding a discussion process initiated in 1995, when the European Commission published a concept article for a European Directive on Implementing Good Clinical Practice. Member states must implement the directive through national legislation by May 2004. The essential aims of the directive (European Directive 2001/20/EC 2001) are to harmonize the various national administrative procedures necessary to start a clinical trial and to set pan-European legal standards for protecting all clinical trial participants.

According to the directive, all trials must have a sponsor who will assume full responsibility and liability for the entire study (in case it is multicenter). In the case of multicenter studies it is the REC of the institution where the study coordinator is located who has to authorize/reject the proposal. RECs in other participating institutions can only make comments on the content of the protocol, notifying them to the REC of the coordinating center, and modify the informed consent procedures and forms locally, within 60 days of receipt of a standard trial application. The REC of the coordinating institution is also formally charged with long-term monitoring. All trials are meant to comply with the intensive monitoring standards required by the Good Clinical Practice regulations.

Despite the generally good intentions of the directive, serious concerns and criticisms have been raised. As recently reported in a *Lancet* editorial ("Who's afraid," 2003), the directive was "initially conceived and drafted as a way of facilitating commercial drug development to give Europe's pharmaceutical industry a competitive edge." The needs of noncommercial clinical trials were not even considered, let alone discussed in earlier drafts of the directive.

Concerns have been expressed that the new European Directive has been led too much by industry and overinfluenced by the intention to facilitate commercial research rather than the protection of research participants (Cave & Holm, 2002). This comes as less of a surprise considering that all the European Union's drug regulatory activities—including those of the European Medicine Evaluation

Agency (EMEA)—are incorporated into the Industry Directorate rather than into the Public Health Directorate, as it would be far more logical and appropriate.

As it stands, the proposed legislation will impede publicly-funded trials without improving the quality of trials or patients' safety (Medical Research Council [MRC], 2003). A recent UK Medical Research Document (MRC, 2003) summarizes major issues that are likely to emerge from the application of the new directive:

- The requirement for a single sponsor does not fit the collaborative approach to sharing of responsibilities in multicenter publicly-funded trials;
- The introduction of a rigid approach to monitoring and pharmacovigilance may not be appropriate in many trials of already marketed products;
- Charities and other noncommercial entities will be unwilling to assume the risks and administrative complexities implied by being "sponsor" (in the new sense defined by the directive);
- The authorization process becomes too burdensome;
- There is a lack of clarity over transitional arrangements;
- There is a threat to important trials of emergency treatments in patients unable to give consent; and
- The increased costs of conducting trials, in conjunction with the limited public funds available, will inevitably result in fewer trials being funded.

Although the main changes introduced by the directive cannot be modified by individual countries, it remains to be seen how different member states will react to the new European Clinical Trial Directive given that it provides a framework in which they must redefine and revise their ethical review system and rules. It will also be important to see whether a strong request for modifications of the above rules, which are likely to hamper publicly-funded research, will emerge in line with the arguments set out in the UK MRC document (MRC, 2003).

SOME URGENT ACTIONS TO IMPROVE RECs ACTIVITIES

With due consideration to the differences among European countries in the organization and legislation relating to RECs (Italian Cochrane Centre, 2002), a few actions should be conceived urgently. While none of them can be fully implemented by individual RECs, and require infrastructural and legislative interventions that are the prerogative of health and regulatory authorities at national and/or European level, increasing the awareness of RECs is a necessary first step to achieving the profound changes that have been discussed in this article.

1. *RECs should require that each research project be supported by a systematic review of studies relevant to the question(s) being addressed and that some essential information be submitted with the research protocol they have to assess*. The only way to reduce redundant research and to avoid unethically designed studies (ie, unwarranted use of placebo) is to have access to all the relevant information about research already carried out. Easy access to sources of systematic reviews of studies conducted in a given area—such as the Cochrane Library (2003)—is essential to assess whether the proposed research is relevant, addresses unanswered question(s), or is simply repeating or reassessing what is already known (Chalmers, 2001). In each new proposed protocol RECs should be able to find the clinical and epidemiological justification(s) of the new research proposed. An important example in this direction is the UK MRC requirement that all research applications should be accompanied by a systematic review spelling out what is already known in an area and what kind of new knowledge the new study seeks to add.
2. *RECs should be enabled to have access to all information on ongoing studies*. It is of international concern that it is

not possible to access information about all initiated clinical trials (Dickersin & Rennie, 2003). Given the high level of fragmentation and redundancy that characterizes the current practice of clinical research, together with the repeatedly demonstrated tendency of scientists to publish their positive findings more often than negative ones (publication bias), a comprehensive international register of all trials would provide information about which trials have been started and to what extent a proposed trial is warranted.

3. *Evaluation of research protocols by RECs should be based on explicit criteria and undergo comparative evaluation*. Comparative analyses of the procedures and criteria used by RECs for assessing research protocols should be encouraged and stimulated. Resources to do this should be given as part of the infrastructural funding of activity of RECs. Data should be exchanged, either through the national/regional databases implemented by regulatory authorities—see the registry implemented by the Italian Ministry of Health (Ministero della Salute, 2003)—or by establishing newsletters, bulletins, or electronic journals with this specific aim.
4. *Potential conflict of interests of the members of RECs should be disclosed and assessment of research protocols made publicly available*. There is mounting concern that professionals serving in RECs may have conflicts of interest jeopardizing the independence of their activities. As a recent US survey indicated (Campbell et al., 2003) half of the faculty members serving in IRBs served as consultants to the industry. This is a problem that should be openly discussed. Moreover, awareness of this problem should lead to public disclosure of the results of the assessment of research protocols.

   The Danish model (see Table 1), and public accessibility of the deliberations of RECs, deserves more attention by the international community.
5. *RECs should do their best to prevent publication bias or selective suppression of study results*. Although the role of RECs in the public dissemination of the results of research is not addressed explicitly in international codes or national regulations governing human research, they have been criticized for not ensuring public dissemination of research they approve (Antes & Chalmers, 2003; Kravitz, 2000; Mann, 2002). Although it may be difficult for RECs to follow studies to publication, there are 2 ways in which they can address selective publication of favorable results (ie, publication bias): (*a*) by making sure that the contracts between the sponsors and the research institution where the study will be conducted does not include clauses that allow the former to veto the full publication of the results; and (*b*) by registering in national and international registries of ongoing studies all the protocols that they assess. Attempts to make RECs accountable for this function are still rare, but an encouraging shift in this direction is beginning to emerge—see the recent guidance issued by the Italian Ministry of Health (Martini et al., 2003)—and it is reasonable to expect RECs to take a strong position in order to make this happen.
6. *Coordination rules among RECs are needed, especially in countries where a decentralized model has been implemented*. Experience in many countries has followed a sort of *pendulum shift*, with countries that now rely on large number of RECs without a formalized mechanism to avoid duplication and disagreement (ie, Italy, Spain, Germany), countries that are slowly moving toward a more centralized system (ie, the Netherlands), and others where efforts are underway—not without problems and contradictions—to harmonize these functions (ie, United Kingdom) (Cave & Holm, 2002). Especially in countries

who choose the decentralized model, as Italy did in 1998 (Decreto Ministeriale, 2003), health authorities bear a special responsibility for making sure that coordination and communication is maximized. Experience of creating multiple layers (ie, special committees for multicenter studies such as in the United Kingdom) has not being particularly encouraging, especially if the respective responsibilities (of, say, local and regional RECs) are not specified and coordination and exchange of information not fostered.

7. *Organized training programs should be offered to all RECs*. An effort should be made to provide more training and education to REC members—especially lay members and patients' representatives—in order to guarantee a truly multidisciplinary evaluation. The comparative analyses of the "real-life operation" of RECs should be an essential component of these training programs. This training/educational effort is most urgent in those situations where RECs are highly decentralized. National/regional health authorities should be held accountable for seeing that these educational programs are offered and that they are of good quality. A superficial look at the European situation (Table 1) does not provide any evidence that there is a consensus about the standard desirable membership for RECs. It follows from the issues discussed above that expertise in management of scientific information as well as in critical appraisal of research methodology and relevance is of great importance, together with lay members with at least basic skills of research methods and communication.
8. *The spectrum of problems to which RECs currently pay attention needs to be clarified*. Should RECs only evaluate experimental studies (the vast majority of which are pharmacological) or should they also assess the ethical implications of observational studies? Legislation varies in this respect in different countries and the new European Directive seems to consider only interventional trials. To be sure, if all observational studies are to be examined by RECs in the same depth as interventional trials, their collapse is a possible outcome. Once again, explicit rules are needed as observational studies can help the uptake in clinical practice of interventions of proven effectiveness, but they can also be very dangerous if used as "Trojan horses" to introduce unproven new treatments/technologies in routine clinical care. This may happen when, as part of research protocols, complex and invasive diagnostic procedures or follow-up schemes of unproven effectiveness are required as prerequisites for the implementation of a research study.

CONCLUSIONS

There is no doubt that the world of clinical research is facing a profound crisis. New opportunities for progress in medicine (Lenfant, 2003) raise questions about whether the scientific community is able to defend research inspired by a concern for the best interests of the patients and the public.

The reasons for these concerns are many, ranging from the lack of independence of researchers, the dominance of commercial interests, the decreasing leadership role of academia (Angell, 2000), and the lack of policy and financial investment in research by healthcare systems (Garattini & Liberati, 2000). In such a complex scenario it is unrealistic to expect that RECs alone can improve the situation. Cultural and healthcare policy shifts are needed to change the current state of affairs. But RECs should not wait for these. They should instead become more active in the defense of patients' rights, endorsing the more integrated concept of ethics that has been discussed above.

Finally, a rarely discussed issue concerns the responsibilities of funders of RECs for ensuring that RECs function well, with the resources and infrastructure needed to enable

them to work effectively along the lines discussed in this article. Do policy makers care at all about what their RECs do? Do they consider at all the potential role of RECs when taking their "micro" clinical governance decisions as well as their "macro" allocative and distributive options? Greater accountability of policy makers and managers is needed here and should become part of the ongoing discussion on whether and how health services act to effectively protect patients' and society's best interests.

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