Chapter 5

Ethical review

Ethical review

Introduction

5.1 An effective system for ethical review of research provides a crucial safeguard for research participants. While this process is typically undertaken by independent Research Ethics Committees (RECs), there are still many countries in the developing world in which these bodies are absent, ineffective or under-resourced. In addition, there may not be a pool of sufficiently trained and independent people to serve on such committees. As we have said, the inequalities in resources that exist between developed and developing countries pose significant risks of exploitation when externally sponsored research is carried out. The structure of RECs, the scope of their work and the mode of their operations are therefore particularly important in the context of research in developing countries.

5.2 A critical issue is whether there should be separate scientific and ethical review, and whether review should take place in both the sponsor's country and the country in which research is to be conducted (the host country). The independence of RECs is crucial and their sources of funding need thorough consideration. The scope of the responsibilities of RECs also needs to be carefully defined, including their role after a trial has begun, addressing conflicts when more than one ethics committee is involved, and ensuring adequate training for committee members in order to build capacity, skills and experience (see also NCOB, Chapter 8).

5.3 In the Workshop, the following issues were discussed:

- should there be separate scientific and ethical review of research?
- where should review take place?
- what kind of funding and support is appropriate for a REC in the host country? and
- what is the role of a REC after the approval of research?

Should there be separate scientific and ethical review of research?

Guidance

5.4 The guidance generally agrees that ethical review of research should take place and that it should be conducted by at least one independent REC[1] (Appendix A, Table 4). However there are different views regarding the need for separate scientific and ethical review, and whether or not it is appropriate for a REC to review the scientific validity of a study.

5.5 NCOB 2002 recommends that scientific and ethical review should, where possible, be undertaken separately because they have different purposes. This may, but will not necessarily, require the establishment of two committees.[2] In contrast, WMA 2000, CIOMS 2002 and EGE 2003 do not require a separate committee for scientific review.[3] CoE 2004 requires independent examination of the scientific merit of a proposal, followed by ethical review and approval by a 'competent body'.[4]

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1 WMA 2000, paragraph 13; CIOMS 2002, Guidelines 2 and 3; CoE 2004, Articles 9 and 10; EU 2001, Articles 3, 6 and 9; EGE 2003, paragraph 2.8; NCOB 2002, paragraph 8.2.

2 NCOB 2002, paragraphs 8.4 and 8.5.

3 WMA 2000, paragraph 13; CIOMS 2002, Commentary on Guidelines 2 and 3; and EGE 2003, paragraph 2.8. All agree that ethical and scientific review must take place.

4 CoE 2004, Article 7 states: 'Research may only be undertaken if the research project has been approved by the competent body after independent examination of its scientific merit, including assessment of the importance of the aim of research, and multidisciplinary review of its ethical acceptability.' The phrase 'competent body' is used to indicate that in some countries the ethics committee may be the competent body, whereas in others the competent body might be a Ministry or a regulatory agency that would take the opinion of the ethics committee into account, see Explanatory Report, paragraph 28. See also Article 9: *Independent examination by an ethics committee*.

Workshop discussion

5.6 During discussion, there was broad agreement that both the scientific quality, and the ethical issues raised by the proposed research should be reviewed but there was disagreement as to how this should be achieved. Ideally, and where feasible, it was suggested that these review processes should be separated (see also Box 5.1). In Kenya, for example, a scientific committee usually reviews the scientific protocol before it is submitted to an ethics committee. If the scientific committee does not have enough expertise, an external Kenyan expert is sought to review the protocol. In a much smaller country such as Fiji, there are not currently enough suitably qualified experts to make it possible to create two separate committees. One suggestion was that it might be more appropriate to specify that a REC has a duty to ensure that there is adequate review of both the ethical and the scientific aspects of a proposal, rather than stating how this should be achieved.

Box 5.1: **Ethical review in a host country – South Africa (case study contributed by Professor Ames Dhai)**

In South Africa, the National Health Act No. 61 (2003) makes it a legal requirement that any research related to healthcare must have approval from a REC registered with the National Health Research Ethics Council. The Council, appointed by the Minister, is responsible for registering and auditing RECs.

There are currently more than 20 RECs in the country, including Provincial Research and Ethics Committees, RECs in tertiary institutions and private RECs. The Department of Health's Clinical Trials Guidelines (2000) recommend that a REC should include members who have the qualifications and experience to review and evaluate the scientific, clinical, and ethical aspects of the proposed trial.* Most RECs in the country are, therefore, able to conduct both scientific and ethical review, although the processes are often separated. They include:

- Institutional RECs (for example, eight are attached to medical schools): scientists on the committee who have appropriate expertise review the scientific aspects as part of the appraisal of the ethical issues. A separate scientific committee in the institution will also conduct an independent scientific review of undergraduate and postgraduate research projects. The same members may serve on both committees.
- MRC of South Africa Ethics Committee: a scientific review must have been conducted before a project is submitted to the Committee. However, there is also scientific expertise on the Ethics Committee itself.
- Committees of pharmaceutical companies: a pharmaceutical company will usually have an internal scientific committee to review a proposal when sponsoring clinical trials. The local REC will also examine both the scientific and ethical aspects of the proposal.

* South Africa Department of Health (2000) *Guidelines for good practice in the conduct of clinical trials in human participants in South Africa*, Guideline 8.2. Available: http://www.doh.gov.za/docs/policy/trials/trials-full.html Accessed on: 4 Feb 2005.

5.7 Delegates also discussed the development of regional committees for scientific and ethical review. A number of independently established regional fora for RECs have been established such as the Pan-African Bioethics Initiative (PABIN) under the auspices of the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER). These committees assist with the development of expertise for ethical review, facilitate education and provide technical support. It was suggested that they might also have a useful role where a particularly difficult case is being reviewed, or one that raises new issues. However, such committees need direct

funding for their establishment and continued maintenance, and may not be able to expand their roles accordingly.

Where should review take place?

Guidance

5.8 One of the main points of disagreement in the guidance concerns the degree of involvement of the host country in the review process (Appendix A, Table 4). Three documents recommend that ethical review is undertaken in the host country. For example, CoE 2004 requires that an ethical review by an independent ethics committee be performed 'in each State in which any research activity is to take place'.[5] NCOB 2002 recommends that research should be reviewed in both the sponsoring country(ies) and the host country(ies) in which research takes place.[6] EU 2001 states that an opinion on the ethics of the proposed research should be given by each Member State participating in the trial.[7]

5.9 Other guidelines are less stringent. CIOMS 2002 does not necessarily require host countries to have a distinct fully functioning REC, although representatives from the host countries should be involved in the ethical review process.[8] Similarly, EGE 2003 allows the review to be conducted by a mixed committee, with representatives from both EU Member States and host countries.[9] WMA 2000 is the only guidance that does not address the need to have a REC in the host country.

Workshop discussion

5.10 During discussion, it was observed that proposals for externally sponsored research often have to be submitted to multiple reviews in both the host and sponsor country. A proposal may be reviewed by the REC at the local institution, the REC of the host country, the RECs of collaborators in the sponsor country, internal committees of the sponsors, and by any institutions where laboratory samples are analysed. Concerns were expressed that multiple review can cause long delays and a number of examples were cited. For example, for a study in Malawi, it took one and a half years for a protocol for a vaccine trial to be reviewed. Similarly, in a partnership to conduct a clinical trial of a rotavirus vaccine in India, it took nine months for a protocol to be reviewed by four different RECs. Each REC has a different schedule of meetings. Passing a proposal sequentially between the four committees can take several months. If one REC makes alterations to a proposal, the others will often want sight of the revised version, causing further delays. However, if researchers send their proposal to several committees simultaneously, and the different committees request different revisions, re-circulation of the new draft between all parties can also cause delays (see also Box 5.2).

5.11 If the review process is to achieve its aim of improving the quality of research, the process needs to be made more efficient. One possibility, discussed during the Breakout Groups, would be to improve mechanisms for communication between different RECs reviewing the same protocol. Methods discussed included: encouraging the exchange of information between committees; copying all correspondence to the other RECs as well as to the investigator; and facilitating visits between committees of the host and sponsor countries.

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5 CoE 2004, Article 9. Article 29 also considers the possibility that research might take place in a country that is not party to this Protocol, or in a country where no suitable body for the review of research exists, see Appendix A, Table 4.

6 NCOB 2002, paragraph 8.22.

7 EU 2001, Articles 3.2a and 9.

8 CIOMS 2002, Commentary on Guideline 3.

9 EGE 2003, paragraph 2.8.

Improving the channels of communication would help reduce tensions and conflicts between committees, develop consistency of decisions and also enable better understanding about the local context in which the research is to take place.

5.12 It was suggested that in some circumstances, the responsibilities between committees could be devolved, with individual RECs reviewing only parts of a proposal. This idea accords with CIOMS 2002. These guidelines suggest that RECs in the sponsor country have a specific responsibility to review the scientific methods, whereas committees in the host country should determine whether the objectives of the research are responsive to the health needs of that country, review the detailed plans for compliance, and assess the ethical acceptability of the research proposal in light of the local community's customs and traditions.[10] (See also paragraph 6.23 for further discussion of the role of a REC in assessing the research priorities of a country.)

5.13 For some issues, it was considered essential to include local expertise in the review process. The host REC, with knowledge of the local and cultural context, may be better placed to comment on issues concerning research priorities, consent, inducements and the protection of research participants. However, as discussed earlier (see paragraphs 2.14–2.16 on consent), innovative methods may be required to ensure adequate lay representation (see also Box 6.1). Many RECs already included lay members, but the importance of ensuring that they could contribute effectively needed to be emphasised.

5.14 Another issue concerned the primacy of the host and sponsor committees. In general, it was considered more important to have dialogue rather than dominance between different committees, although there was a need to recognise that committees may differ in their expertise. However, delegates suggested that in most situations the local host committee should be able to make the final decision. In practice, however, it was considered unlikely that a sponsor would be willing to fund a project where either the host REC or the sponsor country's REC had not given approval. Some sponsors require a proposal to have received local REC approval before it is submitted for funding. Such a requirement may prove burdensome for a local committee. If a grant is then not approved, an already under-resourced REC will have wasted both time and effort.

5.15 Some delegates suggested that a substantial expansion in the number of externally sponsored clinical trials in developing countries was likely to occur over the next decade. Greater investment in research by private foundations, and the pharmaceutical industry, and new initiatives such as the European and Developing Countries Clinical Trials Partnership (EDCTP) could be expected to increase pressure on local ethics committees. Under these circumstances, more effective committees that can function well at the local level would be essential.

10 CIOMS 2002, Commentary on Guideline 3.

Box 5.2: **Ethical review in a host country – Brazil (case study contributed by Professor Carlos Brites)**

The National Ethics of Research Committee (CONEP) was established by the Brazilian National Health Council (CNS) in 1996 (Resolution 196/96). CONEP is responsible for the evaluation of all research involving humans, particularly projects involving genetics, human reproduction, indigenous populations, biosafety issues, research supported by foreign countries or institutions, or involving the export of biological materials. CONEP reviews projects after approval has been given by the local REC. It also has a regulatory and advisory role, and manages disagreements between local RECs and researchers.

After a period of adaptation, the system is now considered to be operating well and conflicts between CONEP and investigators are rare. However, there are still concerns about the time taken to resolve issues raised by specific projects. Because a project must be approved at two different levels, it usually takes three to four months for final approval to be received.

What kind of funding and support is appropriate for a REC in the host country?

Guidance

5.16 The guidance agrees that ethical review of research should be conducted by a REC independent of undue financial or political influence[11] (Appendix A, Table 4). However, there is conflicting advice as to the type of support or funding that may be appropriate to enable a REC to function effectively. EGE 2003 states that EU Member States may provide funds directly for capacity building and maintenance of RECs in host countries. CIOMS 2002 considers that sponsoring countries have a responsibility to support the development of capacity of RECs in developing countries, but does not state whether this contribution should be provided to the host country directly or indirectly.[12] In contrast, NCOB 2002 suggests that it is the responsibility of national governments to ensure the functioning of a REC, and recommends that committees should be funded indirectly to prevent problems of bias.

Workshop discussion

5.17 A number of delegates described difficulties faced by RECs in their own countries (see Box 5.3). The situations described reflected problems experienced in several countries, including for example, Peru. It was suggested that direct financial support by the sponsor to the REC may not be the best solution. Instead, funds could be put into a central pool for allocation to individual RECs. However, there were concerns that some institutions did not honour their commitment to support RECs. In the case of collaborative research, for example, a substantial proportion of the funding that was sometimes allocated to the institution for indirect costs often failed to be translated into funding for REC activities.

5.18 A number of different ways in which sponsors could assist the development of RECs in host countries were considered. These included the provision of training, general resources such

11 WMA 2000, paragraph 13; CIOMS 2002, Guideline 2; CoE 2004, Article 10; EU 2001, Article 9; EGE 2003, paragraph 2.9; NCOB 2002, paragraph 8.20.

12 CIOMS 2002, Commentary on Guideline 20: 'External sponsors and investigators have an ethical obligation to contribute to a host country's sustainable capacity for independent scientific and ethical review and biomedical research.' However, Guideline 2 states that: 'sponsors of research and institutions in which the investigators are employed should allocate sufficient resources to the review process. Ethical review committees may receive money for the activity of reviewing protocols but under no circumstances may payment be offered or accepted for a review committee's approval or clearance of a protocol.' This suggests direct funding may be acceptable. NBAC guidelines also agree that 'US sponsors and researchers should assist in building capacity of ethics review committees in developing countries'. See National Bioethics Advisory Commission (2001) *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* (Bethesda: NBAC), Recommendation 5.7.

as IT and communications equipment, and providing a direct fee for specific services. It was noted that if a committee introduced a charge for reviewing a project to cover the costs, the charge should apply regardless of whether or not the project was approved. In some countries, the fee had sometimes only been charged if a project was approved.

5.19 The importance of providing training for members of RECs was also emphasised. Sponsors could contribute by providing training to members of committees to enhance the skills and understanding of the ethical review process. Initiatives to develop capacity for ethical review were seen to be particularly valuable and sponsors could play an important role in encouraging such programmes. For example, the Wellcome Trust sponsors training opportunities for members of ethics committees in developing countries through its Biomedical Ethics Programme.[13] Delegates pointed out that an adequate infrastructure was crucial to ensure that knowledge acquired could be put into practice.

Box 5.3: **Difficulties faced by local RECs – Kenya (case study contributed by Dr Job Bwayo)**

In Kenya, members of the REC are expected to offer their services voluntarily, although a small amount of money may be available to compensate for time and travel expenses. Almost all of the members have been trained according to good clinical practice guidelines issued by ICH (see paragraph 1.12). They also receive annual training funded by foreign sponsors. However, the rapid turnover of trained staff makes it very difficult to sustain continuity.

Most members are not directly involved in research and find the review of large numbers of research protocols burdensome. The REC has limited office space in a hospital and a university, with no facilities for communication, photocopying or for keeping records. Although there are computers, there is no Internet connection and no access to a resource centre. This makes it difficult for members to perform literature searches or to familiarise themselves with specialised subjects under review.

An independent office for the REC with adequate administrative support is needed. However, this development would require significant additional funding. A small fee is charged for review of protocols but the funds received are retained by the institution and not used to support the REC. Current funding from the government, which is given to the institution rather than direct to the REC, is not adequate to sustain an independent REC.

5.20 Another means of providing additional funding for RECs could be for committees to charge for some of the functions that they perform, such as assessing research proposals at an early stage. It was also suggested that institutions could impose a charge for reviewing grant proposals to provide a source of internal funding to support the administration, and infrastructure required by a REC. However, care would need to be taken to avoid possible conflicts of interest.

5.21 A number of delegates asked about the availability of advice to guide those concerned with establishing RECs. It was noted that the WHO had produced guidelines giving general

13 The Wellcome Trust Ethics of Biomedical Research in Developing Countries grant schemes. Available: http://www.wellcome.ac.uk/funding/medicalhumanities/biomedicalethics. Other examples include initiatives funded by the Fogarty International Center (International Bioethics Education and Career Development Award, see http://www.fic.nih.gov/programs/bioethics/bioethicsaward.html); Harvard University (International Fellowship in Health Research Ethics, see http://www.hsph.harvard.edu/bioethics) and International Research Ethics Network for Southern Africa (IRENSA) (see http://www.irensa.org) (Accessed on: 4 Feb 2005).

standards of practice, including operating procedures and recruitment of members.[14] This advice could provide a sound basis for initiating discussion and could be adapted to fit local circumstances. PABIN, SIDCER and the Council of Europe had also published some relevant literature (see Appendix D).

What is the role of a REC after the approval of research?

Guidance

5.22 Some elements of the guidance (WMA 2000, CIOMS 2002, EU 2001) suggest that RECs have an obligation to follow up research or to conduct monitoring.[15] CIOMS 2002 for example states that:

> 'The ethical review committee should conduct further reviews as necessary in the course of the research, including monitoring of the progress of the study.' [16]

Workshop discussion

5.23 There were some concerns that requiring a REC to monitor a research study after it had begun would increase the already burdensome workload of RECs. In most cases additional resources for monitoring would not be available. Some RECs might be able to achieve passive monitoring. At the very least, where ethical approval was time-limited, a REC might ask for a report before granting renewed approval. In the Caribbean and Pakistan, for example, some RECs give approval for a project to be conducted for one year. The researcher is then asked to provide an annual report on the conduct of the study and to confirm that the protocol is unchanged in order for the approval to be renewed. However, the process had proved to be inefficient because of incomplete reporting and follow-up of non-responders. Furthermore, in many countries, reports from researchers are received by data and safety monitoring boards, which lack a clear mechanism for communication with RECs.

5.24 Several delegates commented that RECs were not always seen to be consistent in their decisions. In some cases, there was anecdotal evidence of researchers 'shopping around' until they found a committee that gave a favourable decision on a project. This practice raised questions about how RECs themselves were reviewed, and whether it was necessary to conduct a wider or more systematic audit of their work. Some delegates thought that this process would be helpful and could be used to evaluate whether there were conflicts of interest or particular complaints about the way a committee functioned. However, others felt that it would add an extra level of unnecessary bureaucracy for members of RECs and could lead to further delays. It was suggested that it might be useful to consider a mechanism for accreditation of RECs. Alternatively, the standards set out by WHO (paragraph 5.21) could be used as the basis for internal review. The RECs could also be audited by local regulatory authorities or international bodies.

Summary of discussion about ethical review

5.25 All agreed that the ethical review of research played a crucial role in protecting research participants. The fact that the process in the host and sponsor countries was beset by a number of problems, ranging from logistical delays to more substantive differences of opinion that could not be resolved by consultation with the guidance, was a major concern.

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14 World Heath Organization (2000) *Operational Guidelines for Ethics Committees That Review Biomedical Research* (Geneva: WHO).

15 WMA 2000, paragraph 13; CIOMS 2002, Guideline 2; EU 2001, Article 3.

16 CIOMS 2002, Guideline 2.

5.26 Several themes emerged throughout the Workshop:

- RECs have a duty to ensure adequate review of both ethical and scientific aspects of research proposals.
- In order to realise the benefits of ethical review, the process needs to be made much more efficient.
- Innovative methods of collaboration could be used to improve communication between different RECs, particularly between committees in the host and sponsor countries.
- Responsibilities might be devolved between committees. For some issues, the local expertise of the host REC is crucial.
- RECs in developing countries face serious difficulties through a lack of funding and a need to maintain independence.
- A particular problem is a lack of expertise among members of RECs. Initiatives to develop expertise in ethical review, through training and capacity building, are crucial.
- There were concerns that requiring a REC to monitor research after it had begun would increase the already burdensome workload of RECs.