Appendix A: Comparison of guidance on research related to healthcare in developing countries

Table 1: Guidance relating to consent

Guidance	Relevant sections	Text and notes
WMA 2000	Paragraph 22	*Provision of information:* Participants 'must be adequately informed about: • the aims and methods of the study; • the sources of funding and possible conflicts of interest; • the institutional affiliations of the researcher; • the anticipated benefits and potential risks; • the discomfort it may entail; and • the right to abstain from taking part in the study, or to withdraw from it at any time without reprisal.' [Paragraph 22] *Recording consent:* Written consent is preferable but 'non-written' consent can be acceptable in some cases: 'After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.' [Paragraph 22] *Other points:* Paragraph 23 addresses the process of obtaining consent 'if the subject is in a dependent relationship with the physician or may consent under duress.' Paragraphs 24–26 consider how consent should be obtained when potential participants are legally incompetent, physically or mentally incapable of giving consent or for children.
CIOMS 2002	Guidelines 4 - 7	*Individual informed consent* 'For all biomedical research involving humans the investigator must obtain the voluntary informed consent of the prospective subject or, in the case of an individual who is not capable of giving informed consent, the permission of a legally authorized representative in accordance with applicable law.' [Guideline 4]
		Who should give consent? Community consent may be required but should never replace individual consent. 'In some cultures an investigator may enter a community to

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Table 1: Guidance relating to consent *(continued)*

Guidance	Relevant sections	Text and notes
CIOMS 2002	Guidelines 4 - 7	conduct research or approach prospective subjects for their individual consent only after obtaining permission from a community leader, a council of elders, or another designated authority. Such customs must be respected. In no case, however, may the permission of a community leader or other authority substitute for individual informed consent.' [Guideline 4, Commentary] *Provision of information:* 'Before requesting an individual's consent to participate in research, the investigator must provide the following information, in language or another form of communication that the individual can understand', then lists 26 items including aspects of the design of the trial (randomisation, double blinding); possible health risks for participants, and treatment options; issues relating to data protection; and questions of liability in the case of disability or death resulting from injury related to the research.' [Guideline 5] The commentary on Guideline 4 also addresses the importance of the 'process' of obtaining consent. *Recording consent:* 'Consent may be indicated in a number of ways. The subject may imply consent by voluntary actions, express consent orally, or sign a consent form. As a general rule, the subject should sign a consent form, or, in the case of incompetence, a legal guardian or other duly authorized representative should do so.' [Guideline 4, Commentary] *Waiving consent:* 'Waiver of informed consent is to be regarded as uncommon and exceptional, and must in all cases be approved by an ethical review committee.' [Guideline 4] 'Investigators should never initiate research involving human subjects without obtaining each subject's informed consent, unless they have received explicit approval to do so from an ethical review committee. However, when the research design involves no more than minimal risk and a requirement of individual informed consent would make the conduct of the research impracticable (for example, where the research involves only excerpting data from subjects' records), the ethical review committee may waive some or all of the elements of informed consent. [Guideline 4, Commentary] *Continued*

Table 1: Guidance relating to consent *(continued)*

Guidance	Relevant sections	Text and notes
CIOMS 2002	Guidelines 4 - 7	*Inducements:* 'Subjects may be reimbursed for lost earnings, travel costs and other expenses incurred in taking part in a study; they may also receive free medical services. Subjects, particularly those who receive no direct benefit from research, may also be paid or otherwise compensated for inconvenience and time spent. The payments should not be so large, however, or the medical services so extensive as to induce prospective subjects to consent to participate in the research against their better judgment ('undue inducement'). All payments, reimbursements and medical services provided to research subjects must have been approved by an ethical review committee.' [Guideline 7]
CoE 2004	Article 13, 14	*Who should give consent?* Individual consent required: 'No research on a person may be carried out… without the informed, free, express, specific and documented consent of the person.' [Article 14] *Provision of information:* Article 13 lists the information that should be addressed during the consent process: 'Persons being asked to participate in a research project shall be given adequate information in a comprehensible form… [covering] the purpose, the overall plan and the possible risks and benefits of the research project: i. of the nature, extent and duration of the procedures involved, in particular, details of any burden imposed by the research project; ii. of available preventive, diagnostic and therapeutic procedures; iii. of the arrangements for responding to adverse events or the concerns of research participants; iv. of arrangements to ensure respect for private life and ensure the confidentiality of personal data; v. of arrangements for access to information relevant to the participant arising from the research and to its overall results; vi. of the arrangements for fair compensation in the case of damage; vii. of any foreseen potential further uses, including commercial uses, of the research results, data or biological materials; *Continued*

Table 1: Guidance relating to consent *(continued)*

Guidance	Relevant sections	Text and notes
CoE 2004	Article 13, 14	viii. of the source of funding of the research project. … and their right to refuse consent or to withdraw at any time without being subject to any form of discrimination.' [Article 13] Methods of providing the information are also discussed in the Explanatory Report, paragraph 72. *Recording consent:* Consent must be documented. 'Express consent may be either verbal or written as long as it is documented. Best practice demands that written consent be obtained, except in exceptional circumstances.' [Explanatory Report, paragraph 79] *Inducements:* Details of all payments and rewards to be made in the context of the research project must be considered by the ethics committee. [Appendix: Information to be given to the ethics committee] *Other points:* Article 15 discusses protection of persons not able to consent to research; Article 19 discusses research in emergency clinical situations, when a person is not in a state to give consent.
EU 2001	Article 3.2	*Who should give consent?* Individual consent is required: 'A clinical trial may be undertaken only if: …(d) the trial subject or, when the person is not able to give informed consent, his legal representative has given his written consent after being informed of the nature, significance, implications and risks of the clinical trial.' [Article 3.2 d] *Provision of information:* 'A clinical trial may be undertaken only if, in particular: the trial subject or, when the person is not able to give informed consent, his legal representative has had the opportunity, in a prior interview with the investigator or a member of the investigating team, to understand the objectives, risks and inconveniences of the trial, and the conditions under which it is to be conducted and has also been informed of his right to withdraw from the trial at any time.' [Article 3.2 b]

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Table 1: Guidance relating to consent *(continued)*

Guidance	Relevant sections	Text and notes
EU 2001	Article 3.2	*Recording consent:* Verbal consent may only be obtained if the participant is illiterate: '…if the individual is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation.' [Article 3.2 d] *Other points:* Opening paragraphs (3) and (4) discuss the involvement of persons incapable of giving legal consent in clinical trials. Article 4 discusses consent for research involving minors, and Article 5 discusses trials on incapacitated adults not able to give informed legal consent.
EGE 2003	Paragraph 2.7	*Who should give consent?* Consent of family or community leader may be required in addition to individual consent: 'The involvement of people with knowledge of the local conditions and traditions and able to defend the interest of those affected by the project is necessary to guarantee the most appropriate procedures of informing of the potential participants in a clinical trial. According to the local situation, it may be appropriate to seek agreement on the implementation of a research project from persons representative of or invested with a certain authority within the community, or the family. However, free and informed consent always has to be given by each individual involved in a trial.' [Paragraph 2.7] *Recording consent:* Does not indicate how consent should be best recorded.
NCOB 2002	Chapter 6	*Who should give consent?* Consent of senior family member or community leader may be required in addition to individual consent: 'We recommend that, in circumstances where consent to research is required, genuine consent to participate in research must be obtained from each participant. In some cultural contexts it may be appropriate to obtain agreement from the community or assent from a senior family member before a prospective participant is approached. If a prospective participant does not wish to take part in research this must be respected.' [Paragraph 6.22, and discussion 6.18-6.22]

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Table 1: Guidance relating to consent *(continued)*

Guidance	Relevant sections	Text and notes
NCOB 2002	Chapter 6	*Provision of information:* 'Information sheets and consent forms must be designed to assist participants to make informed choices. We recommend that the information provided should be accurate, concise, clear, simple, specific to the proposed research and appropriate for the social and cultural context in which it is being given.' [Paragraph 6.40, and discussion 6.4–6.17] *Recording consent:* Verbal consent is acceptable only if written consent is inappropriate: 'Where it is inappropriate for consent to be recorded in writing, genuine consent must be obtained verbally. The process of obtaining consent and the accompanying documentation must be approved by a research ethics committee and, where only verbal consent to research is contemplated, include consideration of an appropriate process for witnessing the consent.' [Paragraphs 6.37-6.40] *Inducements:* 'We recommend that dialogue is needed with sponsors, external and local researchers and communities to ensure that any inducements to take part in research are appropriate to the local context, especially in circumstances where the research exposes participants to a risk of harm. Decisions about appropriate levels of inducement will need to be justified to local research ethics committees.' [Paragraph 6.32, and discussion 6.25–6.32] *Other points:* Uses concept of 'genuine consent' instead of 'informed consent': 'Ensuring that consent is genuine requires care in detecting a lack of consent. The apparent genuineness of consent can be defeated by a number of circumstances, including coercion, deception, manipulation, deliberate misdescription of what has been proposed, lack of disclosure of material facts, or conflicts of interest. To obtain genuine consent, health professionals must do their best to communicate information accurately and in an understandable and appropriate way. The information provided to participants must be relevant, accurate and sufficient to enable a genuine choice to be made.' [Paragraphs 6.4-6.5]

[1] The concept of genuine consent was introduced by the NCOB in its 1995 Report, *Human Tissue: Ethical and Legal Issues*, paragraph 6.20.

Table 2: Guidance relating to standards of care

Guidance	Relevant sections	Text and notes
WMA 2000	Paragraph 29	*The standard of care that should be provided to the control group during research:* 'The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.' [Paragraph 29] *The use of placebos:* Placebos may be used only 'for compelling and scientifically sound methodological reasons' or when the risks to the participant and the condition being studied are minor. A 'Note of clarification on Paragraph 29 re. the use of placebos' was published in December 2002: 'The WMA reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available under the following circumstances: - Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or - Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the participants who receive placebo will not be subject to any additional risk of serious or irreversible harm.' [Note of clarification on Paragraph 29]
CIOMS 2002	Guideline 11	*The standard of care that should be provided to the control group during research:* 'As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or 'no treatment'.' [Guideline 11] New terminology was introduced in 2002: 'established effective intervention' used as a term for reference treatment, to include all current interventions, 'including the best and the various alternatives to the best.' [Introduction]

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Table 2: Guidance relating to standards of care *(continued)*

Guidance	Relevant sections	Text and notes
CIOMS 2002	Guideline 11	*The use of placebos:* 'Placebo may be used: • when there is no established effective intervention; • when withholding an established effective intervention would expose subjects to, at most, temporary discomfort or delay in relief of symptoms; • when use of an established effective intervention as comparator would not yield scientifically reliable results and use of placebo would not add any risk of serious or irreversible harm to the subjects.' [Guideline 11] The commentary to Guideline 11 discusses the specific cases when the use of a placebo in place of an 'established intervention' may be morally justified. For example, a health authority in a country where an established effective intervention is not generally available or affordable, and unlikely to become available or affordable in the foreseeable future, may seek to develop an affordable intervention specifically for a health problem affecting its population. 'Ethical review committees will need to engage in careful analysis of the circumstances to determine whether the use of placebo rather than an established intervention is ethically acceptable. They will need to be satisfied that an established effective intervention is truly unlikely to become available and implementable in that country.' [Guideline 11, Commentary]
CoE 2004	Article 23	*The standard of care that should be provided to the control group during research:* 'Research shall not deprive participants of necessary procedures… In research associated with prevention, diagnosis or treatment, participants assigned to control groups shall be assured of proven methods of prevention, diagnosis or treatment.' [Article 23.2] 'It is expected that a proven method of treatment that is available in the country or region concerned be utilised.' [Explanatory Report, paragraph 120] *The use of placebos:* 'The use of placebo is permissible where there are no methods of proven effectiveness, or where withdrawal or withholding of such methods does not present an unacceptable risk or burden.' [Article 23.3]

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Table 2: Guidance relating to standards of care *(continued)*

Guidance	Relevant sections	Text and notes
EU 2001	Article 19	Does not address placebo-controlled trials or standard of care issues. *The obligations of sponsors:* 'Unless Member States have established precise conditions for exceptional circumstances, investigational medicinal products and, as the case may be, the devices used for their administration should be made available free of charge by the sponsor.' [Article 19]
EGE 2003	Paragraph 2.10, 2.12	*The use of placebos:* 'The use of placebos should be regulated in developing countries in principle by the same rules as in European countries. Any exception must be justified: an obvious one is when the primary goal of the clinical trial is to try to simplify or to decrease the costs of treatment for countries where the standard treatment is not available for logistic reasons or inaccessible because of cost. It may thus be justified to derogate from the rule of best proven treatment. The justification of using a placebo must be clearly demonstrated in the research protocol submitted to the ethical committees and especially approved by the local committee.' [Paragraph 2.10] It should be noted that 'two members of the Group recorded their dissent, considering 'that the use of placebo for the purpose of developing low cost treatment could mean accepting a 'double standard' for poor and rich countries.' *The obligations of sponsors:* Where research participants would not receive a standard of care because of its cost, it must be provided by the sponsor: 'In industrialised countries, the reference treatment used in a clinical trial may be provided by the healthcare services, while the new drug being tested is provided by the sponsor. When a trial is implemented in a country or community where patients cannot benefit from the standard treatment because of the cost, it is then up to the sponsor to provide it.' [Paragraph 2.12] Paragraphs 1.24, 1.32, 1.34 and 2.10 also discuss the issues raised by the provision of different standards of care
NCOB 2002	Chapter 7	*The standard of care that should be provided to the control group during research:* Research below the universal standard of care can be justified in some cases. 'We recommend that in setting the standard of care for the

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Table 2: Guidance relating to standards of care *(continued)*

Guidance	Relevant sections	Text and notes
NCOB 2002	Chapter 7	control group of a particular research project the context in which the research is to be conducted be carefully evaluated. A suitable standard of care can only be defined in consultation with those who work within the country and must be justified to the relevant research ethics committees. Wherever appropriate, participants in the control group should be offered a universal standard of care for the disease being studied. Where it is not appropriate to offer a universal standard of care, the minimum standard of care that should be offered to the control group is the best intervention available for that disease as part of the national public health system.' [Paragraph 7.29] 'In exceptional circumstances, research may be proposed which involves the use of a standard of care that is lower than the best available intervention as part of the host country's public health system for the disease being studied. For example, researchers may wish to demonstrate that what is deemed to be the best treatment available through the host country's public health system is ineffective, or even harmful, by comparing it to a placebo, or an apparently lesser standard of care… If an aim of research into healthcare is to improve current forms of treatment, then there may be circumstances in which it is justified to compare current local practice with a new treatment, in the local setting.' [Paragraph 7.30] The Report also discusses standard of care as it relates to two more specific forms of research: (a) research into preventive measures; and (b) trials comparing different standards of care. *The provision of care to all trial participants:* 'We recommend that before research beings, agreement should be reached about the standard of care that should be provided to participants in research who already have or who develop diseases other than the disease being studied. We conclude that the minimum standard of care that should be offered is the best intervention available as part of the national public health system. Any proposal which contemplates care of a lower standard deviation must be justified to the relevant research ethics committee.' [Paragraph 7.35]

Table 3: Guidance relating to what happens after the research is over

Guidance	Relevant sections	Text and notes
WMA 2000	Paragraph 30	*Should post-trial treatment be provided?* 'At the conclusion of the study, every patient entered in the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods.' [Paragraph 30] A Note of clarification on Paragraph 30 was issued on May 2004: 'The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.' [Note of clarification on Paragraph 30] *Who should supply treatment or provide interventions?* Does not address who has an obligation to supply treatment.
CIOMS 2002	Guideline 10	*Who should supply treatment or provide interventions?* The sponsor should provide post-trial access to treatment: 'Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that: - the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and - any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.' [Guideline 10] The commentary on Guideline 10 clarifies the concepts of 'responsiveness' and 'reasonably available', stating that sponsors and investigators should consult with relevant stakeholders of the country where the research is to take place, 'including the national government, the health ministry, local health authorities, concerned scientific and ethics groups, non-governmental organisations such as health advocacy groups, and representatives of the communities of those who might participate in the study.' [Guideline 10, Commentary] 'The issue of "reasonable availability" is complex and will need to be determined on a case-by-case basis. Relevant considerations include the length of time for which the intervention or product developed, or other agreed benefit, will be made available to research subjects, or to the *Continued*

Table 3: Guidance relating to what happens after the research is over *(continued)*

Guidance	Relevant sections	Text and notes
CIOMS 2002	Guideline 10	community or population concerned; the severity of a subject's medical condition; the effect of withdrawing the study drug (e.g., death of a subject); the cost to the subject or health service; and the question of undue inducement if an intervention is provided free of charge.' [Guideline 10, Commentary]
CoE 2004		Does not address the issue. The Appendix to the Protocol, which covers information to be given to the research ethics committee, does not stipulate that information about post-trial access to treatment is required or should be proved to participants during the consent process.
EU 2001		Does not address the issue.
EGE 2003	Paragraph 2.13	*Should post-trial treatment be provided?* Requires provision of successful treatment to all participants upon completion of the trial, even if treatment would need to be provided for a lifetime: 'In industrialised countries, free supply of a proven beneficial new drug to all the participants of a trial after the trial is ended is the rule as long as it is not yet available through the normal health care system. In developing countries, the same rule must be applicable even if this implies supplying the drug for a lifetime if necessary. Moreover, there should be an obligation that the clinical trial benefits the community that contributed to the development of the drug. This can be e.g. to guarantee a supply of the drug at an affordable price for the community or under the form of capacity building. The protocol of clinical trials must specify who will benefit, how and for how long.' [Paragraph 2.13] *Who should supply treatment or provide interventions?* However, EGE 2003 does not address who should be responsible for supplying treatment or maintaining relevant facilities.
NCOB 2002	Chapter 9	*Should post-trial treatment be provided?* Acknowledges that it may not be possible in all cases to ensure post-trial access and suggests that possible post-trial treatment options should be clarified before the trial begins: 'We endorse the 2001 National Bioethics Advisory Commission's (NBAC) recommendation that researchers should

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Table 3: Guidance relating to what happens after the research is over *(continued)*

Guidance	Relevant sections	Text and notes
NCOB 2002	Chapter 9	endeavour before the initiation of a trial to secure post-trial access for effective interventions for participants in the trial and that the lack of such arrangements should have to be justified to a research ethics committee.' [Paragraph 9.31] *Who should supply treatment or provide interventions?* Does not address who will supply treatment: 'Responsibility for making a vaccine, treatment or other intervention available will not lie solely with any one group. If a national government has agreed to allow a trial to take place, it presumably accepts some responsibility to act on the results. However, some form of external aid or subsidy may be necessary before any intervention can be made more widely available and there will need to be negotiations between the various interested parties.' [Paragraph 9.36]

Table 4: Guidance relating to ethical review

Guidance	Relevant sections	Text and notes
WMA 2000	Paragraph 13	'The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.' [Paragraph 13] Does not require a separate scientific review committee or discuss where review should take place.
CIOMS 2002	Guidelines 2, 3, 20	*Should there be separate scientific and ethical review?* Scientific review does not need to be performed by a separate review committee: '*Ethical and scientific review*: Committees in both the country of the sponsor and the host country have responsibility for conducting both scientific and ethical review, as well as the authority to withhold approval of research proposals that fail to meet their scientific or ethical standards.' [Guideline 3, Commentary] *Where should review take place?* While Guideline 2 discusses ethics review committees, Guideline 3 specifically addresses ethical review of externally sponsored research. Review should take place in both sponsoring and host country, although a host country is not always required to have a distinct fully functional REC in all cases: 'An external sponsoring organization and individual investigators should submit the research protocol for ethical and scientific review in the country of the sponsoring organization, and the ethical standards applied should be no less stringent than they would be for research carried out in that country. The health authorities of the host country, as well as a national or local ethical review committee, should ensure that the proposed research is responsive to the health needs *Continued*

Table 4: Guidance relating to ethical review *(continued)*

Guidance	Relevant sections	Text and notes
CIOMS 2002	Guidelines 2, 3, 20	and priorities of the host country and meets the requisite ethical standards.' [Guideline 3] 'When a sponsor or investigator in one country proposes to carry out research in another, the ethical review committees in the two countries may, by agreement, undertake to review different aspects of the research protocol … The ethical review committee in the host country can be expected to have greater competence for reviewing the detailed plans for compliance, in view of its better understanding of the cultural and moral values of the population in which it is proposed to conduct the research … However, in respect of research in host countries with inadequate capacity for independent ethical review, full review by the ethical review committee in the external sponsoring country or international agency is necessary.' [Guideline 3, Commentary] *Funding and support for a REC in the host country:* 'The review committees must be independent of the research team, and any direct financial or other material benefit they may derive from the research should not be contingent on the outcome of their review.' [Guideline 2] 'The regulatory or other governmental authorities concerned should promote uniform standards across committees within a country, and, under all systems, 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.' [Guideline 2, Commentary] Sponsoring countries have a responsibility to support the building of capacity of RECs in developing countries. However, the guideline does not state whether this contribution should be provided to the host country directly or indirectly: 'Many countries lack the capacity to assess or ensure the scientific quality or ethical acceptability of biomedical research proposed or carried out in their jurisdictions. In externally sponsored collaborative research, sponsors and investigators have an ethical obligation to ensure that biomedical research projects for which they are responsible in such countries contribute effectively to national or local capacity to design and conduct biomedical research, and to provide scientific and ethical review and monitoring of such research.' [Guideline 20]

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Table 4: Guidance relating to ethical review *(continued)*

Guidance	Relevant sections	Text and notes
CIOMS 2002	Guidelines 2, 3, 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.' [Guideline 20, Commentary] Recommendation 5.7 of the NBAC 2001 guidelines concurs: 'Where applicable, U.S. sponsors and researchers should assist in building the capacity of ethics review committees in developing countries to conduct scientific and ethical review of international and collaborative research.'[2] *Role of a REC after the approval of research:* 'The ethical review committee should conduct further reviews as necessary in the course of the research, including monitoring of the progress of the study.' [Guideline 2]
CoE 2004	Article 7, 9 – 12, 29	*Should there be separate scientific and ethical review?* Supports a scientific review of research protocols, by a 'competent body' (separate from discussion of ethical review): '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.' [Article 7] 'It is acknowledged that in some countries, the ethics committee could also act as the competent body while in other cases or in other countries, the competent body might be a Ministry or a regulatory agency, which would take the opinion of the ethics committee into account.' [Explanatory Report, paragraph 28] *Where should review take place?* Each State in which any research activity takes place should provide ethical review and an Appendix lists the information that should be given to the ethics committee for consideration: 'Every research project shall be submitted for independent examination of its ethical acceptability to an ethics committee. Such projects shall be submitted to independent examination in each State in which any research activity is to take place.' [Article 9] *Continued*

[2] National Bioethics Advisory Commission (2001) *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* (Bethesda: NBAC).

Table 4: Guidance relating to ethical review *(continued)*

Guidance	Relevant sections	Text and notes
CoE 2004	Article 7, 9 – 12, 29	Article 29 considers the possibility that research might take place in a country which is not a member of the Protocol, or in a country where no suitable body for the review of research exists. In such cases, the sponsors or researchers: 'shall ensure that, without prejudice to the provisions applicable in that state, the research project complies with the principles on which the provisions of this Protocol are based. Where necessary, the [sponsors and researchers] shall take appropriate measures to that end.' [Article 29] 'In addition to complying with all the conditions applicable in the State in the territory of which the research is to be undertaken, the principles on which the provisions of this Protocol are based must be complied with… For example, there may not be a body capable of undertaking appropriate independent scientific and ethical evaluation of research in the country, but the principle of the research project being submitted to an independent body for review must be observed this does not imply that a body in the state Party to the Protocol has the authority to approve research in the non-Party State if that State does not approve the research, or to override its regulations.' [Explanatory Report, paragraph 138] 'In the case where the research must be undertaken in States not having well established systems of protection, the provisions could foresee the obligation to submit the research project to an ethics committee of the Party concerned.' [Explanatory Report, Paragraph 140] *Funding and support for a REC in the host country:* 'Parties to this Protocol shall take measures to assure the independence of the ethics committee. That body shall not be subject to undue external influences.' [Article 10]
EU 2001	Article 3, 6, 9	*Should there be separate scientific and ethical review?* Implication that the ethics review should include both scientific and ethical review: 'The ethics committee shall consider… (a) the relevance of the clinical trial and the trial design… (c) the protocol…' [Article 6.3 a-c] *Where should review take place?* A single ethical opinion should be given by each state participating in the trial and a competent authority in the host country: *Continued*

Table 4: Guidance relating to ethical review *(continued)*

Guidance	Relevant sections	Text and notes
EU 2001	Article 3, 6, 9	'A clinical trial may be initiated only if the Ethics Committee and/or competent authority comes to the conclusion that the anticipated therapeutic and public health benefits justify the risks and may be continued only if compliance with this requirement is permanently monitored.' [Article 3.2 a] 'The sponsor may not start a clinical trial until the Ethics Committee has issued a favourable opinion inasmuch as the competent authority of the Member State concerned has not informed the sponsor of any grounds for non-acceptance.' [Article 9] *Funding and support for a REC in the host country:* Discussion not necessarily related to trials outside EU countries, but states that: 'For the purposes of implementation of the clinical trials, Member States shall take the measures necessary for establishment and operation of Ethics Committees.' [Article 6.1]
EGE 2003	Paragraph 2.8	*Should there be separate scientific and ethical review?* EGE 2003 does not require a separate scientific review committee. Issues that should be considered during evaluation of a research protocol are listed in paragraph 2.9. *Where should review take place?* 'The scientific and ethical evaluation of the research protocol should be carried out by ethical committees from all countries involved. Host countries need to have a legal and ethical framework in order to take part in the clinical trial evaluation effectively and independently… When no local ethics committee exists, then the evaluation should be done by a mixed committee involving representatives from both EU Member States and host countries. It is essential that the members of this committee are independent and include persons representing participants' interests. If it is not possible to involve such an independent local representative in the evaluation, then no clinical trial should be implemented in the country.' [Paragraph 2.8] *Funding and support for a REC in the host country:* 'The group strongly supports EU initiatives to build local ethical committees in the host countries. It should be considered as a priority in terms of capacity building.' [Paragraph 2.8]

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Table 4: Guidance relating to ethical review *(continued)*

Guidance	Relevant sections	Text and notes
NCOB 2002	Chapter 8	*Should there be separate scientific and ethical review?* A separate scientific committee should conduct a scientific review: 'There are concerns that, in a single ethics committee, the distinction between the review of the science and the ethics, which have quite different purposes, may be ill defined… We conclude that these two forms of review should, where possible, be kept separate. This may, but will not necessarily, require the establishment of separate committees.' [Paragraph 8.5] *Where should review take place?* Separate ethical reviews should take place in both countries: 'We recommend that externally sponsored research projects should be subject to independent ethical review in the sponsor's country(ies) in addition to the country(ies) in which the research is to be conducted.' [Paragraph 8.22] 'all developing countries should have in place a properly constituted and functioning system for the independent ethical review of research. This will include the establishment of effective research ethics committees.' [Paragraph 8.16] *Funding and support for a REC in the host country:* 'Developing countries may determine that the most appropriate means of reviewing externally-sponsored research is via an independent national research ethics committee. In such circumstances the establishment, funding and proper operation of independent national research ethics committees should be the responsibility of national governments. No research should be conducted without review at the national or local level.' [Paragraph 8.16] 'We conclude that there is a need for creative approaches to providing support, especially financial support, for research ethics committees, without compromising their independence. Sponsors should determine how they can meet the costs of ethical review without compromising the independence of the research ethics committee and should be responsible for meeting the costs of reviewing externally-sponsored research.' [Paragraph 8.20]