RESEARCH ETHICS

Research ethics committees in Europe: implementing the directive, respecting diversity

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With the recent Clinical Trials Directive, a degree of harmonisation into research ethics committees (RECs) across Europe, including the time taken to assess a trial proposal and the kinds of issues a committee should take into account, has been introduced by the European Union (EU). How four different member states—Hungary, Portugal, Sweden and the UK—have chosen to implement the directive is shown. Although this has resulted in four very different ways of structuring RECs, similar themes are present in all four cases, such as centralisation of control over RECs within member states, harmonisation of REC procedures across the EU and increased role of political decision making with regard to such committees.

the suitability of the investigator and supporting staff; ... (g) the adequacy and completeness of the written information to be given and the procedure to be followed for the purpose of obtaining informed consent ...

Given the detailed nature of the directive with regard to how RECs should review an application, it is interesting to see how this piece of legislation has been interpreted by different member states, and the effect it has on the “shape” of different REC systems across the EU.

This paper presents preliminary research from the ED-REG-HAR project funded by the European Commission, which is examining the effect of the directive on RECs in four EU member states: Sweden, Hungary, UK and Portugal.⁶ These countries were chosen for comparative reasons, given the differences between them in terms of the extent of pharmaceutical company activity, gross domestic product and less tangible factors such as ethical values.⁷ The project is primarily ethnographic in methodology and uses observation of RECs, supported by interviews with committee members and other key players in each country. The aim of this paper is to present preliminary data from this project, exploring the different ways in which the directive has affected the structure surrounding RECs in four different member states, and to draw broader conclusions about the relationship between the EU and research ethics in member states.

The recently published report of the Ad Hoc Advisory Group on NHS research ethics committees (RECs)¹ has stimulated a variety of critical responses.^{2–4} Yet, so far, discussion of the UK’s REC system has tended not to fully consider the European context of recent changes. With the implementation of the Clinical Trials Directive, the role of the European Union (EU) in ethical decision making in member states has expanded considerably.⁵ This directive aims at harmonising the running of clinical trials across the EU as part of broader trends in drug regulation and relates to ethical issues through the role of RECs in the clinical trial process. Under the directive, “A clinical trial may be initiated only if the Ethics Committee ... comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks” (Article 3.2.a), where an ethics committee is “an independent body in a Member State, consisting of healthcare professionals and non-medical members” (Article 2.k).

In addition to setting out these points of membership and requiring ethics committees to reach their decision on a clinical trial proposal within a set time (60 days), the directive also presents some points of practice for conducting an ethical review. For example, in Article 3, it is stipulated that

In preparing its opinion, the Ethics Committee shall consider, in particular: ... the relevance of the clinical trial and the trial design; ... whether the evaluation of the anticipated benefits and risks ... is satisfactory ... the conclusions are justified; ... the protocol; ...

ANALYSIS

This section presents a description of the REC system in each of four countries before and after the directive was implemented, highlighting elements that have changed as a result of this EU-level intervention.

Sweden

Discussion around ethics and medical research developed in Sweden in the wake of the first Declaration of Helsinki in 1964. Provisional committees and review boards were established at faculties of medicine in the larger universities,

Abbreviations: CES, Comissões de Ética para Saúde; CEIC, Comissão de Ética para a Investigação Clínica; EU, European Union; GYAB, Committee for Application of remedies; IKEB, Institutional Ethics Committee; KEOB, Research Ethics Medical Committee; KFAB, Clinico-Pharmacology Subcommittee; KFEB, Clinico-Pharmacological Ethics Committee; MFR, Swedish Medical Research Council; OGYI, National Institute of Pharmacology; REC, research ethics committee; UKECA, UK Ethics Committee Authority

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with the backing of the Swedish Medical Research Council (MFR) and the Ethical Delegation of the Swedish Society of Medicine (now known as the Medical Association). These early medical RECs were located at the larger universities and university hospitals.⁸

In all, there were 10 ethics committees, with a wide scope of activity. Formally they were only advisory boards, and researchers were not obliged by law to get an approval for their projects, but as most sponsors required ethical review before financing any research, almost all research passed through these ethics committees. In addition, under university rules, all larger student projects, PhDs and other research projects conducted on humans at the universities had to be approved by these committees.

In January 2004, in accordance with the EU directive, these committees were replaced by RECs established as independent government bodies although in some cases they have inherited some of the members and administrative staff of the preceding committee. All staff and offices are rented from a host institution, usually a university, where the REC formally has its residence. Six regional RECs are now present in Sweden: Lund, Gothenburg, Uppsala, Linköping, Stockholm and Umeå, and one central committee, at the Swedish Research Council in Stockholm, which serves as an appeal board for cases that are either turned down by an REC, or when an REC is indecisive.⁹

All regional committees must have at least two chambers, one for medical and pharmaceutical research and one for other research. The committee chair is always a judge and each chamber has 10 members representing the research community and 5 laymembers representing the public. The central ethics committee also has a judge as a chair and six members, of whom four are researchers and two are laypeople. The government appoints all members and chairpersons. The RECs are expected to meet 10–12 times a year and all cases to be decided on within 60 days. The RECs are designed to be self-financed, it costs around £1200 to submit an application for clinical trials or multicentre research. The members are given a small sum in remuneration, around £2000 annually.

Hungary

Established in 1982, the first REC in Hungary, called the Research Ethics Medical Committee (KEOB), was a subcommittee of the Committee for Application of Remedies (GYAB). Composed of representatives of Hungarian pharmaceutical companies (at the time all state owned), KEOB was established to facilitate the implementation of the Declaration of Helsinki. At the time only a few clinical trials took place in Hungary; all of them were conducted by Hungarian pharmaceutical companies. The duty of the GYAB was to decide which chemicals should enter phase I, II or III trials; the role of the KEOB was to give an ethical opinion on the cases. During the 1989 transition to democracy, changes in this system established a Science Research Ethics Committee, with a subcommittee called the Clinico-Pharmacology Subcommittee (KFAB). In the late 1980s and early 1990s, there were still few national clinical trials going on in Hungary and the KFAB had to make decisions on 3–4 protocols a year. At the same time, regional RECs were established, which had higher workloads as, in the beginning, only they were responsible for phase I and phase II trials taking place in their regions; such protocols handed in to the regulatory agency were passed to KFAB, whereas the trial sponsors in the case of phase III or IV trials asked ethical permission from regional committees.¹⁰

Legislation implementing the directive has been in place since 1 July 2002, removing the rights of the regional RECs to review pharmaceutical research and establishing the central

Clinico-Pharmacological Ethics Committee (KFEB) that decides on all protocols for pharmaceutical research on humans. Based in Budapest, the KFEB has 20 members, many of them prominent members of regional RECs, most of whom are leading medical doctors, with two lawyers, two non-physician health professionals and one patient group representative. The committee meets once a month, dealing with 20–30 new protocols at each meeting. Each protocol is presented by a member before being decided on by the committee. The complete decline of a protocol is rare (between 4 and 6 a year), although every year about 30 applications are returned with the request for some changes. Members receive a quarterly payment for their work as experts. In addition to this national REC, each institution taking part in human experiments must have an Institutional Ethics Committee (IKEB) that monitors trials and decides whether local human and technical resources are adequate for a particular trial. Any research on humans requires permission from the regulator, the National Institute of Pharmacology (OGYI), which in turn first requires ethical permission from the KFEB and the IKEBs.¹¹

The UK

Stimulated by medical whistleblowers in the 1950s and 1960s (particularly Pappworth's *Human guinea pigs*¹²), RECs in the UK developed as a local response to concerns about clinical research. This resulted in the setting up of more than 200 independently minded local RECs with their origins in local need, responsible to the health authorities and with the ability to review applications for research being carried out in their region. The 1990s saw a rise in concern on the part of researchers that the large number of local REC applications or approvals required to start multisited projects (such as clinical trials or epidemiological studies) was hampering research.¹³ In 1997, the Department of Health sought to introduce a degree of centralisation and standardisation by setting up 10 multicentre RECs, based in the regions, responsible to the Department of Health and with the ability to review applications on research in more than five sites.¹⁴ The relationship between local RECs and multicentre RECs has been characterised by a degree of tension, as local RECs retain the right to comment on and reject (for local reasons) multicentre research approved by a multicentre REC.

In 2000, as a prelude to the introduction of the directive, the Department of Health set up the Central Office for Research Ethics Committees, a body with the responsibility to coordinate RECs and improve the workings of the system. Unlike in some other member states, none of these changes were supported by legislation. Rather, the system was based on guidance and advice from the Department of Health.

In the UK, the directive was implemented through The Medicines for Human Use (Clinical Trials) regulations, which came into effect in April 2004. The UK government made ostensibly minimal changes to the REC system, setting up a new body, the UK Ethics Committee Authority (UKECA) consisting of the Secretary of State for Health, the National Assembly for Wales, the Scottish Ministers and the Department for Health. The role of the UKECA is to recognise RECs and allow them to assess clinical trials applications; in reality, the day-to-day operations of the UK ethics committee authority are devolved down to the Central Office for Research Ethics Committees, which in turn has set up regional offices for research ethics committees, which will have a management role.

The result of this is a system with two types of committees: "recognised" and "authorised". Recognised RECs are able to review applications of clinical trials and are subdivided into type 1 committees recognised for reviewing phase I trials (ie, healthy volunteers) throughout the UK; type 2 committees

recognised for reviewing clinical trials (non-phase I) taking place only at sites within a region defined by the geographical remit of their own appointing authority; and type 3 committees recognised for review of clinical trials of medicinal products (other than phase I trials in healthy volunteers) taking place at any site in the UK. Then there are the authorised RECs, which can review proposed projects (other than clinical trials and projects on prisoners) that will take place at a single site (<http://www.corec.org.uk>).

Portugal

In May 1995, the Portuguese government created Ethics Committees for Health (Comissões de Ética para Saúde (CES)) by legally requiring every Portuguese hospital to set up an ethics committee;¹⁵ according to the Department of Health, by 2000, more than 95% of Portuguese hospitals had established a CES. From 1995 to 2005, the CES functioned independently in hospitals and health centres coordinated in five administrative subregions, each of which was directly responsible administratively to the Ministry of Health. Each CES is made up of seven members drawn from medical doctors, nurses, pharmacists, jurists, theologians, psychologists and sociologists, each having a 3-year mandate with the possibility of renewal for another 3 years. Until 2005 CES had a dual role, acting both as RECs (reviewing research protocols and having the legal power to prevent a trial from taking place in a particular hospital), and as advisory clinical ethics committees, in the case of complex medical issues. An interesting point of comparison is the close relationship between these committees and academic bioethics: CES members are required to have a reasonable knowledge of fundamental principles in bioethics¹⁶ giving Portuguese CES a pedagogic role lacking in RECs of other member states (eg, UK). Opinion, methods, decisions and theoretical documents produced by CES are of great relevance as they have an effect on attitudes and opinions of professionals in their respective health institution.¹⁷

On 20 January 2005, the Portuguese Republican Assembly transposed the Directive 2001/20/EC into Portuguese law. The main effect of this was to create a new body, the Ethics Committee for Clinical Investigation (CEIC, Comissão de Ética para a Investigação Clínica), which started its activities on 6 May 2005. Originally the role of CEIC was to act as a clearing house for clinical trials applications, deciding which CES should assess a particular trial, oversee the operation of CES (in terms of support and resources), assess their competence, and enforce the 60-day time limit for decisions.¹⁸ In practice, CEIC has centralised assessment of all clinical trials in Portugal which has created some tensions with CES, which are left without a role to play in clinical trials appraisal. The 34 members of the CEIC, some of whom are members of existing CES, were nominated by the government, and include several medical doctors and academics, dentists, pharmacists, nurses, civil servants working for the general health service, jurists, a finance specialist, an economist and a priest.

CONCLUSION

By attempting “to harmonise legal and ethical procedures associated with clinical trials across Europe”¹⁹, Directive 2001/20/EC makes explicit what has been implicitly clear for some time; RECs are drug regulators, albeit atypical ones in terms of their composition and procedures. As such, we may look to changes in the formal drug regulation system in the EU for pointers about the future direction of further changes in the REC system. For example, in the directive’s requirement for RECs to make their decisions within 60 days, we may hear echoes of the political pressures that have been

put on European drug regulators over the past decade to introduce progressively more rapid approval of drugs.²⁰

Clearly, the directive introduces a considerable degree of centralisation into national REC systems, although the form this takes depends on contextual and contingent features in each country. In the UK, at the end of 15 years of repeated attempts by the Department of Health to centralise control over more than 200 independently minded local RECs, the only new body created by the directive is the UKECA, which is more a regulatory requirement than a committee that will actually sit. In contrast, the other three countries have set up central RECs, which all perform slightly different functions, whether it be as appeal board (Sweden), as central distributor of clinical trials protocols (Portugal) or as ethical assessor of protocols in parallel with local committees (Hungary). At the moment, a clinical trial run across the EU needs one REC approval from each member state taking part; we should not be surprised if, in the future, further centralisation makes one REC approval adequate for the whole EU.

Hand in hand with centralisation is the need for harmonisation of REC decision making. Traditionally, harmonisation of drug regulatory systems has been driven by industry’s desire to reduce development costs for new drugs and permit a straightforward marketing of products across different regulatory domains. The European Commission is clearly of the opinion that further harmonisation of RECs across Europe is desirable, noting that “To cope with the growing demand for high-quality and rapid assessment, some harmonisation and simplification of practice is needed to reduce confusion and delay, and even to circumvent the national barriers that some of the current diversity of approaches imposes.”²¹ This effect of European integration on RECs has long been expected.²²

In this context, harmonisation is rarely argued for: more often it is simply stated to be a desirable feature of REC decision making that is self-evident. The underlying assumption seems to be that if there is diversity in opinion between RECs over the same protocol, then something must have gone wrong. Although there may be problems with how a committee reaches its decisions, it is perfectly possible for ethical decisions to be at odds with each other but still be well argued and justified; there can be a range of equally valid views on the same clinical trials protocol.²³ Thus there is a need for debate on increased harmonisation of REC systems, both at the national and EU level, not just about mechanisms to produce harmonisation, but also a fundamental debate about the need for harmonisation itself, and whether it is compatible with the independent nature of RECs required by European law.

Finally, the ways in which these member states have sought to implement the directive are clearly different, especially with regard to the role of politicians and their control of the new REC systems. In the UK, the political nature of the UKECA is controversial, with debate in the House of Lords suggesting that because of its composition it is impossible to claim that RECs are free from political interference.²⁴ It has been suggested that “the UK is alone in its decision to exercise political control over its ethics committees”.²⁵ Whether the UKECA does amount to political control over RECs or not is something that can be debated; the UK government views such claims as fantasy.²⁶ But clearly in countries such as Sweden, for example, political appointment of REC members has been introduced under the new system and is largely unproblematic. Different member states have different political cultures, and we should not be surprised that in Sweden, with its institutional history and culture of corporatism, formal political appointment to RECs does not raise the kind of issues it may do in the UK.

As Europeans, we can no longer think of RECs as individual, discrete bodies in which ethical debates are played out in isolation. Nor can bioethicists assume that training REC members in ethical decision making is as influential on outcomes as may be assumed. We need to see RECs in their context, as parts of an international regulatory system for pharmaceutical products, subject to the pressures of different interest groups at different levels (EU, national and local). If we are to understand RECs and the decisions they make, we must understand what they have become.

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