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WORKING DOCUMENT

Draft Guide for Research Ethics Committee Members

This document is intended to be used as a tool for research ethics committee members. The text has been elaborated by the Group of Specialists on Biomedical Research (CDBI-CO-GT2) working under the authority of the Steering Committee on Bioethics (CDBI) of the Council of Europe. The Guide does not provide new principles but highlights the ethical basis for the principles laid down in the European instruments covering biomedical research and indicates operational procedures to facilitate their implementation.

At its 37th plenary meeting, the CDBI decided to declassify the draft Guide for consultation. It is a working document which may still be subject to modifications, in particular in the light of the comments which will be made during the consultation process which will end on 31 March 2010

WORKING DOCUMENT

TABLE OF CONTENTS

WORKING DOCUMENT

1. INTRODUCTION

"Today's research is tomorrow's healthcare" – this simple statement encapsulates the ultimate justification for biomedical research.

Whether carried out by means of physical interventions on patients or on healthy volunteers or, by use of stored human tissue, cells, or data obtained by questionnaires, biomedical research aims in all cases to diminish prevailing uncertainties and improve our understanding of health and disease. The results obtained should ultimately contribute to ever more appropriate healthcare tailored to the needs of patients.

Research may be beneficial for individual participants or for a specific group of persons, or may enhance basic biomedical knowledge. Although the need for new research must in principle be justified on the basis of preceding evidence, the results cannot be predicted accurately. Research must be carried out freely but only subject to specific provisions for the protection of human beings.

These provisions also prevent research projects from exposing participants or a population at large to undue risks.

The justified need for biomedical research and the protection of human rights and fundamental freedoms of research participants have to be weighed up against one another; the assessment of this balance may be complex. For example, when considering risk, the degree of risk that may be acceptable in research on a new treatment for advanced cancer may be unacceptably high in research on a new treatment for a mild infection.

Research may be conducted at local/regional, national, or, increasingly, international level. The growing international dimension has prompted the development of internationally accepted ethical principles for biomedical research – for example, as set out in the Council of Europe Convention on Human Rights and Biomedicine and its Additional Protocols as well as in other legally binding instruments. Furthermore other sources of ethical guidance are widely accepted internationally, foremost among these being the World Medical Association *Declaration of Helsinki: ethical principles for medical research involving human subjects*, and the Council for International Organizations of Medical Sciences (CIOMS) *International Ethical Guidelines for Biomedical Research Involving Human Subjects.*

The 1975 amended version of the Declaration of Helsinki referred to the basic principle that the protocol of a proposed research project should be submitted to an independent body for "consideration, comment, and guidance". This was an important step in the evolution of what are now known as "Research Ethics Committees".

Research Ethics Committees (RECs) provide independent advice on the extent to which a biomedical research proposal complies with recognised ethical standards. The REC must be satisfied about the scientific quality of the research proposal and of its conformity with national law; scientific quality and conformity with law may be assessed by the REC per se or by other competent bodies. RECs therefore play a

central part in the research process. Further to their role in the protection of participants, they specifically help to ensure that research is soundly based and trustworthy, and consequently that medical interventions and treatments prescribed to patients have been assessed adequately. In this way, RECs help ultimately to improve the quality of health care. RECs play an increasingly important part in the dialogue with the public concerning ethical aspects of biomedical research.

To assist RECs in fulfilling their important role this guide is designed to highlight, from a European perspective, the key ethical issues that they are likely to face when they review research proposals involving human beings[1]. It has to be noted that the guide was elaborated taking as a reference research projects involving an intervention on the participants (interventional research). However, considering the large diversity of biomedical research involving human beings that RECs may have to review (the modalities of which go form physical intervention to the use of stored biological samples, as well as collected data,…) some parts of this guide, such as the Chapter 4 concerning research ethics committees, or certain sections of Chapter 5 concerning confidentiality and right to information or access to research results, may be relevant for all these research projects.

The guide does not provide new principles but highlights the ethical basis for the principles laid down in the European instruments covering biomedical research. Additionally the guide outlines operational procedures as a basis on which RECs can develop their own organisational methods. The guide is intended to be useful in practice, succinct and readable.

2. ETHICAL PRINCIPLES

This Chapter highlights the ethical basis for the principles laid down in the instruments covering biomedical research involving human beings.

All research involving human beings should be conducted according to ethical principles, which are universally recognised, in particular:

- Autonomy,
- beneficence and the related principle of non-maleficence,
  as well as,
- justice.

These principles are reflected in biomedical ethics guidance from various sources and in legally binding instruments for the protection of biomedical research participants e.g. the Convention on Human Rights and Biomedicine *(see Chapter 3).* The principles are interrelated and this interrelationship should be taken into account when considering their application.

This Guide *(see especially Chapter* 5) outlines how these fundamental principles and those deriving from them are applied in practice.

[1] This guide does not address the ethical issues pertaining to the use of animals in research.

Underpinning these principles, from which other ethical considerations flow, is the need to respect and protect human dignity and the corollary principle of primacy of the human being. The latter is of particular relevance in the field of biomedical research. In accordance with this principle, the interests and welfare of the human being participating in research must always prevail over the sole interest of science and society. Priority must always been given to the former and this must take precedence over the latter in the event of conflict between them. Provisions laid down in legal instruments and guidance for the protection of biomedical research participants should be interpreted in this light.

Autonomy

Respect for autonomy acknowledges a person's capacity to make personal choices. In the context of biomedicine there are further implications: (a) that an individual should be provided with the necessary conditions to exercise his or her autonomy; and (b) that a person whose autonomy is diminished or impaired should be protected from harm and abuse.

In biomedical research, the principle of autonomy is exercised in particular through the process of free and informed consent. Whereas medical practice is expected to confer a health benefit for the patient, the very nature of biomedical research means that it is uncertain whether an individual will benefit from research participation and this is not the main purpose of research. A potential research participant must therefore be provided with appropriate, accurate and understandable information about the research project before being asked to choose whether or not to participate.

To enable a person to make an informed decision, the information must include a comprehensible description of the research procedures envisaged, their purpose, and foreseeable risks and benefits *(see Chapter 5 for detailed discussion).* To ensure that the information is comprehensible, the way and form in which it is provided is especially important.

Free and informed consent also implies that potential research participants must not be coerced or unduly influenced. It is extremely difficult to achieve a complete lack of influence, but influence that would lead individuals to accept, in particular, a higher level of risk than would otherwise be acceptable to them, would be considered undue. Undue influence may be financial in nature but would also include, for example, attempts to influence close relatives, or veiled threats to deny access to services to which individuals would otherwise be entitled.

Particular attention must be paid to dependent and vulnerable people *(see Chapter 5)*, whose proposed participation in a research project must always be justified specifically. In general, proposed research participants must be the least vulnerable necessary to achieve the goals of the research.

Special provisions are also needed, as outlined in Chapter 6, to ensure appropriate protection of persons who, according to law, are not able to give valid consent because of their age (minors), a mental disability, a disease or for other reasons.

Research on stored human biological materials may raise particular problems with regard to consent. Specific provisions may be necessary to ensure that the materials

are used in conformity with appropriate information and consent procedures *(see Chapter 9)*.

An important principle closely related to autonomy that has particular relevance for biomedical research is the principle that access to, control of, and dissemination of personal information collected for the purposes of research, or resulting from research, must be protected from inappropriate disclosure and treated as confidential.

Beneficence and non-maleficence

The principles of beneficence and non maleficence encapsulate the moral obligation to maximise potential benefit and minimize potential harm.

The principle of beneficence has further implications, in particular that the design of the research project is sound and meets accepted criteria of scientific quality. It also implies that the researchers are competent to carry out the research in accordance with relevant professional obligations and standards and to ensure appropriate protection of the research participants.

Nevertheless, an element of risk, including risk of harm to participants, is inherent in the research process. Research on human beings may therefore only be undertaken when there is no alternative method which could provide comparable results.

Research may also entail some risks and benefits for participants' families and society at large, but any risk of harm and burden (such as constraints or discomfort) will primarily be borne by the participants. In addition, and depending on the nature of the research, direct benefit for research participants may be limited or absent.
The balance between harms and benefits is therefore critical to the ethics of biomedical research. A research project should proceed only if its foreseeable risks and burdens are not disproportionate to its potential benefits. In practice, this means that all research projects must undergo a thorough comparative risk/benefit assessment.
The nature of the risk may not only be physical but also, for example, psychological. The risk for private life has also to be taken into account. Research may as well involve social or economic risks. Although the anticipated overall benefits of the research project must clearly be higher than the potential risks, the research may not be considered justified if there is a particularly high risk of serious harm; there comes a point when a certain nature and level of risk will never be deemed acceptable even if the person gives consent to participate in such research.

Risks must always be minimized. Furthermore, for research involving persons unable to consent in particular, if the research has no potential for direct benefit, the additional principle of minimal risk and minimal burden[2] applies – that is, the

[2] Research with minimal risk is that which, in terms of the nature and scale of the intervention(s), would result in an individual case, in no more than a very slightly detrimental and temporary impact on the health of the person concerned. Minimal burden is considered as that for which the expected discomfort, which might be associated with the research, will be at most temporary and very slight for the individual. Examples of research with minimal risk and minimal burden include:
- obtaining bodily fluids non invasively, e.g. taking saliva or urine samples or cheek swab,
- at a time when tissues samples are being taken, for example during a surgical operation, taking small additional tissue samples,
- taking a blood sample from a peripheral vein or a sample of capillary blood,

research must entail no more than minimal risk and minimal burden for such participants.

Justice
The principle of justice encompasses fairness and equity. This principle has been generally defined in relation to biomedicine, but also has particular relevance for research.
The key question is who ought to receive the benefits of research and bear its risk and burden. In biomedical research involving human beings, this implies that the distribution of risk and burden on the one hand and benefit on the other be fair – a principle known as distributive justice.

Distributive justice has implications especially for the selection of research participants. Selection criteria should be related to the purpose of the research and not merely based, for example, on the ease with which consent is likely to be obtained. Conversely, this principle also requires that groups of individuals who are likely to benefit from the research are not generally excluded.
Distributive justice has particular relevance in practice for research in countries with very limited resources *(see Chapter 8)* and for research involving vulnerable populations *(see Chapters 6 and 7).* Such research should be responsive to health needs relevant to the countries/population concerned so that they stand to benefit from the outcome and possible applications of the research.

Ensuring respect for ethical principles: independent scientific and ethical evaluation
The ethical principles laid down in the instruments and guidance covering biomedical research aim to protect the dignity, rights, safety and well being of the research participants. Independent examination of the scientific merit of a research project and review of its ethical acceptability are central to ensuring respect for these principles *(see Chapters 4 and 5).*

3. LEGAL ASPECTS

3.A Introduction

From a legal standpoint, research projects must comply with the national law of the country where the research will be carried out. In turn, the national law of each country must fulfil the requirements of any international laws/treaties to which the countries concerned have subscribed. It is therefore important for RECs to be satisfied that projects conform with the applicable legal standards.

REC members will need to familiarise themselves with their national legislation pertaining to biomedical research.
Over and above this there are several legally binding instruments and other non-legally-binding but generally accepted aspects of guidance that apply across Europe, these are outlined below.

- minor extensions to non-invasive diagnostic measures using technical equipment, such as ultrasonography, an electrocardiogram following rest, one X-ray exposure, one computed tomographic exposure or one magnetic resonance imaging exposure without contrast medium.
However, for certain participants, even these procedures might entail risk or burden which cannot be considered minimal. Individual assessment is therefore essential.

3.B Sources

Various standard-setting instruments deal with biomedical research, whether at world, European or national level.

From the legal standpoint, the chief concern is whether or not a text is binding, i.e. whether it lays down the obligation of compliance or whether its provisions represent good practice with no such legal obligation.

These various standard-setting instruments are thus classified according to their legally non-binding or binding character.

3.B.1. Non legally binding instruments

These are the most numerous.

At the world level, some of these instruments were drawn up in the framework of professional associations, others within international organisations.

The best-known instrument of professional origin is the Declaration of Helsinki, drawn up by of the World Medical Association and adopted for the first time in 1964 with several subsequent amendments.

The Universal Declaration on bioethics and human rights, drawn up within UNESCO, contains certain provisions on research[3].

The CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects and the ICH, E6 Good Clinical Practice guidelines, drawn up by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use are also of special interest.

3.B.2 Legally binding instruments

At the European level, biomedical research is governed by three binding instruments. One is a European Community text (Directive 2001/20/EC[4] of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products[5] for human use[6]).
The others, drawn up within the Council of Europe, Convention on Human Rights and Biomedicine (Oviedo Convention) and its Additional Protocol concerning Biomedical Research are binding in the States where they have been ratified.

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[3] Universal Declaration on bioethics and human rights, in particular : article 2, article 3, article 4, article 6, article 7, article 8, article 15, article 19, article 21.
[4] Binding also for the contracting states of the European Economic Area (EEA) Iceland, Norway, and Liechtenstein
[5] "medicinal product" is defined by the Directive as any substance or combination of substances presented as having properties for treating or preventing disease in human beings. Any substance or combination of substances which may be administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological or metabolic action , or to making a medical diagnosis."
[6] OJ L 121, 1.5.2001, p. 34.

At world level, the sole legally binding provision is Article 7 of the Covenant on Civil and Political Rights[7], drawn up within the United Nations, but it only addresses one aspect of research[8]

Domestic law often contains provisions on biomedical research, whether in texts dedicated to this question or in more general texts.

This Guide refers essentially to the three legally binding European instruments. Since the provisions of domestic law may vary between countries, the references to it serve to illustrate the different ways in which a single principle may be applied. The references to non-binding instruments are likewise for illustrative purpose**s**.

3.B.2.1 The Oviedo Convention and Additional Protocol concerning Biomedical Research

Drawn up within the Council of Europe by the Steering Committee on Bioethics, the Oviedo Convention and its Additional Protocol concerning Biomedical Research constitute international treaties. Their provisions are legally binding in respect of the countries which have ratified them.
The Convention provisions apply to research projects in the sphere of health where such research involves an intervention on a human being. This includes, in particular, research on medicines, but also other types of research such as fundamental research.

3.B.2.2 Directive 2001/20/EC

Directive 2001/20/EC is applicable to the Member States of the European Union and the contracting States of the European Economic Area (EEA), Norway, Iceland, and Liechtenstein.

The Directive's provisions apply to clinical trials on medicinal products for human use, performed in any Member State of the EU/EEA. Non-interventional trials as defined in Article 2(c) of the Directive are not covered. (EC)

4. RESEARCH ETHICS COMMITTEES (RECs)[9]

4.A REC - Description

Research Ethics Committees (RECs) are multidisciplinary, independent groups of individuals appointed to review biomedical research protocols involving human beings to help ensure in particular that the dignity, fundamental rights, safety, and well-being of research participants are duly respected and protected.

[7] International Covenant on Civil and Political Rights:
article 7. "No one shall be subjected to torture or to cruel, inhuman or degrading treatment or punishment. In particular, no one shall be subjected without his free consent to medical or scientific experimentation
[8] *Concerning this question, see:*
Declaration adopted by CDBI at its 31st plenary meeting (20-23 November 2006)
United Nations Convention on the Rights of Persons with Disabilities
[9] It is considered that this term covers ethics committees or other bodies authorised to review biomedical research involving interventions on human beings.

RECs may be established at local, regional or national level. They may be appointed by institutions or by regional or national authorities and are increasingly provided for by law. Their scope as a local, regional or national REC is defined by the appointing authorities**.**

Transnational research is discussed in *Chapter 8.*
Although there may be some differences with respect to the appointment and work of RECs among different European countries (and in other parts of the world), RECs should be established and function according to commonly accepted ethical principles and procedural standards (*see 4B below*).

4.A.1. Roles and activities of RECs in the research process

RECs have specific roles before, during, and after a biomedical research project is authorized and conducted, and the results are evaluated and reported. Their responsibilities and practical duties therefore encompass the entire spectrum of biomedical research (see overview in *Figure 4.1*).

- *roles* aim to fulfil RECs' main objective – to ensure that biomedical research is conducted ethically. RECs' composition and collective expertise in ethical and scientific issues, as well as their working methods and overall functioning, should provide assurance that they are trustworthy and can carry out their duties effectively. (*see Figure 4.1).*

- *complementary activities*. There is a general trend, which is to be welcomed, for RECs to take on complementary activities with the aim of improving the overall culture of biomedical research, enhance communication between researchers/research institutions and society, and raise awareness of ethical issues in biomedical research.
For example, RECs or their national organisations may become involved in public dialogue about ethical issues or take on an educational role about research ethics policy and decision making.

Figure 4.1 Roles of RECs in the research process

Research phase	Planning, preparation	Review	Conduct	Final evaluation
Roles	consultation with researchers	ethics review of the research proposal	follow up of the research project**;** possible re-review	Review reports from the researchers

4.A.1.1 RECs' roles before research begins – ethics review of research proposals

As their primary objective, RECs ensure that the biomedical research proposals they consider are ethically acceptable before being approved. In this way RECs also provide public assurance that unethical research is avoided and that good quality, ethically sound research is encouraged.

RECs fulfil this objective conducting an ethics review of research proposals (*see Chapter 5*) and by issuing written opinions on their ethical acceptability.
RECs evaluate the ethical acceptability of a research proposal from two main standpoints:

- from the standpoint of the ethical implications of the research conduct, foreseeable research outcomes, and potential consequences of research results for society. 'Society' can encompass both local and wider contexts and may include the potential interests of future generations.
- from the standpoint of the prospective research participants to safeguard their rights, dignity, safety, and well-being.

When evaluating a biomedical research proposal (*see Chapter 5*), RECs need to consider the ethical issues involved in accord with applicable ethical principles accepted both by the given society and internationally.

The REC must be satisfied about the scientific quality of the research proposal and of its conformity with national law; scientific quality and conformity with law may be assessed by the REC per se or by other competent bodies.

RECs are not responsible for reviewing the ethical aspects of clinical practice.

Clinical Audit

The so-called 'grey' area of clinical audit is more problematic. In general, the distinction between research and audit is as follows. Research is about obtaining new knowledge; about finding out what is or will become best practice – eg, the research question would be 'what is the most effective way of treating pressure sores?'.
Clinical audit is about quality; about finding out if best practices are being followed – eg, the audit question would be 'How are we treating pressure sores and how does this compare with accepted best practice?'.
Clearly the distinction is not absolute and so the need for REC review cannot be precisely defined. One suggested approach is to concentrate on three key questions:
i. is the purpose of the proposed project to try and improve the quality of patient care in the local setting?;
ii. will the project involve measuring practice against standards?;
iii. does the project involve anything being done to patients which would not have been part of their normal routine management.? If the answer to the first two questions is 'yes' and to the third 'no', then the project is probably clinical audit; otherwise it is probably research.

REC review and the EC Clinical Trials Directive (2001/20/EC) – the single opinion requirement

In European Union (EU) countries, the Directive applies to clinical trials of medicinal products[10]. The Directive requires that multicentre clinical trials to be carried out in a single Member State must receive a favourable opinion on their ethical acceptability from a single REC. When multicentre trials are to be carried out in more than one

[10] See footnote 4

Member State simultaneously, the Directive requires that a single opinion is given for each Member State involved in the trial.

RECs' independence
RECs must be independent and demonstrably able to make decisions without undue political, professional, institutional or market influence. This crucial requirement should be duly reflected in the procedures for appointing REC members, in the requirements for REC membership, and in the procedures for dealing with potential conflicts of interest.

REC review and implications for publication of research results
Most scientific journals, when considering a submission involving human research participants, will require that the research had been approved by a REC. In this way, RECs also contribute to the scientific and ethical quality of the research that is done.

4.A.1.2 RECs' roles during the research
RECs should follow up, as appropriate and according to national practice, the conduct of research projects that they have approved and may need formally to re-examine them in view of new developments and relevant knowledge acquired during the research.

This is especially important when the research entails a non-negligible level of risk, or where it is expected to generate clinically relevant information which could affect – positively or negatively – the safety, health or wellbeing of the research participants.

The purpose of follow up is to establish whether, in the light of any new developments during its conduct, the research can continue unchanged according to the original proposal, or whether modifications in the project have become necessary, or, even, if the research needs to be discontinued (*see Chapter 5*).

Follow up can usually be achieved by REC review of project reports that the researchers (or research sponsors where appropriate) are usually obliged to provide on a regular (at least annual) basis

RECs should also have a designated mechanism (*see Chapter 4.B*), that allows them to react as appropriate to any serious information received during the course of the research project for example concerning the safety and well being of the research participants including, where appropriate, interim information concerning the efficacy of a medicinal product being studied. This should be done promptly and duly documented.

The actions available to the researchers, sponsors, and RECs (in addition to taking immediate measures taken to protect the health and well-being of the research participants) include protocol amendments, or a temporary suspension or termination of the research.

4.A.1.3 RECs' roles after the research

The roles of RECs after the research is completed (*Figure 4.1*) are currently rather limited. This is not generally regarded as the most important use of REC expertise and moreover RECs seldom have the legal competence, the time and other resources to function effectively for this purpose.

One area in which RECs' responsibilities tend to be more visible is in helping to ensure that the obligations of researchers and their institutions or sponsors of research to the research participants, and/or to the groups or society from which they were recruited, are fulfilled as specified in the original research proposal. For example, researchers' or sponsors' obligations may entail the offer of health-related information revealed within the research to the research participants, or provision of specific health care or other benefits. These issues may be especially prominent when research is conducted in developing countries, in vulnerable people, or in marginalised or disadvantaged population groups. Although RECs do not have any legal powers to demand that such obligations are fulfilled, their moral status and influence can help to resolve issues that arise.

Another ethical obligation of the researchers or of the sponsors of research is to make the conclusions of the research available to the research participants in a form that is comprehensible to them and to society by means of fair and adequate publication. Sometimes, for commercial or other reasons, research results, especially 'negative' results, are suppressed; such biased under-reporting is not only unscientific and unethical but has also harmed patients, for example when adverse effects of treatments have been concealed. Although several mechanisms are being introduced to aid transparent reporting of research information - e. g. the requirement for pre-registration of any clinical trial on medicinal products in a public database before the trial begins (see chapter 5) - RECs can still help by being attentive to this important issue as it pertains to projects completed under their supervision.

4.A.2 Composition of RECs

4.A.2.1 Expertise

In view of national legal requirements and owing to the needs and characteristics of their work in particular institutional or regional contexts, the number of members and composition (professional and other expertise represented) of RECs may vary considerably. They should, however, share several key features reflecting the principles and goals of their work - the effective and trustworthy ethical review of research projects submitted to them.

To fulfil their tasks and responsibilities, RECs should possess collective expertise in the fields or disciplines deemed necessary for their work.

The appointment mechanism should ensure that potential REC members provide an appropriate balance of scientific expertise, philosophical, legal or ethical backgrounds, and lay views. All REC members, whether professional or lay members, should have an equal standing. This may pose a special challenge in societies with a long tradition of strong respect for authority or social hierarchy.
It is generally accepted that professional members of RECs include scientists, medical professionals, lawyers, and persons with specific expertise in ethics. Other

useful disciplines include epidemiology, clinical pharmacology, pharmacy, psychology, sociology, and biostatistics**.**

Lay members of RECs are usually defined as having no specific qualification with respect to biomedical research, medicine, or health care. They are expected in particular to reflect the views of the public as well as those of patients.

REC members should be able to strike an appropriate balance between achieving the greater common good that can be brought about by biomedical research and recognising and protecting the human dignity, rights, health and wellbeing, and interests of research participants. Above all, they must ensure that, where there is a conflict, the interests and welfare of the people participating in research prevail over the sole interest of society or science.

REC members should have a basic understanding of the importance of research and how it can benefit human health and welfare. They should be able to understand the principles of research and research methods, the research context, and the practicalities of carrying out biomedical research. They must be able to make their own independent judgements when considering the ethical issues involved in the research proposals placed before them.

RECs should be multidisciplinary and reflect an appropriate range of professional and lay views and take into account gender balance. Depending on specific projects under review, there should be a satisfactory mechanism for seeking additional advice (e.g. by inviting external experts).

The crucial requirement for RECs is to be independent of the researchers and their sponsors, as well as of their establishing institution or authority. The mechanisms designed to achieve this independence should be reflected in their appointment and membership renewal process, as well as in their working methods and decision making.

In gaining and sustaining recognition of their moral authority, RECs' composition should reflect the prevailing cultural tradition. They should be able to demonstrate their impartiality, transparency, good will, and ability to foster and use dialogue when communicating with other parties in the field of biomedical research.

4.A.2.2 Specific posts – Chair, Vice-Chair, Administrator

RECs should appoint appropriate people to lead the committee. All RECs should have a Chair and Vice-Chair who command the respect of REC members.

An Administrator should be made available to the REC on a full or part time basis, backed by administrative support.

The responsibilities and tasks of the REC Chair, Vice Chair, and Administrator (*see Figure 4.2*) should be clearly specified, for example in the REC's rules of procedure or standard operating procedures (SOPs). Anyone appointed to chair a REC should have gained the necessary experience by being a REC member for some time previously and should be offered specific training to carry out the duties and tasks of a Chair effectively.

Figure 4.2. Typical duties and responsibilities of REC Chair, Vice-Chair, and Administrator

Chair	• prepares, convenes, and chairs regular and extraordinary REC meetings, • represents the REC before the appointing authority and to the public, • elaborates the plans of REC meetings and other activities, • ensures timely response to applications • signs official REC documents, especially the REC's opinions on ethical acceptability of the research proposals under its review, and other documents, • coordinates, leads, and oversees the work and various activities of the REC and of its secretariat, • prepares and submits the REC budget, • oversees and proposes educational/training activities for REC members and for the REC as a whole • provides, on behalf of the REC, specific consultations with researchers, the management of its research institution or appointing authority, • where appropriate, takes decisions on behalf of REC, for example for emergency situation or minor action.
Vice-Chair	• fulfils the duties of the Chair in his/her absence • can be asked to perform additional specific tasks, such as overseeing a part of the REC agenda
Administrator	• provides administrative support, including preparation of documents for REC, prepares minutes of REC meetings for REC review work and other activities, • prepares, with the help of the REC Chair and Vice-Chair, documents for REC meetings, • prepares the minutes of REC meetings,

4.A.3 REC appointment and renewal process

The processes by which REC members are appointed and membership is renewed should be transparent and fair. The process should be free of partisanship that might hamper the independence of the committee.

The term of office of REC members, including the option of membership renewal, must be clearly prescribed, bearing in mind the need to maintain an appropriate balance between continuity of accumulated expertise and appointment of new members.

The issue of maintaining independence with respect to ethics review and follow-up of reviewed research projects highlights the management of possible conflicts of interest. Consequently, when people are appointed to be REC members, they should declare any actual or potential conflicts of interest with respect to the work of the REC and agree to declare any conflicts that may arise subsequently. Such declarations should be documented and kept up to date. People appointed REC members should be given a document of appointment. It may be useful for them to receive written specifications of their duties established by that appointment.

4.A.4 Initial and continuing training of REC members

REC members should receive appropriate independent initial and continuing training relevant to their role in the REC. In addition to general training for all members, training courses should be adaptable to individual members' needs. Training should lead in particular to a fair understanding of:

i. ethical principles and their application in biomedical research;
ii. research design and methods; and
iii. practicalities of conducting research. Training should be adapted to the REC's specific needs.

It should also be responsive to requests from REC members.

It may be useful to organise regular meetings or conferences of RECs to share experience. It is also helpful for RECs to meet with representatives of regulatory authorities and experts in specific fields related to biomedicine.

4.A.5 Confidentiality

Any information provided to RECs should be treated as confidential by all REC members and by REC staff. Any external experts who are invited to give an opinion to the REC about a particular research proposal should likewise keep the information confidential.

Another aspect of confidentiality concerns the need to promote free and open discussion among REC members when they review proposals. Since free discussion is crucial if RECs are to fulfil their review duties, the content of such discussions should be kept confidential This holds also of details on the decision making process.

4.A.6 Accountability of RECs

RECs should be accountable to their appointing body or authority, according to the provisions given in national law or in other documents issued by national competent bodies or institutions. The appointing authority should satisfy itself that the REC functions according to the applicable rules.

RECs should provide sufficient information about their work - ethics review, research follow up, and other activities - to their appointing institution or authority by means of well structured regular reports, which should not reveal confidential details of the research or its participants. Such reports, in their entirety or in the form of an executive summary, should also be made available publicly, for example on a REC, institution, or regional authority web site.

4.B Method of Working

RECs should carry out their work according to procedural standards as set out in the Statutes and Rules of Procedure

4.B.1 Statutes

REC statutes, which must conform to applicable national legislation, are issued by the appointing institution or authority. They define the main issues concerning the REC's establishment, scope and work. They should be publicly available.

Statutes should be revised and amended as necessary by the issuing institution or authority in consultation with the REC.

An example of the typical content of REC Statutes is given in the *Figure 4.3*.

Figure 4.3 Typical content of REC Statutes

- Appointing institution or authority
- Scope of activities
- Nature of REC's decision - advisory or legally binding
- Membership (required disciplines/specialties, lay members, etc.)
- Procedures for appointing members and chair
- Duties and responsibilities of members and administrative officers
- Procedure for membership renewal
- Management of conflicts of interest*
- Communication with the regulatory authorities
- Confidentiality (members, staff, invited external experts*)
- Principles of decision-making (consensus, voting)*
- Procedure for dealing with dissenting opinions*
- Administrative support, including staffing and budgeting
- Fees (if any) for members and invited experts
- Requirements and principles of documentation and archiving, including regular reports*

* *details to be specified in the Rules of Procedure*

4.B.2 Rules of Procedure

Rules of Procedure are usually developed by RECs and where appropriate approved by the appointing institution or authority. They should specify how a REC is to function in an effective and transparent manner. They should be made publicly available, as for the REC's Statutes.

An example of the typical content of REC Rules of Procedure is given in the *Figure 4.4*.

Figure 4.4 Typical content of REC Rules of Procedure

Assessment of a submitted research project

- Entitled applicant / application form
- Confirmation of receipt of completed application for review or request for further information
- Arrangements for dealing with conflicts of interest
- Distribution of the application to REC members
- Allocation of reviewing tasks (e.g. appointment of *ad hoc* rapporteurs)
- Arrangements for obtaining external expertise
- Relations with other bodies involved in the research assessment
- Ways of communication with research applicants or sponsors, including any possibility of meeting with them, before decision is made
- Process of REC decision-making, including quorum for meetings and any voting procedure
- Procedures for expedited review
- Content and form of the reasoned decision
- Deadlines for giving the applicant the REC's decision
- Procedures for the applicant's response to the REC's decision

General rules of procedure

- Duties and responsibilities of Chair and Vice Chair
- Preparation for and conduct of plenary meetings, including minutes
- Other administrative procedures including management of documentation
- If applicable, arrangements for following up research projects
- Requirements for producing regular reports
- Procedures for preparing information for the public

Plenary meetings

Plenary meetings are the most important REC activity. At these meetings REC members review research proposals and decide on their ethical acceptability. A schedule of meeting dates should be announced in advance and REC members must be given sufficient time to review relevant documents before each meeting.

Appointment of ad hoc rapporteurs

To ensure competent and thorough ethics review, it is good practice to designate individual REC members as ad hoc rapporteurs for proposals. Rapporteurs are invited to present their detailed reviews to the whole committee before a proposal is discussed, and ideally to submit a short written report that can be circulated to all REC members ahead of the meeting.

Administrative procedures

RECs must establish administrative procedures so that they can keep track of documents at all stages of the review process. The REC Administrator is also responsible for practical organisation of plenary meetings, including the despatch of meeting papers and the preparation and distribution of minutes.

Archiving of the documents

According to national law, RECs are required to archive a substantial number of documents. Since some of the documents may contain sensitive information (e.g. personal data, or information relating to intellectual property) secure archiving facilities, including electronic archives, are essential and should be made available to the REC by the appointing institution or authority.

4.B.3 Follow up of an ongoing research project

The working methods that RECs may adopt when following up an ongoing research project are listed below:

- Review of regular reports,
- Review of regular safety reports,
- Mechanism for dealing with any serious information regarding conduct or outcomes/results of the research.

4.B.4 REC self-evaluation tools

In addition to an independent audit or inspection where appropriate (*see Chapter 4.C*), RECs should have mechanisms for periodically evaluating the quality of their work and functioning to see whether there is room for improvement.

Typical self-evaluation tools are:

- Free discussion among REC members during a specified time at plenary meetings
- Preparation and discussion of the REC regular reports
- Completion and evaluation of a REC self-evaluation questionnaire
- Structured REC self-evaluation exercise

4.B.4.1 Discussion*:* RECs should periodically devote time to free discussion about their method of working, when members should be encouraged to voice any concerns and to propose ways of improving REC performance. Formal training may enhance REC functioning. Drafting of the regular report may also be used as an opportunity for informal self-evaluation of the REC, for example in relation to the number of research projects reviewed.

4.B.4.2 Self-evaluation: Several self-evaluation tools have been developed to help RECs, mostly by use of self-administered questionnaires that are completed either by individual REC members or by the REC as a whole. Such questionnaires, used periodically, can provide a valuable overview and appraisal of REC activities, and additionally offer the possibility of collating new ideas and proposals for improvement. Structured self-evaluation exercises involving external experts are also increasingly used and would need to be specifically budgeted for by the REC appointing institution/authority.

4.B.5 Exchange with other bodies

RECs should make appropriate contacts and exchange information with other relevant bodies that are taking part in the review, authorization, and follow-up of research projects at regional, national, or international level. Such contacts encourage harmonization of the ethics review system with respect to both ethical and procedural standards. Information exchange also permits identification of scientific trends and enhances overall REC knowledge about research results that may have a bearing on their work. Information about regulatory and guidance documents and about REC training opportunities can likewise be shared. In addition, the sharing of

knowledge may permit early identification of ethically dubious or unacceptable research activities.

4.C Independent audit of REC functioning

There is increasing national and international interest in ensuring that REC review attains the highest possible standards concerning the protection of research participants and the communities from which they are drawn. In this regard independent audit of RECs can make important contributions to the quality of the ethics review process by encouraging RECs to develop standardized policies and procedures that help to promote the consistent application of ethical principles. Independent audit also provides a means for checking whether RECs are adhering to the policies and procedures that they claim to be following. External audits usually focus on issues such as committee membership, operating procedures, and the documentation of meetings. Auditors check that a REC has a structure and composition appropriate to the amount and nature of research being conducted in its institution/region; has appropriate management and operational procedures; reviews protocols in a timely fashion according to established procedure; adequately and effectively communicates decisions to investigators; and has appropriate practices regarding documentation and archiving.

5. INDEPENDENT REC EXAMINATION OF A RESEARCH PROJECT

5.A General

For each application, the REC must establish at the outset whether, according to national law, it is legally competent to deal with the applicant and the research proposal. If not, the applicant should be directed to the competent REC.

If the REC is competent, the next step is to ascertain whether the applicant or his/her authorized representative is entitled to submit a proposal. The right of application may differ depending on the type of research. For clinical trials of medicinal products as defined by the Directive 2001/20/EC, the sponsor[11] is the entitled applicant.

In some States, a national competent authority such as a Ministry or a regulatory agency is involved in decision-making regarding research projects. In that event, the interrelation between the REC and the national authority must be respected according to national law, taking into account the nature of the research proposal.

Application process

The application should be in writing and dated. Electronic submissions should be accepted by the REC. The REC should acknowledge receipt and have established procedures for safeguarding the confidentiality of the submitted research project. The form should specify a designated contact person responsible for correspondence and for dealing with any queries that the REC might have.

11. The Directive defines a sponsor as “an individual, company, institution or organization which takes responsibility for the initiation, management and/or financing of a clinical trial”

The REC must be assured that the application satisfies its requirements and those prescribed by law. Initial scrutiny should ascertain that the applicant has included all documents pertinent to ethics review of the research proposal (*see 5B below and Figure 5.1*).

If all the requirements for submission have been met, the REC should inform the applicant that the assessment will begin. The information should include the anticipated timetable for review and mention the possibility that, if more documents or specific information are required, the timetable would need to be revised accordingly. The information should also make clear that if the applicant is invited to discuss the proposal in person, he or she will take no part in the decision-making procedure.

When the REC meets to review proposals, members must be asked to declare any conflicts of interest pertaining to the applications under review (*see Chapter 4A*).

5.B Information to be provided to and examined by the REC

Figure 5.1 outlines the information necessary for REC review; this can be adapted according to the nature of the research proposal.

Figure 5.1 Description of the project

- Name of the principal researcher, qualifications and experience of researchers and, where appropriate, the person responsible for clinical care of participants
- Funding arrangements
- Aim of and justification for the research based on the most up-to-date review of scientific evidence
- Methods and procedures envisaged, including statistical and other analytical techniques
- Comprehensive summary of the project in plain language
- Statement of previous and any concurrent submissions of the research project for assessment or approval and outcome of those submissions

Participants, consent, and information

- Justification for involving human beings in the research project
- Criteria for inclusion/exclusion of research participants
- If appropriate, method of randomisation
- Type of study: unblinded, single or double blinded
- Selection and recruitment procedures
- Reasons for use or absence of control groups, including justification for placebo
- Treatment of control group
- Description of the nature and degree of foreseeable risks that may be incurred through research participation
- Nature, extent, and duration of the proposed interventions, and details of any burden imposed by the research
- Arrangements to monitor, evaluate, and react to contingencies that may have consequences for the present or future health of research participants and/or other persons affected by the research or its results
- Timing and details of information for proposed research participants, including proposed methods for provision of this information

- Documentation or any visual or other material to be used for seeking consent, or, in the case of persons unable to consent, authorisation for participation in the research
- Arrangements to ensure respect for private life research participants and to ensure the confidentiality of personal data
- Arrangements for dealing with information that may be generated during the research and be relevant to the present or future heath of participants and their family members
- Proposals for health care after the end of the research project

Other information

- Description of the research facilities
- Details of all proposed payments and rewards for research participation
- Details of all circumstances that might lead to conflicts of interest and that may affect the independent judgement of the researchers
- Details of any foreseen potential further uses, including commercial uses, of the research results, other data collected in the research process, or biological materials
- Details of all other ethical issues as perceived by the researcher
- Details of any insurance or indemnity to cover damage arising in the context of theresearch project

Description of the project

The application must contain sufficient information to enable thorough REC review and should clearly identify the principal or lead researcher. For collaborative research, the other researchers should channel all relevant information via the principal researcher, who will be the main point of contact with the REC. The REC must be satisfied that all researchers are appropriately qualified.

The REC should pay particular attention to the scientific justification for the proposed research. This information is essential if RECs are to help prevent inappropriate research. Systematic reviews of research results, in animals as well as human beings, and, if applicable, their combination by the statistical technique of meta-analysis are especially important. The proposed research methods and procedures should be described in enough detail for the REC to judge whether they are likely to expose participants to any undue risk – e.g., if a pharmacological substance is to be used, the REC needs to have adequate information about its safety and its pharmacological and toxicological properties.

The requirement for a comprehensive summary of the research in plain language is important not only to aid the understanding of lay members of the REC but also to ensure adequate comprehension by other REC members who may not be familiar with aspects of the research being reviewed.

It is important for the REC to be aware of previous and concurrent submissions of the research project, and the outcome if known. For example, if another REC has already rejected the proposal, a new REC needs to know this to decide whether the proposal has been changed in response to legitimate concerns, whether the researchers are merely “shopping around” in the hope of finding another REC that will give a

favourable opinion, or if a previous negative decision was unjustified for whatever reason.

Justification for involving human beings in the research

The applicants must justify why they are proposing to conduct the research in human beings. The REC will need to be satisfied not only that the research holds out the ultimate prospect of improving people's health (see Introduction) but also that similar results cannot reasonably be obtained by other means, for example by mathematical modelling or research in animals. It naturally follows from this principle that the REC should not countenance invasive research methods if non-invasive methods would be similarly effective.

Inclusion and exclusion criteria

The determination of the size of study groups should depend on the project, taking into account statistical consideration. Whether categories of people are eligible to take part in research will depend on the research design. The applicants must justify their proposed inclusion and exclusion criteria. This is both to guard against inappropriate inclusion (e.g. carrying out research in people unable to consent which could be carried out in those able to consent) and to protect against inappropriate exclusion (e.g. on the grounds of gender or age). Legitimate exclusion criteria might, for example, be related to the nature or stage of disease or to concurrent medication that might interfere with a medication being studied. Particular care should be taken with women of reproductive age, but the often wholesale exclusion of women from research in the past has led to lack of knowledge about the effects of prescribed treatments in women, with potentially dangerous consequences.

Healthy volunteers

Biomedical research may involve healthy people, for example in physiological studies, in studies of vaccines (which, being prophylactic agents, are generally given to healthy individuals), or in studies to determine the safety and pharmacological profile of potential new medicines. Researchers who plan to recruit healthy volunteers must abide by the general ethical principles pertaining to biomedical research. In addition, the REC must be satisfied that the research will entail no more than acceptable risk and acceptable burden for those participants. For safety reasons, it is advisable to restrict the number of participations for each individual volunteer.

The researchers also need to satisfy the REC that they have procedures for confirming that the volunteers are healthy and suitable for inclusion in the research according to pre-determined criteria – e.g., in drug studies it would be appropriate to determine whether a volunteer has any allergies or has previously received a pharmacologically related substance. The REC should pay particular attention to the adequacy of the research setting and medical supervision. Volunteer studies are often conducted in designated non-hospital-based facilities but should nevertheless have access to an appropriate level of medical care, especially in the event of emergencies *(See Safety and supervision below).* The REC should also look carefully at any proposed payments or rewards for volunteers (*see below)* to ensure that inappropriate payments or rewards do not attract people simply as a means of making money.

Justification for control groups

To obtain reliable evidence, it is often essential to compare the effects of the new method with those of a control method in participants drawn from the same participant population. This is the principle of comparing "like with like", which is fundamental for achieving unbiased results. The applicants should therefore give their reasons for the presence, and especially the absence, of control groups, together with details of the proposed control method. Participants assigned to a control group should receive a proven effective preventive diagnostic or therapeutic method. Placebo may only be used as the control method under strictly defined conditions (*see below).*

Use of placebo

Placebo is an inert substance or a sham procedure. Biologically, the use of placebo is similar to non-treatment. However, there is scientific evidence that placebo may in some cases produce effects similar to those of treatments both regarding benefits and adverse reactions – this is known as the "placebo effect".

As noted above, placebo may only be used as the control method under strict conditions – i.e., when there are no methods of proven effectiveness, or when withdrawal or withholding of such methods does not present an unacceptable risk or burden. Consequently, the REC should pay particular attention to the foreseeable risk or burden. No other reasons would be ethically acceptable.

An ethically unacceptable reason to conduct a placebo controlled study instead of having control groups on standard treatment is that such studies tend to be cheaper and faster, since in particular the number of patients required demonstrating the effect is usually smaller.

The checklist in Figure 5.2 outlines the question that the REC should consider when reviewing a placebo-controlled study.

Figure 5.2 Specific questions relating to REC review of placebo-controlled studies

- Is there a compelling scientific reason to carry out a placebo-controlled study?
- Is there a known treatment of proven effectiveness?
- If so, is it safe for the patients to go without such treatment for the period required by the project? In other words, is the additional risk acceptable?
- Is the additional burden imposed on the patient by unrelieved symptoms acceptable? Would there be an additional burden as a result of the patients' condition on their families/carers?
- Will the patients be informed about the possibility that they may be assigned to a placebo group?
- Does the study involve patients unable to consent? Is the level of the additional risk and burden within the acceptable limits for research on such patients *(See Chapter 6 below)?*
- Are there measures in place for early detection of a seriously unfavourable course of the disease in patients on placebo that would necessitate appropriate intervention? Is there provision for an appropriate timely interim analysis?

Benefits and risks

For any biomedical research involving human beings, the researchers must ensure that the risks and burdens of research participation are not disproportionate to any potential benefits. Risks and burden should always be minimised. This key requirement stems from the ethical principles of beneficence and non-maleficence (*see Chapter 2*).

For interventions that hold out the prospect of direct benefit for the participant, a higher degree of risk and burden may be acceptable – e.g., as noted above (*see Chapter 1*), the degree of risk and burden acceptable in research on a new treatment for a serious condition such as advanced cancer would be unacceptable in research on a minor infection. Risk and burden may not only be physical but also psychological or social, while potential direct benefits include those of a palliative as well as curative nature.

There may also be benefits of research for advancement of scientific knowledge and society in general. When these are the only foreseen benefits, the REC must be satisfied that the research will entail no more than acceptable risk and acceptable burden for the participants. (*For persons unable to consent see Chapter 6*.)

Recruitment arrangements

Recruitment of research participants is governed by three key principles:

i. that the participation is voluntary;
ii. that recruitment is appropriate to the research question and methods (see Inclusion and exclusion criteria above); and
iii. that participants are chosen in a non-discriminatory manner.

Biomedical research relies on the participation of volunteers, who must understand from the outset that they are free to decline to participate (and subsequently to withdraw) without giving a reason and with no detriment to their care.

The REC application should clearly describe the means of recruitment, for example by advertisement or by personal contact connected with the provision of medical care. If planning to contact potential participants, researchers should avoid inadvertently distressing them or their families – e.g., they should ensure that contact details are correct, that the individual is still alive, and that there are no special reasons for avoiding contact such as recent bereavement. The application should also outline the steps that the researcher will take to safeguard privacy and confidentiality during the recruitment process. If the researchers plan to use preliminary screening questionnaires to aid recruitment, they should supply this information to the REC. For records-based research it is accepted best practice that the initial approach should be made via a doctor or other healthcare professional familiar with the participant.

Information for potential participants

The REC should pay particular attention to the proposed way in which information will be presented to potential participants. The information must be given verbally, if appropriate with the help of an independent interpreter, and accompanied by written participant information, which should be included as part of the application. The information must be clearly written in plain language that is readily understandable by a lay person. For this reason, it is accepted good practice for researchers to obtain a lay opinion on the leaflet before they submit it to the REC. If the circumstances necessitate that information is translated into another language, the REC should be

assured that the researchers have confirmed the accuracy of the information to be presented to participants by back-translation. The participant should receive a copy of the written information leaflet (and that of the signed consent form, see below) to keep. *Figure 5.3* outlines the elements that should be included in the participant information, which can be adapted according to the nature of the study.

Figure 5.3 Typical participant information checklist

- Title of the study
- Introductory invitation paragraph
- What is the purpose of the study?
- Why have I been chosen to take part?
- Do I have to consent?
- What will happen to me if I consent?
- What do I have to do?
- Will my tissue samples or data be used for further purposes?
- Do I have to consent now to this possible further use of my tissue samples or data (separate consent to be required)?
- Can I withdraw my consent during the study?
- What happens if I withdraw my consent?
- What is the treatment/ procedure/etc being tested?
- What are the alternatives for diagnosis/ treatment?
- What are the side-effects of taking part?
- What are the possible disadvantages and risks of taking part?
- What are the possible benefits of taking part?
- What if new information becomes available during the course of the study?
- What happens when the study stops?
- Will my healthcare be continued?
- What happens if something goes wrong?
- Will taking part in this study be kept confidential?
- What will happen to the results of the study?
- Will I be informed, in accordance with the national law, about the results?
- Who is organising and funding the research?
- What is the relation between the researchers and the sponsor?
- Who has reviewed the study?
- Who has approved the study?
- Contact details, including names and telephone numbers, for further information
- Contact details of medical supervisor

Potential undue influence

The REC must be satisfied that the researchers will place no undue influence on people to encourage research participation. Such influence might be financial in nature (*see Payments and rewards below*) but might also take other forms. For example, people who are unwell and weak may feel that they have to agree to participate even if that goes against their wishes. The trust placed by patients in doctors and other health professionals may also lead to undue influence, especially when the health professional is the researcher. In that event, it is best practice to involve an appropriately qualified neutral person in seeking consent (see below). The REC should also pay attention to other sources of undue influence. For example, if

employees were made to feel that continued employment depended on their research participation, or if a junior doctor were made to feel that career progression depended on recruitment of patients to a senior colleague's study. Some groups of people may be especially vulnerable to coercion – e.g. those deprived of liberty *(see below),* military service personnel, or those who are vulnerable within a given society because of prevailing social hierarchy.

Informed consent
Biomedical research involving interventions must not be allowed to proceed unless the potential research participant has given his or her consent (*for person unable to consent see Chapter 6*). For consent to be valid it must be informed (see above Information for potential participants), and freely given, requirements that stem from the ethical principle of autonomy (*see Chapter 2*). A permanent personalised record of the consent should be kept by the researcher as part of the study records. Consent pertaining to research on biological materials or personal data is discussed below in this Chapter and in Chapter 9.

Recording
In addition to providing the participant information (*see above*) to the REC, the researchers must also include their proposed consent form for REC scrutiny. If the research involves people who are unable to consent (*see Chapter 6*) or emergency situations (*see Chapter 7*), the documents relevant to obtaining authorisation for research participation should be submitted.

The standard practice is for participants to give their consent in writing. Exceptionally, where this is not possible, verbal consent is acceptable provided it is properly documented. Particular care should be taken when research involves participants from developing societies (*see Chapter 8*).

Arrangements for seeking consent
The researchers must clearly outline their proposed arrangements for seeking consent. The REC needs to know who will seek the consent to be able to judge not only whether that person is sufficiently knowledgeable about the research but also to be assured that the process is not unduly influenced. The REC should be satisfied in particular that the potential participants will be given adequate time to consider the participant information (*see above*), and to ask questions, before deciding whether or not to join the study.

Scope of the consent
The scope of the consent being sought should be clear to the REC and in general will be specific to the research project in question. If subsequent use of research records or biological specimens is envisaged, it is best practice for researchers to anticipate this possibility in their original consent process. (*See below in this Chapter and Chapter 9*)

Safety and supervision
Assessment of health status of research participants
The REC must be satisfied that the research protocol outlines appropriate methods for assessing the health status of potential research participants and that the assessment will be carried out by a suitably qualified clinical health professional. For research involving healthy volunteers (*see above*), a standard clinical examination at

the outset of the project may be all that is necessary – e.g., medical history, physical examination, and laboratory tests or radiological examination if justified. Research involving patients is often linked to their healthcare and the findings acquired in the course of clinical care may be sufficient for research purposes. If not, or if the results do not satisfy the inclusion/exclusion criteria of the research project, the need for additional examinations/tests should be anticipated and included in the research protocol.

Medical supervision of research participants
The application must include the name of a suitably qualified and experienced person who will ensure medical supervision of the participants. In case of emergency this person (or a designated appropriate colleague) must be available for contact by research participants and those responsible for the participants' regular health care. In addition, the medical supervisor and those responsible for the participants' regular health care should liaise about all essential non-research treatments that patients are receiving. The protocol should also designate institutions for emergency treatment, describe their facilities, and note the distance, if any, from the research site.

Information to the ethics committee during the conduct of research
It is important for RECs to keep in touch with projects that they have approved (*see Chapter 4*), generally by review of regular reports from the research team to establish whether, in the light of any new developments, changes in the project have become necessary or even if the research needs to be discontinued. Re-review will also establish whether additional consent needs to be sought from the participants (*or further authorisation from their representatives – See Chapter 6*) and whether the consent form for future participants should be modified.

For specific types of research - e.g. clinical trials of medicinal products (i.e. drug trials) under the Directive - the law defines the adverse events and reactions that are to be notified to the REC. Over and above these legal requirements, the REC may decide that other information is necessary and therefore ask for its inclusion in the protocol.

The REC and the applicant should agree on arrangements for validating any events that occur, for example by means of a Data and Safety Monitoring Board (DSMB). The REC and the DSMB should be clear about their respective responsibilities and about how they will interact. In the light of any events occurring during the project or if new results become available from research in the same field, the REC needs to decide whether the research design should be changed or the research stopped. The applicants must tell the REC about any proposed changes to the project, and if the research has been stopped early and why. They should also notify the REC when the study finishes as planned.
Visits to study sites by RECs are advisable.

New information and protection of research participants
As noted above, in response to events or new scientific information during the course of the research, the REC may need to revise its initial decision about the project. Research protocol and/or the formal decision of the REC should set out how any altered decision and resulting consequence will be conveyed to participants. The REC must be assured that this information is conveyed as soon as possible, and that participants are told whether the REC has asked the investigators to prepare revised

information/new consent forms concerning modifications to the project. At this point, as at any stage during the research, participants' right to withdraw consent must be respected. The content and clarity of information to participants is especially important when the REC has withdrawn a favourable opinion. When the investigators submit a revised protocol to the REC, they must indicate explicitly how the revision has addressed REC concerns.

Confidentiality and right to information

Data protection

Personal information collected in the course of biomedical research must be considered confidential and protected accordingly. For this reason, the data should be stripped of identifiers, as much as possible and as soon as possible.

The applicants must justify the nature and degree of identifiability[12] and the corresponding protective measures to the REC. The applicant should also indicate how long they propose to keep the identifiable data. If identifiable data are to be used, the participants must be informed about the extent of identifiability and who will have access to identifiers, and agree to the use of their identifiable data.

If the researchers plan to use anonymized data, the method of anonymization should be deemed appropriate by a competent institution and the information presented to the REC. Participants must be informed about anonymization of their data; in particular they should understand that as the process of anonymization involves stripping the data of all identifiers, future identification is no longer possible. Since it would be impossible for them to be told about any research' related results pertaining to an individual that might have a bearing on their health, participants should be explicitly asked whether they agree to the anonymization proposed.

Safety

If biological materials (*see Chapter 9*) are to be removed, and stored for research purposes, the REC must be satisfied that the researchers have made provisions to ensure their security and the confidentiality of any information which could be obtained from them. If these provisions are based on law this must be respected. If there is no legal obligation, the researchers must outline their proposed methods for safe storage in the proposal. If materials removed for diagnostic purposes are also intended for research use, the specific protective provisions for research apply only during the research procedure. When research use finishes, any other relevant provisions concerning storage of biological materials must be observed.

Right to know – right not to know

The right to know any information collected about the health of a person, as laid down in Article 10 of the Convention of Oviedo, applies to research. Research participants are not only entitled to have this information as acquired in the course of a research project but also (again in conformity with Article 10) to refuse this

[12] *Identifiable data* are those data which allow the identification of the persons concerned either directly or through the use of a code.
In the latter case, the user of the data may either:
a. have access to the code: the data are hereafter referred to as "coded data"; or
b. not have access to the code, which is under the control of a third party: the data are hereafter referred to as "linked anonymised data".
Non-identifiable data, hereafter are those data which do not allow, with reasonable efforts, the identification of the persons concerned.

information. The REC must be satisfied that both rights are respected by appropriate provisions in the research protocol, taking into account any specific restrictions according to national law. The REC should consider whether the wish of a participant not to be informed about unforeseen results with relevance to health would justify his or her exclusion from the research.

Duty of care

As noted above, research participants are entitled to health-related information collected during the course of research. The information could be part of the research results or acquired incidentally. The researchers should themselves evaluate the relevance of such information for the current or future health or quality of life of participants and may need to consult the REC on this issue. When information is to be offered, this must be done within a framework of healthcare or counselling so that clinical professionals can explain the nature and relevance of the results in a way that is readily comprehensible to participants, and similarly discuss the options available for prevention, treatment, or other course of action. It is important to remember that research results of clinical relevance usually need to be verified by previously validated methods. These discussions with participants must be confidential and the right of participants not to receive such information must be respected.

Availability of research results

Making research results available to the REC and the research participants

As noted in Chapter 4, on completion of the research the investigators must submit a report or summary of their findings to the REC. At this point, the researchers should also confirm their proposals as outlined in the application for publication of the research results in scientific journals or making them publicly available by other means.

The conclusions of the research should be made available, in a comprehensible form, to any participant who wishes to see them. Although provision of this information has to respect the interests of third parties such as the research sponsor or researchers themselves, this should not be used as an excuse to deprive participants of their legitimate right to know the outcome of the research to which they contributed. However a reasonable delay may be acceptable (*see below*).

Research-related results relevant to the current or future health or quality of life of participants are discussed above (*See Duty of care*).

Making research results available for scientific and healthcare purposes

It is important to make available the results of research, whether substantiating the research hypothesis (“positive”), refuting the research hypothesis (“negative**”)** or being inconclusive. Suppression of results not only distorts the research endeavour if other research groups are unaware of them but also can directly affect patients, who may be recruited needlessly to take part in unnecessarily repetitive research. In addition, systematic accumulation and analysis of research results is essential for developing medical treatments – very seldom will the results of a single research project be so clear cut that they have an immediate impact on clinical practice. Rather, progress depends on new research being carried out and interpreted in the context of systematic reviews of all other relevant and reliable evidence. If some of this relevant evidence remains unpublished the totality of evidence is biased and

therefore unreliable. Patients may then continue to receive treatments that are actually harmful, or conversely not receive treatments that would benefit them

The Additional Protocol to the Oviedo Convention concerning Biomedical Research requires that at the end of a study a report or summary be submitted to the REC. In the case of premature termination of a study, a report including reasons for termination should also be submitted. Furthermore, the Protocol requires that the results should be made publicly available in reasonable time, and that the conclusions of the research be made available to participants who request them. The REC must therefore be assured that the researchers have formulated a publication policy and that they have negotiated the policy with any external research sponsors so that they are not contractually inhibited from disseminating their results. A "reasonable" delay in publication is acceptable so as not to prejudice a patent application but should not be used as an excuse to withhold results indefinitely. Only in very exceptional circumstances should a REC agree to non-publication of results – for example if the researchers could convincingly argue that publication would compromise public safety. Even in these circumstances REC members would need to be assured that the research participants had been advised about and had agreed to this unusual measure before giving their informed consent to take part in the research.

There have been particular concerns about biased publication of research results relevant to possible new treatments, especially concealment of "unfavourable" results of drug trials by pharmaceutical companies. To counter this bias and to help ensure the eventual publication of the findings, all trials should be registered by researchers when they begin. REC members can encourage this drive towards transparency by making their ethical approval conditional upon such registration. If national law does not permit conditional approval on these grounds, the REC should still use its position to request free publication of the full research results.

Circumstances that might lead to conflict of interest affecting the independent judgement of researchers

The judgement of a researcher concerning the research must not be influenced, by financial (*See Payments and rewards below*), personal, academic, political, or other interests at any stage. In the application the researcher should therefore set out any circumstances that might lead to a conflict of interest.

The REC should also be made aware of any potentially conflicting role if a clinician is involved both in the research and in the clinical care of the participants. For example, to choose a patient's treatment or to alter it for the purpose of enhancing enrolment in a research project would be ethically unacceptable. If the roles cannot be separated, the REC may wish to ask for additional safeguards to be put in place, especially with respect to obtaining participants' informed consent (*See Potential undue influence above*).

Payments and rewards to be made in the context of the research

The REC application should give details of all payments and other rewards to be made to the researchers, their research institutions, and research participants. This information will enable the REC to judge whether or not the proposed payments and rewards are appropriate.

The REC should be satisfied that any payment and rewards to be provided to participants are appropriate to the burden and inconvenience of the research but not at a level that might encourage them to accept a risk that they would otherwise not accept. Reimbursement for expenses and any financial loss incurred in participation would not be regarded as undue influence as long as it does not represent a substantial proportion of income or the only source of income for the participants in the study.

Researchers should give details of any payments, rewards or material goods that will be provided to them or their institution in return for the research so that the REC can judge whether they are appropriate.

The REC also needs to be aware of the interplay between public and commercial funding of research – e.g., for research into the treatment of a given disease, a commercial funder might offer far larger payments per participant recruited than a public funder, whereas the research design proposed by a public funder may be far more likely to yield results of broad relevance to a particular healthcare setting.

Foreseen potential further uses, including commercial uses, of the research results, data, or biological materials

The REC needs to be aware of any potential further uses of the research results that are foreseen by the researchers. For example, the researchers might already plan to make their results available for combination with results of similar research studies in a meta-analysis, or research in one disease area such as diabetes might have applications in another disease area such as heart disease. Such transparency is especially important if there are foreseen commercial uses of the research results. In addition, it is increasingly common for data and biological materials (*see Chapter 9*) to be archived for use at a later date. As far as possible, such further use should be anticipated by the researchers since it has special relevance for way in which data/materials are stored and for the consent process.

Arrangements for compensation for damage

As the Additional Protocol to the Oviedo Convention concerning Biomedical Research makes clear, any research participant who has suffered damage as a result of participating in the research is entitled to fair compensation according to national law. Compensation conditions and procedures vary from country to country, but in all cases, the researchers should provide the REC with details of any insurance or indemnity to cover damage arising in the context of the research project.

6. PERSONS UNABLE TO CONSENT

The principle of participants' free informed consent is central to the ethical conduct of biomedical research. However, research on persons not able to consent is important for improving the diagnosis, treatment, and prevention of diseases or disorders in these groups Therefore, provided necessary safeguards are met, and the research is authorized by law (see below), individuals who are unable to consent should not be excluded from participating in relevant research.

Before approving such research, RECs should be satisfied that the proposal is scientifically justified and could not equally well be carried out in people who are able

to consent. In general, the research should be potentially beneficial to the health of participants (direct benefit) and any foreseeable risks, including for private life, should not be disproportionate to those potential benefits. When there is no likelihood of direct benefit, research should only proceed, if permitted by national law and with additional safeguards, including:

i. the research aims to enhance scientific understanding of the individual's disease or disorder, that may confer subsequent benefit to the participant or to other individuals with the same or a similar disease or disorder;
ii. the research entails only minimal risk and minimal burden[13] for the participant.

The inability to consent may be partial or total, and may be temporary, fluctuating, or permanent. (For research in emergency situations, see Chapter 7). Importantly, many people who lack the legal capacity to consent can nevertheless understand some information about the proposed research intervention. This information should be presented to potential participants, and their willing cooperation sought, according to their ability to comprehend, and any objection to taking part in the research should be respected.

Research participation of an individual who is unable to consent should be specifically authorized by law. The necessary legal protection is usually provided by a legal representative[14], who must receive all relevant information about the proposed research. When submitting their research proposal to the REC, the researchers must include the documentation that they intend to send the legal representative. The legal representative's authorization, which must be specific and in writing, takes account of the individual's previously expressed wishes and objections, and can be withdrawn at any time. However, such representatives must not authorise participation in research if they consider that, despite the wishes or the lack of objection of the person not able to consent, the research entails excessive risks or burden for him or her.

Figure 6.1 outlines the key questions that RECs should consider when reviewing a research protocol involving individuals who are unable to consent.

Figure 6.1 REC assessment of research in individuals unable to consent

- Is research on individuals not able to consent generally allowed by law?
- Does the research satisfy all relevant conditions for research projects in individuals able to consent?

In addition:

- Have the researchers justified the scientific need to carry out the research in individuals unable to consent?
- Are there any research alternatives of comparable scientific effectiveness that could be carried out in individuals able to consent?
- What is the nature of the inability to consent?
- How will the lack of capacity be assessed by the researchers?

[13] See footnote 2

[14] The legal representative's duties are to represent the interests of the person concerned but the legal representative is not that person's personal advocate.

Research with potential direct benefit for the participant[15]:

- Are risk and burden acceptable in relation to the expected benefit for the participant?

Research without potential direct benefit:

- Have the researchers justified the scientific need for this type of research?
- How will minimal risk and minimal burden be assessed?
- Are there any specific protective provisions prescribed by law and how will they be observed?
- Unexpected research outcomes (See under Section 4.A.1.2 "RECs role during research")

Legal provisions for representation

- Who is the legal representative entitled to authorize participation?
- What information will the legal representative receive about the proposed research?
- How will the research participants take part in the authorization procedure?
- How will participants' objections be registered and notified to the legal representative?
- Is there a designated person to answer any questions participants may have about the research and authorization procedure?
- Should authorization be withdrawn, how will the research participants take part in the decision and procedure to withdraw?

Fig 6.2 Research involving children

Children comprise a distinct subgroup of people who are unable to consent to research participation. They are not small adults - e.g., they differ in disease processes, physiology, and metabolism of medicines. For most research involving children, the legal representative who authorises a child's participation in research will be one or both parents. However, legal representation may vary from State to State and should be verified by reference to national legislation. According to their maturity, which is not a strict function of age, children should be involved as much as possible in decisions about research participation and their agreement (assent) should be sought. Their objection should always be respected. When reviewing proposals involving children, and depending on the expertise of REC members, RECs should consider seeking the advice of those who are experienced in child health research.

A check-list of questions can help REC members decide whether children may ethically be involved in the proposed research.

- Is the disease being studied specific to children with no analogy in adults?
- Will the research increase understanding of child development and /or wellbeing with the aim of improving child health?
- For drug treatments, are the pharmacokinetics known in adults and are they expected to differ in children thus justifying research in this age group?

[15] Articles 15, 16 and 17 of the Additional Protocol concerning Biomedical Research.

- Is the therapy as given to adults unpalatable or difficult to administer in children?
- Is the study of adult disease thought to originate in childhood and is research involving children likely to advance understanding of the natural history of the condition, possibly leading to prevention?
- For research in especially sensitive areas such as illicit drug use, teenage sexuality, or sexual abuse, do the researchers have adequate strategies to handle the issue of confidentiality?

7. RESEARCH IN SPECIFIC SITUATIONS

7.A Clinical emergencies

Introduction

Clinical emergencies refer to those situations where the emergency is unforeseen and prompt action is necessary. – e.g. cardiac arrest, severe stroke, or life-threatening head injury. Effective treatments for many of the conditions giving rise to such emergencies are very limited, so research is essential for the development of sound evidence-based therapies. Without such research, the outcome for patients is unlikely to improve. However, the conduct of research in clinical emergencies is ethically problematic because it is impossible to fulfil the central ethical and legal requirement of obtaining the person's informed consent and, because of the urgency of the situation, it is equally impossible to obtain authorisation (*see Chapter 6*) for the person's research participation. However, exceptionally, research without consent/authorisation may be permitted by national law with strict safeguards.

7.A.1 Protective conditions

Of the two legally binding European instruments pertaining to biomedical research (*see Chapter 3*) – Directive 2001/20/EC and the Council of Europe Additional Protocol concerning Biomedical Research – only the Protocol specifically addresses research in emergency situations. The protective conditions set out in the Protocol (Article 19) are that:

i. research of similar effectiveness cannot be carried out in non-emergency situations;
ii. the project has been approved specifically for emergency situations; and
iii. any previously expressed objection of the participants that is known to the researchers has to be respected.

The Protocol allows for research without the potential for direct benefit under the additional protective condition that the research must entail no more than minimal risk and minimal burden[16]. For example, in head injury such research might involve the use of brain scans with the aim of discovering more about the way in which injury leads to brain swelling.

Finally, the Protocol requires that, as soon as possible, research participants, or if applicable their representatives are provided with all relevant information about the

[16] See footnote 2

research participation and their consent or authorisation for continued participation is requested.

7.A.2 REC Review

Figure 7.1 outlines the key questions for REC members when they review projects concerning emergency clinical situations.

Figure 7.1: Key questions for REC review

- Is it possible to achieve similar results by carrying out research on people in non-emergency situations?
- Will research participants be in a state that will prevent them from making an informed decision?
- How urgent is the situation? Is the time limit so strict that locating representatives for authorization is impossible?
- Does the research have the potential to produce direct benefit for the research participants?
- If there is no potential for direct benefit, does it aim to produce results capable of benefiting other research participants or other people with the same disorder/condition?
- What is the risk and burden associated with the research?
- If there is no potential direct benefit are the risk and burden minimal?
- What procedures have the researchers set out to ensure:

➢ that authorization is obtained from the research participants' representatives as defined by law?

➢ provision of all relevant information concerning participation in the research project to participants or, if applicable, their representatives as soon as possible after involvement of the participants in the research?

➢ that consent or authorisation for continued participation is sought as soon as possible after involvement of the participants in the research?

7.B Persons Deprived of Liberty

Introduction

The term "persons deprived of liberty" is based on Article 5 of the European Convention on Human Rights. People may be deprived of their liberty not only for security reasons (e.g., for committing an offence under the criminal justice system [prisoners]) but also for health reasons (e.g., for endangering themselves and/or others). The key issue is that they are an especially vulnerable group of potential research participants because of their dependence on others to provide them with food, healthcare, and other amenities of life. Completely denying such people the opportunity to participate in research may harm them by limiting their access to effective and sometimes life-saving therapies. However, in some countries, such research is unlawful.

7.B.1 What are the ethical issues ?

Whilst restriction of research in this group is still regarded as a measure of human rights protection in order to avoid misuse/abuse of such vulnerable people, prohibiting their participation completely may have negative consequences for the following reasons:

- The research may have the potential to benefit research participants, and in certain cases research participation may be the only alternative to non-treatment or ineffective treatment;
- The research may have the potential to benefit people deprived of liberty in general – e.g., multi-drug resistant tuberculosis is highly prevalent in prison populations;
- Finally, people deprived of their liberty retain their autonomy and so should have the right to decide whether to participate in biomedical research.

The first two arguments are very strong because i. denying participation in research with the potential to produce direct benefit (especially when this may be the only alternative) cannot be justified; and ii. without research on certain categories of people deprived of liberty (e.g. prisoners) it would be impossible to develop treatments for disorders that are specific to them/their environment.

Consequently, the main focus of ethical attention is on the issue of research in those deprived of liberty that has no potential to benefit them. Even here, their blanket exclusion from such research would be unfair because it would go against the principle of respect for their autonomy.

The key issue for the REC, before approving any research in people deprived of their liberty, is to be satisfied that there are adequate safeguards to prevent the misuse of participants. Realistically, in some countries such safeguards are currently lacking and so research is still, at least partly, prohibited for this reason.

7.B.2 Criteria for research involvement

Where, according to national law, research in this group is permitted, there should be specific protective measures in addition to the protections for research participants in general. Common protective measures as applied to all types of research involving interventions on human beings, in particular prevention of any undue influence, also apply to research involving persons deprived of liberty. Additional measures apply to research without potential direct benefit.

7.B.3 Additional measures for research with no potential for direct benefit

The most explicit international legal instrument on this subject in Europe is the Council of Europe's Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research, which establishes three specific criteria for such research:

i. research of comparable effectiveness cannot be carried out without the participation of persons deprived of liberty;
ii. the research has the aim of contributing to the ultimate attainment of results capable of conferring benefit to persons deprived of liberty;
iii. the research entails only minimal risk and minimal burden[17].

[17] See footnote 2

The first two criteria prevent exploitation of those deprived of liberty for the benefit of others who are not deprived. So, if the research goals could be achieved through research on people who are not deprived of liberty, research on those who are deprived of liberty should not be allowed. Moreover, even if the first criterion is satisfied, the research must not be carried out if its ultimate aim is not to benefit those deprived of liberty. The last criterion restricts research to that causing no more than minimal risk and burden. All three criteria help to avoid unethical research involving those deprived of liberty.

7.C Pregnancy and breastfeeding

Introduction

Biomedical research involving pregnant women is important to improve knowledge of conditions and treatments of diseases related to pregnancy. These diseases may affect the woman, the foetus or both. The research may or may not have a potential direct benefit. For both types of research, the common criteria applicable to all research must be respected. In addition, the REC must be satisfied that research of comparable effectiveness cannot be carried out on other persons.

For research with potential direct benefit, the risk / benefit assessment must take into account the specific situation of pregnancy. Research without potential direct benefit must contribute to the ultimate attainment of results capable of conferring benefit to other women in relation to reproduction or to other foetuses. In such research the criteria of minimal risk and minimal burden [18] are compulsory.

Where research is undertaken in breastfeeding women, particular care must be taken to avoid any adverse impact on the health of the child.

7.D Cluster Randomised Trials

Cluster randomised trials (CRTs) are increasingly important in public health and health services research, so REC members need to be aware of the special issues that they raise. In CRTs, groups of people – “clusters” - rather than individuals are randomised to intervention and control groups; outcomes are measured on individuals within those clusters. CRTs are also known as group randomised trials or community randomised trials.

CRTs are regularly used in trials of population screening (e.g., in mammographic screening for breast cancer) and of behavioural interventions (e.g., to reduce obesity), where individual randomisation could invalidate analysis of the results. For example, if people in a defined geographical area were randomised individually to screening, those offered screening might talk about this with friends allocated to no screening who might then seek to be screened themselves. Similarly, patients in a clinic who are offered a behavioural intervention to promote weight loss might share this information with other clinic patients, and it would then be impossible to determine whether the intervention was effective. CRTs are also used when the research involves employing a special member of staff in a clinic. For example, in primary care, to see whether the effects of one-to-one education about diabetes from a diabetes nurse are more beneficial to diabetic patients than the standard method of simply handing out educational leaflets to read. To do this, some primary care practices would be randomised to the one-to-one education programme and others

[18] See footnote 2

to the standard care. CRTs are important in developing countries too, for example in research designed to assess the effects of a new type of vaccination against an infectious disease. Since vaccinations have a direct effect on individuals' susceptibility to infection and an indirect effect on risk of transmission of infection to other individuals, the new vaccine would need to be given to some communities and the results compared with those of communities who did not receive the new vaccine. The statistical analysis of CRTs is more complex than that of trials in which individuals are randomised. The researchers should justify their use of a cluster design in the information submitted to the REC; the submission should also contain assurance that the statistical methods proposed by the researchers are appropriate according to the scientific review process. The ethical issues for the REC to consider concern i. agreement for the clusters to be randomised and ii. consent from individuals to receive the intervention. So, in the example of mammographic screening for breast cancer, women could not be asked for their individual consent to the randomisation of their geographical area to screening or no screening. However, if assigned to the screening group they should be asked for their consent to the mammography, and women in both groups should receive information about the trial. Similarly, in the vaccination example, the individuals could not be asked for consent to randomise their districts but should be asked for their individual consent to receive the vaccination. The REC would also need to be satisfied that there was a suitable means of representing the interests of the cluster as a whole – a cluster representation mechanism or guardian. This would determine the participation of the cluster in the proposed research and be able to withdraw the cluster if the research was no longer in cluster's best interests. For example, according to circumstance, the mechanism might be a chief executive in the health service area for mammography screening, or a group of village elders for research into a new vaccination.

REC approval of the research would therefore depend on the cluster representation mechanism confirming that the proposed trial was in the interests of the cluster (and subsequently on not withdrawing that opinion) and an appropriate information and consent procedures for individual trial participants.

8. TRANSNATIONAL RESEARCH

Research projects are often undertaken multinationally, so a REC in one country may be asked to review protocols involving research also in other countries. Sometimes research teams based in different countries collaborate on a single project. On other occasions externally based research organizations fund research to be carried out in a specific country or countries and the researchers involved may come both from the countries concerned and from the country of the funding organization. For example, research into a tropical disease such as malaria would usually need to be carried out in the countries where it actually occurs but the funding organization may be based elsewhere.

8.A Multinational research: review by different RECs

Every multinational research project must be submitted for ethical review to a REC in each State in which research activity is envisaged (the principle is laid down in Article 9 of the Additional Protocol concerning Biomedical Research). Research must only be carried out in States where the REC has given a favourable opinion.

Apart from general protective provisions, the Directive 2001/20/EC also sets out a specific procedural requirement for multicentre clinical trials that are carried out in more than one Member State by requiring each Member State to give one REC opinion, irrespective of the number of RECs involved within each State.

A key ethical concern for multinational research is the possibility that the different countries might have different standards of protection for research participants. The Council of Europe's Additional Protocol concerning Biomedical Research addresses the issue (Article 29) in broad terms by stating that, when research sponsors and/or researchers in States that are party to the Protocol plan to conduct or direct research in States that are not party to the Protocol, they must ensure that the research complies with the principles set out in the Protocol.
The practical issue for a REC involved in reviewing research that is to be conducted internationally is to be satisfied that there is an appropriate mechanism for ensuring the research is conducted to a common set of ethical standards. This might mean getting the formal agreement of research funders/researchers that the research they fund/carry out will be governed by common ethical principles irrespective of research location. RECs in the various countries involved may also need to liaise directly with one another while bearing in mind the independent nature of REC decisions and any prevailing cultural differences particularly regarding informed consent.

8.B Specific issues related to research carried out in developing societies

The term "developing society" can apply to a whole nation but also, importantly, to certain populations or communities within an otherwise developed country that remain under-developed. The ethical issues raised by conducting research in developing societies, especially research that is externally funded, have been the subject of much attention and several international/internationally recognized organizations have issued guidance on this topic. Aspects remain contentious, and ultimately REC members, as well as researchers and research funders, must judge for themselves how to approach the sometimes complex issues raised by the research proposal in question. In some cases they will be able to turn to national guidance that has been prepared in a developing country and that takes account of specific local needs and cultural context. In addition, there have been concerted efforts to enhance REC review capacity in developing countries.

In general, there is broad agreement on the following points:

- Organizations from developed countries should not normally support research, in pursuit of their own goals, involving people in developing societies if that research could be carried out reasonably well in a developed community or country.
- The reason for undertaking the research will be its relevance to the health or healthcare needs of the society in which it is to be carried out, either in the short-term or in the long-term.
- Special care is needed to ensure that the social and economic circumstances of the developing society:
    - do not unduly influence people to participate in research;
    - together with possible poor communications, do not diminish the researchers/research funders respect for the rights and interests of the people involved or the society as a whole.

- Research without the potential for direct benefit to health needs especially careful REC scrutiny, taking account of the balance of risks and benefits to participants in the particular circumstances and setting of the study.
- For a control group in a particular study, the participants assigned to this group should, be offered a method of proven effectiveness for the disease or disorder being studied. Where this is not appropriate, the researchers must justify their decision and should offer, as the minimum standard of care, the best method available for the disease or disorder as part of the national healthcare system in the developing country concerned. The fact that a treatment to be tested may not currently be affordable to the local population should be specially taken into account during REC review. This should not in itself preclude the study on ethical grounds, but the information for research participants should explain the position unequivocally.
- As for other externally funded multinational research, REC review should take place in the host countries as well as the country of the funder. Local review is especially important to judge the ethical acceptability of the research in accord with the customs and traditions of the society concerned.
- Special care is needed to obtain valid informed consent from participants, including the use of reliable intermediaries as appropriate to ensure that the implications of participation are fully understood. In particular, the prospective participants must fully understand that their participation is entirely voluntary and that they are free to refuse to participate or withdraw at any time without loss of any entitlement. Although there is no substitute for individual consent, the cultural need for the potential participant to consult a senior family member or community leader should be respected; in some cases such a person may need to be consulted before the participant's individual consent is sought.
- There should be discussion in advance with relevant parties in the developing society about the plans for the research and for disseminating the results to study participants and local people. In anticipation of any beneficial research results related to therapy, the discussion should include how the treatment/preventive agent might be made available locally after the study has finished.

9. BIOLOGICAL MATERIALS OF HUMAN ORIGIN

The use of human biological materials is increasingly important for biomedical research. Consequently, research participants and the public should have confidence that the materials will be handled and used sensitively and responsibly. It is likewise important that any collections of human biological materials are used optimally and that unnecessary collection of new materials is avoided.

The materials that are taken from human beings for research use fall into two broad categories:

i. those that are destined for immediate use in a specific research project; and
ii. those that are to be stored for future use. The distinction is not absolute in that part of a sample may be used straight away and the remainder retained for use subsequently.

The ethical issues for research involving human biological materials are two-fold:

i. issues concerning initial removal of the material, which necessitates a physical intervention – this is the only time when the physical integrity of a person is at stake and the general protective provisions concerning biomedical research (for example Chapter 6) apply as for any other research intervention;
ii. issues of consent/authorisation and confidentiality concerning use and/or storage of the materials that have been removed. The second group of issues has been the focus of considerable attention and the subject of guidance issued by several international and national organizations.

The legislative framework in this area in Europe is provided by the Council of Europe Convention of Oviedo, 1997, and the Recommendation (2006) 4 on research into biological materials of human origin. The Convention (Article 22) requires participants' free informed consent for the storage and use of materials for a purpose other than that for which it was removed. It further stipulates (Article 21) that the human body and its parts shall not, as such, give rise to financial gain. This does not of itself preclude the licensing/selling of intellectual property rights arising from research in which the samples are used (i.e. this is the same as for other intellectual property rights) but it does mean that those who donate their materials should be informed if those materials might be used for commercial purposes. It also means that researchers should not sell the materials *per se* for a profit, and that donors of materials should not be offered financial inducement to donate samples (reimbursement of reasonable expenses would be permissible).

The Recommendation covers interventions to obtain the materials to be stored for future research and that further research use, the principles governing collections of materials and population biobanks, and the research use of previously stored materials (i.e., residual material from clinical, research, or forensic purposes).

The Recommendation sets out the requirements that research on human materials should only be undertaken after independent scientific and ethical review and, mirroring the Convention, provided the use is within the scope of the donor's consent. It further highlights a key issue for REC review – the extent to which the participants could be identified from their biological materials or associated personal data. In general, identifiability may be achieved directly via accompanying personal data or indirectly via a code that could be held either by the researchers or by a third party. Non-identifiable materials are those for which, with reasonable efforts, there is no possibility of identifying the donor. However, RECs need to be aware that there is no internationally standardized terminology for the identifiability of human biological materials. Consequently, when RECs review a proposal concerning human biological materials they must be satisfied that they understand what degree of identifiability the researchers are proposing, irrespective of the terms actually used in the proposal. When RECs are asked to review proposals concerning the establishment or use of collections and population biobanks they should be satisfied that the proposal includes a satisfactory oversight mechanism and that the conditions governing access for research use of the samples are appropriate and transparent.

Figure 9.1 categorizes the key issues with respect to removal and storage of human biological materials.

Figure 9.1 Key issues pertaining to REC review

- Removal confined to diagnostic and /or treatment purposes – free informed consent as for any clinical procedure; storage according to health service regulations; not within the scope of REC review
- Removal for diagnostic/treatment purposes and for research purposes (dual use) – free informed consent for both types of use; for storage see below
- Removal only for research purposes (a) for defined research project or projects; (b) storage for subsequent projects with aims that are the same as or differ from those of the original research use – free informed consent for the specific project and/or for future projects that may not be foreseeable and depending on the scope of the donor's consent
- Removal for storage in biobanks – as in b) above