Guidelines on the practice of ethics committees in medical research with human participants

Fourth edition

'to search and study out the secret of Nature by way of Experiment'

William Harvey FRCP, 1656

'to gather from the tree of knowledge fruit for the solace and refreshment of mankind'

Thomas King Chambers, Goulstonian Lecture, 1856

September 2007

Royal College of Physicians
Setting higher medical standards

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President's statement

This splendid document maintains a fine tradition of the Royal College of Physicians going back over 20 years to when there was a void of guidance to those tasked with judging the appropriateness or otherwise of clinical research. The landscape is now more crowded and complex, but the need for clear, practical guidelines for ethics committees considering research involving human subjects has never been greater. The fourth edition fills that need through carefully updated and extended guidelines.

Areas such as research on human tissues, embryos and vulnerable groups are all subject to intense scrutiny, not just by lawyers but by the media too. I am proud that this College continues to set the standards that not only allow clinical research but positively encourage it.

September 2007

Ian Gilmore
President, Royal College of Physicians

Foreword

Anyone who contemplates a medical study involving human subjects has to gain approval from an independent research ethics committee. This is the equivalent of throwing a six to start navigating the increasingly complicated regulatory environment in which clinical trials and other studies presently take place. Maps and guides for those unfamiliar with the labyrinth are always to be welcomed, and this one will stand high given its provenance and clarity of content. John Saunders and his committee are to be congratulated on creating a comprehensive, clear and accessible monograph which is easy to navigate and provides valuable information and advice on how the system works and what it is designed to achieve.

It comes at a time when the organisation of research ethics review in the UK is continuing to undergo change with the ambition of reducing bureaucracy and redefining what does and does not require formal review. These initiatives reflect the fact that 10 years ago the uncoordinated activities of some 200 ethics committees caused considerable difficulties for bona fide researchers, and although much has already improved there is still more to be done.

Ethics, originally the only protection for participants in research, has now been joined by the NHS Research Governance Framework which aims to ensure that funded ethical projects are carried out properly. There are also numerous other authoritative bodies that need to approve different types of project, including the Medicines and Healthcare products Regulatory Agency, the Patient Information Advisory Group, the Gene Therapy Advisory Committee and the Administration of Radioactive Substances Advisory Committee. This guide will be a valuable and much used source of advice for those contemplating a clinical trial or other medical study and will, of course, also help those who sit on ethics committees to do their job more effectively.

Nowadays it is to be hoped that ethics review is a collaborative effort between researchers and reviewers without the adversarial elements that have occasionally caused friction and discomfort in the past. Handbooks like this will help to ensure that.

September 2007

Sir John Lilleyman
Medical Director, National Patient Safety Agency

Members of the Working Party

John Saunders (Chair)
John Saunders is a physician at Nevill Hall Hospital, Abergavenny and chairman of the Committee for Ethical Issues in Medicine at the Royal College of Physicians. He was member then chair of North Gwent Ethical Committee (1984–92), vice-chair then chair of Gwent LREC (1992–8) and chair of the MREC for Wales (1998–2006). He has published and taught on research ethics nationally and internationally and participated in numerous working groups at COREC, DH, RCP, RCPCH, MRC, University of Wales, Welsh Assembly Government, Health Protection Agency, Royal Society of Arts etc. His own research experience includes isotopic studies in healthy volunteers and non-therapeutic invasive patient research, basic epidemiology, questionnaire studies and conventional drug trials. In 2004 his contributions to medical ethics were recognised by the honorary appointments of Senior Lecturer at the University of Wales College of Medicine (now Cardiff University) and Professor in the Centre for Philosophy, Humanities and Law in Healthcare, University of Wales Swansea.

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After hospital posts which included neurology, Joan Box worked at the Medical Research Council (MRC) Head Office from 1972 to September 2006. Her responsibilities included research management in mental health and neurological disease, infections, occupational and environmental health and obstetrics and gynaecology. From 1988 to 1992 she was Assistant Director of the Clinical Research Centre, following which she worked on promoting clinical research and liaison with the health departments, National Health Service, medical royal colleges, other research councils, consumers and medical charities. From 2001 Dr Box was Clinical Research and Ethics Liaison Manager at MRC, for which her work included the ethics of research in developing countries and the establishment of an Advisory Group on Public Involvement.

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Malcolm Law is Professor of Epidemiology and Preventive Medicine in the Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine in the University of London. He is interested in the epidemiology and prevention of cardiovascular disease.

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Helen Millar, a member of the RCP Patient and Carer Network, has served on the Committee on Ethical Issues in Medicine for three years. She has just completed ten years as a member of the MREC for Scotland and remains a member of the REC in her local teaching hospital in Glasgow. She has served as a lay member on numerous committees including the Interim Advisory Group for Biobank and the Advisory Group on Public Involvement in the MRC, and she chairs the Chief Scientist's Public Involvement Group in Scotland and the Scottish Patient and Carer Advisory Group of the Royal College of Paediatrics and Child Health. She is also a longstanding member of the professional conduct panel of the Nurses and Midwives Council.

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Shahwar Sadeque is an Educational and ICT Consultant and Chief Executive of TriEs Ltd, an educational software company. Originating from Bangladesh, she has an international perspective

on educational, social and political affairs. She has spent ten years teaching Physics in Sutton, Surrey; six years as a Governor of Kingston University, five years as a Governor of the BBC; twelve years at the Housing Action Trust and six years as Commissioner at the Marshall Aid Commemoration Commission. She has served in a variety of other public offices, most recently as deputy chair of the Immigration Advisory Service. She is a member of the RCP's Committee on Ethical Issues in Medicine and of its Patient and Carers Network. She is also an Associate Hospital Manager at South West London and St George's Mental Health NHS Trust. She was formerly a member of the Patient Information Advisory Group and of the Working Party on Healthcare-related Research in Developing Countries, Nuffield Council on Bioethics.

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Rustam Al-Shahi Salman is a Medical Research Council Clinician Scientist and Honorary Consultant Neurologist at the Western General Hospital in Edinburgh. His research interest is in the clinical epidemiology of neurological diseases, especially stroke. Through his experiences as a researcher he has become interested in the regulatory burden of research governance, and the biases conferred upon research by the requirement for consent. He is a member of the Privacy Advisory Committee of the Information and Statistics Division of NHS Scotland

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Darren Shickle is Professor of Public Health at the University of Leeds with research interests in public health ethics, genetics and sexual health. He was previously a Clinical Reader in Public Health at the University of Sheffield; and Harkness Fellow at the Bioethics Institute at Johns Hopkins University and the Kennedy Institute of Ethics at Georgetown University, USA. He has worked for the European Commission, UK and US governments on ethical issues; and represented the UK on the Council of Europe Ethics Committee. He is a member of the Royal College of Physicians Committee for Ethical Issues in Medicine. He also served on the Working Party on Sudden Unexplained Death in Infancy jointly convened by the Royal Colleges of Paediatrics and Pathology.

Mike Shooter
Mike Shooter is a former consultant psychiatrist working with children and families in the valleys of South Wales. He is the immediate Past President of the Royal College of Psychiatrists, having previously been its Registrar and Director of Public Education. In retirement, he has become president, vice-president, chair or trustee of many mental health organisations. He is an Honorary Fellow of the Royal College of Physicians.

Paul Wainwright
Paul Wainwright qualified as a nurse in Southampton and had a range of jobs in the NHS before moving into higher education. He worked in the Centre for Philosophy and Health Care in Swansea University until 2005 and was a member of the Multi-centre Research Ethics Committee for Wales. He is now Professor of Nursing in the Joint Faculty of Health and Social Care Sciences at Kingston University and St George's, University of London, and chairs the Faculty Research Ethics Committee. He has published extensively on research ethics and research methodology. His general research interests centre around the nature of practices in health care, from both philosophical and empirical perspectives.

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Peter Watkins was consultant physician, working both in acute medicine and specialising in diabetes with considerable experience in clinical research, at King's College Hospital from 1971 to 2000, and

served as Director of Postgraduate Education there from 1989 to 1998. He had previously been Chairman of the Medical and Scientific Section of the British Diabetic Association (1990 to 1993), and latterly Editor of *Clinical Medicine*, journal of the Royal College of Physicians, from 1998 to 2006. He has served on the College's Committee on Ethical issues in Medicine since 1998, and as its secretary from 2006.

Frank Wells
Frank Wells is a former Medical Director of the Association of the British Pharmaceutical Industry; and former Chair of Allington NHS Trust, of Marix Drug Development Ltd, of the Society of Pharmaceutical Medicine and of the Ethics Committee of the Faculty of Pharmaceutical Medicine, RCP. He recently served as Chair of the Wales Cancer Bank. For 10 years he has served on the Independent Scientific and Ethical Advisory Committee of IMS Health and he co-chairs both the European Forum for Good Clinical Practice Ethics Working Party and its subgroup on the Structure and Functions of Research Ethics Committees across the European Union. He is Deputy Chair and Chair Designate of the Retired Members Forum of the British Medical Association (BMA) and a member of the Medical Ethics Committee of the BMA. Before joining the ABPI in 1986, Dr Wells was Under Secretary of the British Medical Association for seven years, and before that for nearly 20 years a General Practitioner in Ipswich. He has taken a special interest in research fraud. He is currently Honorary Secretary of the Worshipful Society of Apothecaries and a member of Suffolk LREC.

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Introduction

The first edition of these guidelines was prepared by Professor DR Laurence at the request of a steering committee set up by the President of the Royal College of Physicians (RCP) at the behest of a meeting of chairmen of ethics committees, and others, held at the College in 1982. It was published in 1984. It was extensively reviewed before publication and warmly received. A second edition under the auspices of the RCP's Committee for Ethical Issues in Medicine appeared in 1990; and a third in 1996. The College had also published two related documents after the first edition: *Research on healthy volunteers* in 1986 and *Research involving patients* in 1990. This edition updates the previous guidelines and also incorporates the subject areas covered in the related 1986 and 1990 documents. The document has been produced by a Working Group under the auspices of the RCP's Committee for Ethical Issues in Medicine. It has benefited by contributions and comments from many others, as listed on page xii (including members of the Intercollegiate Ethics Forum), to whom the College expresses its gratitude.

The aim of these guidelines is to offer a concise summary of the ethics of biomedical research involving human participants. In making that summary, we have drawn upon the work of many others, including guidance from other professional bodies and guidance from the Department of Health and Central Office for Research Ethics Committees, now reconstituted as the National Research Ethics Service (COREC/NRES). This is acknowledged in the text. We hope it will be of value not only to members of research ethics committees (RECs), but also to the research community and all those involved in research governance. To facilitate use in committees, all paragraphs are numbered and a comprehensive index has been provided. Above all we hope that the guidelines will be useful – a guide that REC members will find immediately accessible, especially those without the time or resources to consult other detailed references such as the admirable but bulky King's College London *Manual for research ethics committees.*

The guidelines are, of course, written from a UK perspective and the regulatory and legal requirements will differ elsewhere. Nevertheless, we hope that they may be of interest to all interested in the ethical regulation of research, especially to European colleagues.

Although the guidelines describe the legal background to the work of the research ethics committee, they should not be used as a definitive statement of the law. Those involved in research governance should seek appropriate legal advice.

The changes in these guidelines since the last edition have been extensive and, no doubt, in some places controversial. The working group has, for example, engaged in debate over issues such as the responsibilities for systematic review, the use of the terms 'equipoise', 'uncertainty' or 'risk/benefit ratio', the ethics of sham surgery and so on. Where such controversy exists, we hope we have achieved practical guidance rather than an unhelpful dogmatism, with references that will take the reader to the full debate. We are also aware that change is continuous and, as we go to press, the new version of the *Governance arrangements for research ethics committees* is at an advanced stage of preparation. The RCP Committee for Ethical Issues in Medicine will welcome comments and suggestions. Correspondence should be addressed to the Chair of the Committee at the College.

John Saunders
Chair of the Working Group
Chair, RCP Committee on Ethical Issues in Medicine

1 Background

Early developments

1.1 Although discussion of ethics in medical practice dates back to antiquity, the ethical regulation of research began as a result of experimentation on prisoners without consent in Prussia. In 1891, the Minister of the Interior issued a directive to prisons that tuberculin to treat tuberculosis 'must in no case be used against the patient's will'. The first detailed regulations about non-therapeutic research also came from Prussia in 1900.[1]

1.2 Guidelines for 'new therapy and human experimentation' were issued in Germany in 1931, setting out strict precautions. These included the concept of patient autonomy and informed consent. Some of these regulations were even stricter than the subsequent Nuremberg Code of 1947.

1.3 After the National Socialist Party came to power in 1933 in Germany, abuses of unspeakable cruelty led to the 'Doctors' Trials' in 1947. The three American presiding judges laid down the Nuremberg Code with 10 principles to guide physician-investigators in human experimentation. These principles, particularly the first principle of 'voluntary consent', were primarily based on legal concepts.[2–5]

1.4 The Nuremberg Code was superseded by the Declaration of Helsinki, issued by the World Medical Association in 1964. This has been the subject of numerous amendments (the most recent in Edinburgh in 2000) and clarifications (the most recent in Tokyo in 2004).

1.5 In the UK, the Medical Research Council (MRC) issued its statement 'Responsibilities in Investigations in Human Subjects' in 1963 (**CMND 2382**) emphasising the importance of consent in research[6] and has continued to provide guidance since. The Royal College of Physicians (RCP) published its report in 1967,[7] recommending the establishment of research ethics committees (RECs). Its report was widely circulated by the Department of Health. It was followed by a questionnaire in 1970 to find out to what extent clinical research investigations were then supervised. The College issued further guidance in 1973.[8]

1.6 In 1975, the UK Department of Health and Social Security published guidance (**HSC(IS)153**) endorsing and promoting the RCP proposals. It was not until 1991 when the Department of Health, (together with the Scottish and Welsh Offices), published its document *Local research ethics committees*[9] that RECs were reconstituted to conform to the Department of Health's own recommendations.

First guidelines on the practice of ethics committees

1.7 The first *Guidelines on the practice of ethics committees in medical research* were published by the RCP in 1984, as noted in the Introduction on page xiii.

Regulation in the UK and Europe

1.8 Multiple applications with poor cooperation between RECs and excessive delays led to the establishment of multi-centre RECs in 1997.[10] This was followed by supplementary guidelines for epidemiological research from the Department of Health in an attempt to reduce bureaucracy and delays.[11]

COREC established in 2000

1.9 A Central Office for Research Ethics Committees (COREC) was established in 2000 by the Department of Health to supervise MRECs in England. COREC subsequently published its *Governance arrangements for NHS RECs* (GAfREC) in 2001 and later took over the supervision of all RECs, both local and multi-centre in England. GAfREC followed shortly after the publication of a 'Research Governance Framework for Health and Social Care' in 2001. This set out standards, responsibilities and accountability in research including the need for ethical review.

UK ethics committees established on a legal basis

1.10 In 2001 the European Commission (EC) published its Clinical Trials Directive covering the conduct of clinical trials 'on medicinal products involving human subjects' (CTIMPs) among its member states. The Directive (2001/20/EC) was translated into UK statutes by the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), operative from May 1 2004. For the first time in the UK, ethics committees were established on a legal basis. A UK Ethics Committees Authority (UKECA) was established as a legal entity, consisting of the health ministers of the four UK constituent countries.

Standard operating procedures published in 2004

1.11 Anticipating the UK Regulations, UKECA published standard operating procedures (SOPs) in March 2004. These apply to all NHS research reviewed by NHS RECs. UKECA also 'recognised' certain committees to review clinical trials (which were making up about 20% of applications) and others to review Phase 1 Studies. Gene therapy research had already been excluded from the remit of RECs and its ethical review allocated to the Gene Therapy Advisory Committee (GTAC). GTAC is also the relevant REC for approval of clinical trials and research on humans using genetically modified animal cells, (but not solid organs). Similarly, the UK Xenotransplantation Interim Regulatory Authority (UKXIRA) was responsible for research involving xenotransplantation until it was disbanded on December 12, 2006. Xenotransplantation studies may now be reviewed by RECs.[12] Review of research on prisoners is also delegated to a select number of RECs. COREC itself was subsumed within the National Patient Safety Agency in 2005 and, following the Warner report (below), has become the National Research Ethics Service (NRES).

Warner report: Building on improvement

1.12 Concerns about the operation of the system of ethical review led to the establishment of an Ad Hoc Advisory Group on the Operations of NHS Research Ethics Committees by the Health Minister, Lord Warner, in 2004. Publication of the Warner Report was delayed by the 2005 general election, but its recommendations were accepted by ministers. A Change Advisory Group was set up by COREC to recommend how the report should be implemented, culminating in the publication of *Building on improvement: implementing the recommendations of the Report of the Ad Hoc Advisory Group*[32] in August 2006.

Data protection, human tissue and mental capacity acts

1.13 As well as these regulatory developments, there have been a series of legal changes affecting research practice. In England these include the Data Protection Act 1998, the Human Tissue Act 2004 and the Mental Capacity Act 2005. There have been parallel, but slightly different legal developments in Scotland (for example the Adults with Incapacity (Scotland) Act 2000 and the Human Tissue (Scotland) Act 2006). Official guidance to legislation has also been slightly different in Wales and Northern Ireland.

1.14 Further developments can be anticipated. Research in social care outside the NHS or research in the private sector, for example, are not clearly covered by current regulations. A consultation (2004) on options and guidelines for ethics review of social care research is likely to lead to new guidance. Universities have developed ethics committees for research with human participants in areas such as psychology and it is hoped that duplication can be avoided. Nevertheless there have been extensive changes since the last edition of these guidelines and much that was advisory then is now prescribed by COREC/NRES, the EC Directive etc.

Ethical review in the EU and in developing countries

1.15 The adoption of the EC Directive might have been expected to lead to further harmonisation of ethical review across member states. However, a report on the structure and function of RECs throughout Europe reveals widely varying national differences that are likely to persist. RECs are now established in all European countries.[13–15] The Global Forum in Bioethics in Research has an emphasis on sharing good practice with developing countries and the Network of Ethics in Biomedical Research in Africa, which was funded by the EU under its Science and Society Programme, is providing useful information about the RECs in the 15 participating countries.

2 Research, its benefits and the responsibilities of investigators

Desirability of medical research

RECs have a duty to encourage important ethical research

2.1 We all benefit from living in a society in which serious scientific medical research is carried out. It is in the interests of patients to live in a society which pursues ethical research to discover new investigations and treatment for disease where uncertainty exists. The knowledge of underlying physiological mechanisms gives hope for the future to us as individuals and as a community. Ethical research is a moral good and is the key to prevention of disease and a healthier society. Biomedical research involving human participants cannot legitimately be neglected and should be regarded as an essential part of continuing medical practice. Research ethics committees have a duty to encourage and facilitate important ethical research as well as ensuring that unethical research is not permitted.[16]

2.2 A new principle of research ethics has even been suggested: *Biomedical research involving human subjects cannot legitimately be neglected and is therefore both permissible and mandatory, where the importance of the objective is great and the possibility of exploitation of fully informed and consenting subjects is small.*[17] We suggest 'recommended' rather than 'mandatory'.

Participation in ethical research as a moral obligation

2.3 All of us have benefited by medical research. We suggest that participation in ethical research where there is no or minimal personal risk or cost could be considered a moral obligation.[18] Identifying our moral obligations and acting on them is an integral part of what makes us moral agents.

2.4 Some investigators have reported that people enrolled in clinical trials may have better outcomes than those eligible for the study but not enrolled.[19–21] Such findings have been reported for trials for diseases ranging from cancer to cholera. Suggested explanations include placebo effects, adherence to well defined protocols and better supervision than is offered in routine practice. These possible 'inclusion benefits' are uncertain.[22,23] There may be no net benefit, but there is no evidence of major harmful outcomes overall as a result of participation in well conducted therapeutic trials. As a group, patients in such trials appear unlikely to be harmed by their participation. Their outcomes moreover usually seem to be generalisable to similar patients receiving the same treatment outside trials.[24] Recent experience has reminded us that phase 1 studies may differ and unpredicted harms in first human use have occurred.[25–27]

2.5 Treatment that works in a highly controlled trial also appears to work in routine practice,[24] although this may sometimes require more formal assessment.[28]

Physicians should actively encourage research

2.6 We believe that physicians and others should not be neutral and certainly not antagonistic about supporting or participating in ethical research projects. Such research should be actively encouraged.

2.7 The General Medical Council makes it clear that doctors 'must … help to resolve uncertainties about the effects of treatments' (para 4 f).[29]

2.8 This places particular responsibilities on those involved in the regulation of research, in assessing its scientific validity, its ethical desirability and importance, its welfare provisions and, usually, the arrangements for consent.

2.9 It is generally agreed that:

(i) research investigations on human beings, their health information or their tissues should conform to codes such as those of the World Medical Association's Declaration of Helsinki, and of the World Health Organization (WHO) and its associated bodies.

(ii) investigators should not be the sole judges of whether their research does so conform.

2.10 Clinical trials of investigational medicinal products should also conform with the principles of Good Clinical Practice (ICH).[30] All studies should conform to the MRC's *Good research practice.*[31]

2.11 Although helpful as general statements, the principles in 2.9 do not provide detailed guidance on how they should be applied to individual research proposals.

All research involving patients must be the subject of ethical review

2.12 It is a legal requirement that all research involving trials of medicinal products with human participants shall be subject to independent ethical review. It is a requirement of the Department of Health (and the devolved administrations) that all research involving NHS patients and users, and those identified as participants because of their status as relatives or carers of patients and users, shall be subject to ethical review. Research involving the recently dead in NHS premises, fetal material involving NHS patients, and access to data, organs or other bodily material of past and present NHS patients also requires REC approval (GAfREC 3.1).

Phase 1 research

2.13 Phase 1 research, when a medicinal product is given to a human participant for the first time, often takes place in the private sector. This too requires the approval of a properly constituted REC, recognised by UKECA.

Research involving private patients

2.14 Arrangements for other private sector research have not been defined. NHS RECs may undertake such work. GAfREC states that 'those conducting such external research should be encouraged to submit their research proposals to an NHS REC for advice, and the REC should accept for consideration all such valid applications' (GAfREC 7.22). The College would encourage RECs to review protocols arising from the private sector. It is, as previously noted, a legal requirement under the Regulations implementing the EC Directive that CTIMPs in particular should undergo ethics review by a recognised REC.

RECs and their responsibilities

Several bodies offer other research guidance

2.15 Following the initial publication of these guidelines a number of other bodies have issued useful guidance. These include other medical royal colleges, the MRC, the Association of the British Pharmaceutical Industry (ABPI), the General Medical Council (GMC) and the Council for International Organisations of Medical Sciences (CIOMS).

2.16 Responsibility for appointments to RECs rests with strategic health authorities in England (as appointed agents of the Department of Health), with the Office of the Chief Scientist in the Scottish Executive, with the Secretary for Health and Social Care in the Welsh Assembly Government and with the Secretary for Health, Social Care and Public Safety in Northern Ireland.

Decisions of RECs are made as a result of review proportionate to level of risk

2.17 The implementation plan arising from the *Report of the Ad Hoc Advisory Group on the Operation of NHS RECs* introduced the Research Ethics Service, where decisions are made as a result of review proportionate to the level of risk. Applications to the service can be approved by a 'virtual' sub-committee of two national research ethics advisers, where it is considered that there are no material ethical issues.[32]

The main aim of research ethics review is the protection of research participants

2.18 The objectives of RECs – and the Research Ethics Service – are to maintain ethical standards of practice in research, to protect participants in research from harm, to preserve their rights and to provide reassurance to the public that this is being done. RECs should also promote research that is of real value.[33] They provide independent advice to participants, researchers, funders, sponsors, employers, care organisations and professionals (GAfREC 2.1). The goals of research and research workers should always be secondary to the dignity, rights, safety, and well-being of the research participants (GAfREC 2.3). In the words of the Helsinki Declaration, 'considerations related to the well-being of the human subject should take precedence over the interests of science and society' (A4).

2.19 The main aim of research ethics review is to protect research participants. However, by identifying potential problems with and requiring appropriate changes in research proposals, researchers, the institution in which they work and the funding body can also receive some degree of protection from complaint or claims of negligence. Research ethics committees may also be able to identify methodology or locations of research etc which may be unsafe and pose risks for the researcher.

2.20 An entirely new treatment is likely to present a greater risk than one already in widespread use. Research between many established treatments or interventions is undoubtedly still needed to resolve uncertainties. We note that the current requirements for ethical review (with detailed and lengthy information sheets, for example), discourage such evaluations, yet no additional participant protection should be needed. While patients participating in any such evaluative study often have the inconvenience of additional visits, blood samples etc., the accusation of 'double standards' has substance.[34,35] In continuing routine practice no special permission or information is required compared with the clinical trial. RECs should avoid making disproportionate demands in such situations.

Participants in research

Patients should not be denied the opportunity to help in the advancement of medical knowledge

2.21 Subject always to adequate safeguards, patients should not be denied the opportunity to help in the advancement of medical knowledge. As far as is practical, the benefits and burdens of research should be fairly distributed among all groups and classes in society and from both men and women.[36,37] Equity demands that no group should bear more than its fair share of the burdens and no group be deprived of its fair share of the benefits of research.

2.22 Nevertheless, there is no 'right' to participate in research. Opportunities for such participation will always depend on geography and timing.

Recruitment

2.23 Aspects of recruitment to research studies are covered in a variety of sections of this document where specific issues arise. However, there are some broad general observations.

2.24 It is essential that in the course of inviting a patient to participate in research, an investigator must make it clear that the patient is free to decline to participate (or to later withdraw) without giving a reason, that a decision to decline will be accepted without question or displeasure and that the patient will then be treated as though the matter had not arisen and without any disadvantage to future care.

2.25 Research involving human participants cannot proceed if potential participants cannot be persuaded to take part, so there is inevitably some pressure on investigators to recruit creating a temptation to use inappropriate methods.

2.26 When local investigators, to whom research projects have been subcontracted, are reimbursed on a per-capita basis the pressure to recruit becomes financial as well as scientific or professional. Competitive recruitment, with centres in different locations being encouraged to recruit as rapidly as possible until the overall recruitment target for the study has been met, also places additional pressures on local investigators.

2.27 As stated in 2.21 above, the burdens and benefits of participation in research should be distributed equitably. No group should be excluded without reasonable grounds. Age, sex and ethnicity are not of themselves sufficient grounds for exclusion from a study. The population from which a sample is drawn should include a proper representation of the types of people likely to be affected by the conditions under study in the research or to whom the findings will be applied. We note particular concerns regarding the unjustifiable exclusion of members of ethnic minority groups.[38–42]

2.28 Participation in research should be voluntary and informed but participants should not be invited to take unacceptable additional risks. The concept of equipoise (or that of minimal risk) means that there are some things that we should not ask people to do (see 5.18). Whether or not the risk and burden are acceptable will be considered carefully by the ethics committee that considers the research project. In this limited sense, RECs could be said to operate with a degree of paternalism. The final decision on whether or not the risk and burden are acceptable will be made by the person concerned when they decide to give or withhold consent.[43]

2.29 Rewards and incentives for participation are appropriate but should be proportionate in the context and not so substantial as to constitute coercion or to encourage someone to take a risk (as opposed to giving up time and effort) that he or she would not otherwise be prepared to take (see 10.12).

2.30 A new method should be tested against the best current prophylactic, diagnostic or therapeutic methods (Helsinki C29) and such methods should always be available outside participation in research.

2.31 'Such methods' should refer to standard treatment, ie the best normally available within a given jurisdiction. We acknowledge that defining standard care may be difficult even within the UK and creates particular difficulties in countries where resources are more limited.[44]

Vulnerable research populations

2.32 Some research populations are vulnerable and need special protection (Helsinki A8). Respect for persons includes respect for an individual's capacity to make reasoned decisions, and protection of those whose capacity is impaired or who are in some way dependent or vulnerable.

2.33 Clinical investigators have an ethical obligation to maximise benefits and minimise harms and wrongs. Risks of research must be reasonable in relation to expected benefits; research design should be sound and investigators competent both to conduct the research and to safeguard the welfare of research participants.

Patient–doctor relationship is based on trust

2.34 The patient–doctor relationship is based on trust, and the understanding that the doctor is concerned to put the interest of the individual patient first. Patients generally believe this and it is essential that their confidence should not be impaired. Within an individual doctor–patient relationship there is a risk that research could involve subjugation of this interest: priorities of the trial may take precedence over individualised care.[45,46] The nature and extent of this 'therapeutic misconception'[47] must be clearly known to and understood by participants. Lack of truthfulness or frankness about research on the grounds, for example, that the research is 'harmless' and that consent need not be obtained because the process of obtaining it 'will cause needless anxiety', is a breach of this relationship. Transparency is essential to the maintenance of trust.

2.35 Transparency is equally important in the relationship between doctors or research teams or corporate bodies such as health trusts with industry or commercial bodies.[48] The RCP has published a report on *The relationship between physicians and the biomedical industry*.[49]

2.36 It is a general rule that people who are participants in research, whether they are healthy or sick, should be made clearly aware of their position and of the nature of the research. Any investigator who proposes to depart from this rule should be prepared to justify the procedure before a REC or even in a court of law.

Information on research must be given to all those normally responsible for the patient's care

2.37 Clinical responsibility for all patients in the NHS (and usually in private practice) ultimately falls on their general practitioners and/or consultants. GPs, consultants or other healthcare providers, to whom the information is relevant, should be informed, with the patient's consent, when experimental research is conducted with their patients by their colleagues or by others. Sometimes a patient is attended by more than one consultant, eg surgeon and anaesthetist. In such cases, the consultant who is responsible for the overall care of the patient should always be involved alongside any others.

Consent to research must be given and must be voluntary

2.38 A principle of the Helsinki Declaration is that participants' consent to their participation in research must be voluntary. To ensure that this consent is valid participants must be sufficiently informed about the research and, in non-emergency research, have adequate time to make an unpressured decision. Consent should normally be recorded by the participant's

signature on an appropriate form. As discussed below (4.56, 5.31, 8.22), special considerations apply when participants are unable to give consent, including research with children. The REC may also choose to waive the requirement for consent in low risk research, for example, some types of health records research (see 7.19).

2.39 In addition to ensuring that participants are informed and have given consent, every effort should be made to ensure that participants have an opportunity to comment and ask questions and that they know that they can, if they wish, easily withdraw from a research investigation without giving reasons and without prejudice to their continued treatment (see also 5.34). It is a requirement for a favourable opinion that the REC is satisfied with the steps to be taken if participants voluntarily withdraw during the course of the research (GAfREC 9.15.f).

Developments and improvements in REC structure and organisation

2.40 Despite well publicised concerns about bureaucratic delays, procedural anomalies, variable working practices and inconsistent decision making,[50–54] the RCP believes that there has been a general raising of standards and increasing uniformity of practice among RECs. This has been assisted by training of members, the publication of guidelines and the establishment of COREC with the development of GAfREC, SOPs and MREC chair's meetings. The reduction in the total number of RECs resulting from regulatory changes should assist further improvements in UK training programmes for REC members and more consistent decision making.

2.41 Nevertheless, we remain concerned about the **speed** of regulatory review. The working group has been impressed by the frequency with which this complaint is raised by the research community. The RCP supports all reasonable steps to expedite and simplify the process of ethical review and of research and development (R&D) approval, provided its rigour is maintained.

2.42 Originally RECs were established as *local* committees. Their geographical remit expanded with the 1991 recommendations, while MRECs have always had a national remit, their decisions carrying validity throughout the UK. It has been increasingly recognised that there are no truly local *ethical* issues, although there may be important local considerations of facilities, population factors etc that are properly the concern of research governance regulatory functions.[55] These functions are now the responsibility of NHS RandD departments. In any case, *Building on improvement* removes the distinction between MRECs and LRECs.

RECs should remain independent of hospitals or primary care trusts

2.43 It is essential that RECs remain independent of hospital or primary care trusts (and their equivalents in the devolved administrations) while research governance structures should be the responsibility of trusts.

Phase I studies

2.44 Historically, pharmaceutical companies, contract research organisations and other independent organisations set up research ethics committees specifically for the purpose of reviewing protocols for Phase I healthy volunteer studies. Recognising the need for such committees to be seen to be independent and properly trained, ABPI produced guidelines in 1997 for Phase I studies. Many of the specifically Phase I RECs have now been disbanded, with the recognition that Phase I studies must be reviewed by independent RECs accredited by UKECA. The ABPI document has been revised and expanded to provide information on the

ethical review process in all phases of drug research.[56] Those few RECs that remain outside the conventional REC system should be accredited by UKECA and be required to follow GAfREC and COREC/NRES SOP standards.

Scientific quality

2.45 While the prime responsibility of a REC is to advise its appointing authority on all matters pertaining to the ethics of research involving human participants, the extent to which scientific quality, design and conduct should be considered continues to cause difficulty. Badly planned, poorly designed research that causes inconvenience to subjects and may carry risk is unethical. Plainly, a highly rigorous scientific evaluation is beyond the capacity of most RECs and 'it is not the task of the REC to undertake additional scientific review' (GAfREC 9.9). The Research Governance Framework makes it clear (paras 2.3.1 and 2.3.2) that the sponsor is responsible for ensuring the quality of the science: 'Research which duplicates other work unnecessarily or which is not of sufficient quality to contribute something useful to existing knowledge is in itself unethical'. Moreover, 'All proposals for health and social care research must be subjected to review by experts in the relevant fields able to offer independent advice on its quality. Arrangements for peer review must be commensurate with the scale of the research'. Nevertheless, GAfREC (9.12, 9.13) makes clear that the REC should 'be adequately reassured about ... the scientific design and conduct of the study. While the REC is not itself responsible for a systematic review[57] of previous work, it should ensure that review of previous work has taken place. This could involve an external scientific opinion to the REC as to its adequacy. In addition, if dissatisfied with the adequacy of the scientific review of the study itself, it should require re-submission.

2.46 Scientific guidance should be available through COREC/NRES according to the Warner Report[32] (recommendation 2) and the newly established research ethics advisers (*Building on improvement*) should be able to assist. It is our view that where peer review has been carried out by an expert committee of a funding body such as the MRC or a member of the Association of Medical Research Charities, this should normally be accepted as evidence of scientific validity. Similarly, most expert review by large pharmaceutical companies produces protocols of high scientific quality. This does not, of course, exclude the possibilities that ethical concerns may arise from a particular design of study or that scientific amendments may lead to an ethically more acceptable protocol. It is not the role of the REC to re-write inadequate protocols but to make an informed judgement on the protocols submitted to it.

2.47 The REC, then, should not normally reject an application on grounds of inadequate scientific quality unless it has satisfied itself that it has adequate knowledge and expert advice to justify this step. As the Warner report[32] states: 'In the unusual situation of a REC having reservations about the quality of the science proposed, they should...refer to COREC for scientific guidance.'

Student projects

2.48 Students of medicine or paramedical or nursing disciplines often undertake projects as part of their courses. The prime object of such projects is to train students in research methodology (including making an application to the REC). We acknowledge that many

projects will not produce significant benefit for the participant or for mankind in general: in that sense they are better described as (educational) *projects* rather than research. It is appropriate to invite participation in such projects since the training of students is in itself of benefit to mankind. Such projects should not normally carry more than minimal inconvenience, discomfort or risk (eg most questionnaires).

2.49 The educational significance of such projects should be clearly explained to participants. It may not be appropriate for RECs to apply the *scientific* criteria to student projects that apply to research, eg participant numbers or selection criteria.

Two issues for which RECs are not responsible

2.50 In previous editions of these guidelines, advice was given on investigators' skills, supervision and premises. These responsibilities have been rightly removed from RECs and belong to research governance structures in trusts.

2.51 Similarly, RECs should avoid responding to requests for advice about the ethics of clinical practice. The RCP has published a report with advice on clinical ethics.[58]

Scientific fraud and misconduct

2.52 The investigation of alleged scientific fraud or misconduct is not the role of the REC. However, rigorous review by research ethics committees can provide a powerful preventative measure in reducing research misconduct as well as providing a culture in which it is more difficult for research misconduct to flourish.[59] Nevertheless, occasionally the REC may be the recipient of such allegations. If it believes that such allegations should be investigated, it should ensure that a more appropriate body is involved. This might be the research sponsor or the research governance committee. Formal guidance on the investigation of such allegations is available from the MRC[60] in the UK. More recently, funding has been obtained by UniversitiesUK for the establishment of a UK panel to share experience and good practice although it has no powers to investigate. The Secretary of this body, the UK Research Integrity Office (UKRIO), is at UniversitiesUK, Woburn House, 20 Tavistock Square, London, WC1H 9HQ. In addition, research sponsors and/or appropriate assessment committees should be aware that independent experienced advice on the investigation of suspected research misconduct is commercially available.

Committee on Publication Ethics

2.53 The Committee on Publication Ethics (COPE) was founded in 1997 to address breaches of research and publication ethics.[61] Guidelines include how to deal with suspected misconduct. Concerns regarding publishing irregularities such as plagiarism, falsification or fabrication may be referred to COPE for advice. The Secretary of COPE is currently based at BMJ Publishing Group Ltd, BMA House, Tavistock Square, London WC1H 9JR.

Serious adverse events

2.54 Under the EC Clinical Trials Directive, RECs must be informed of serious unexpected adverse events (SUSAR = suspected unexpected serious adverse reaction). The Medicines and Healthcare products Regulatory Agency (MHRA) has the responsibility for monitoring

safety in clinical trials through its access to EudraCT (European Clinical Trials Database) and RECs usually have difficulty interpreting adverse event reports without knowing their frequency. Nevertheless, there may be occasions where a SUSAR in a trial of treatment for a minor condition may lead the REC to withdraw its favourable ethical opinion. Responsibilities of RECs in dealing with SUSARs are set out in the COREC SOPs (page 158, version 3.0).

Monitoring of studies

2.55 Plainly it is impracticable, even if it were desirable, for the REC to monitor in detail the conduct of ongoing investigations, but RECs should not lose contact with studies that have been approved. The annual report from the principal investigator should be reviewed at the REC meeting. These should contain details and not merely minimal information.

2.56 Ethical issues are not confined to the question of whether to start a research project. They can also include when to stop: for example, in order to avoid needlessly prolonged use of a less effective treatment in a serious condition, a therapeutic trial should provide for interim or sequential analysis as the trial progresses by a 'data and ethics monitoring committee'. Trials should not be terminated simply because of commercial interest,[62] but for reasons pertaining to efficacy, safety or feasibility. Premature discontinuation of trials for strategic reasons deceives the patients, jeopardises the patient–doctor relationship and harms the medical community.

2.57 Studies from the patient's or public perspective of the experience of research participation are still few in number, relative to the enormous numbers of research studies being carried out.[63] We still do not confidently know, for example, what are the key factors in the decision to participate in research.[64] We would wish to encourage projects in this area (see also 5.29).

Methodological research

2.58 Methodological studies have found important discrepancies between the protocols and publications of randomised trials. These finding have undermined the credibility of clinical research.[65] RECs are not able to ensure that a trial has been carried out without unacknowledged protocol deviations, such as changes in definitions of outcomes. Even while maintaining the confidentiality of the protocol, accredited external reviewers should be able to examine files without explicit permission from applicants and therefore without the bias introduced by a permission seeking process. Whether construed as audit or methodological research, the importance of assuring the integrity of medical research protects both study participants and future patients.

Publication of research findings

2.59 It is unacceptable in principle that an investigator should agree to conditions that may prohibit or impair the possibility of publication, though some delay may sometimes be acceptable. This applies whether the sponsor of the research is a pharmaceutical company, a government department or any other agency. Investigators should agree a publication policy in advance and RECs should be aware of what this is.

2.60 There have been major concerns about bias in the publication of drug trial results.[66] There have been instances of trials showing negligible benefit of an active drug against a control, or greater than expected adverse effects, being concealed by the pharmaceutical industry 'burying'

results to protect its own interests or by editorial choice.[67,68] This distorts the medical literature, impairs meta-analyses and undermines the confidence of doctors and patients alike. It is important that the REC does all it can to ensure that the publication of negative results is not precluded in advance or otherwise impeded by the sponsors. The RCP wholeheartedly supports the registration of all clinical trials to help ensure their eventual publication, irrespective of results and would like to see approval of applications conditional upon such registration. Registration of trials[69,70] and publication of all results is the way to prevent publication bias – the tendency whereby favourable results are published more frequently and more rapidly.[71]

2.61 Similar concerns have been expressed about the role of pharmaceutical industry staff in the execution of clinical trials and in the writing of articles based on them. In some cases it has been alleged that the medical authors played little part in the running of the trial or added their name to an article 'ghost written' for them. While it may be beyond the power of the REC to eradicate such unethical practice completely, it should ask for a clear statement of the roles of those running the trial and of publishing policy before granting approval. This would have the unqualified support of the Faculty of Pharmaceutical Medicine. In a similar way, the names of non-contributing heads of academic departments should not be added to the list of an article's authors.

Allocation of resources

2.62 Although the allocation of resources has ethical implications, consideration of this is an issue for NHS management. Those who distribute resources will require that a project has the approval of the REC but REC approval carries no implication that resources ought to be provided. R&D or research governance committees are generally charged with this responsibility. *The care provider remains responsible for the quality of all aspects of the care of their patient or users, whether or not they are involved in research.*[72] We acknowledge that the development of research governance structures has added complexity to the regulation of research and difficulties for many investigators.

2.63 The adjudication of the REC should not take into account the possibility that the results of medical, social or environmental research might later give rise to demands for implementation that may be expensive. Such matters are, of course, of legitimate concern to those responsible for allocating scarce resources.

Membership and methods of working

2.64 Members of RECs need to be people of goodwill, with a high regard for humanity, for truthfulness and for the continued advance of science in the interest of society. Those who are totally opposed to research investigations or experiments on humans should be left to oppose the system from outside and should not be invited on to the committee. On the other hand, individuals who are acquiescent and may be thought likely to give automatic approval are also not suitable members. A majority of the professional members should be mainly employed in providing clinical care.

2.65 Among the members some individuals other than professional investigators should be able to look at applications critically from the participant's point of view. This role may be taken by a number of different individuals, but particularly by lay members.

2.66 For the community to have confidence in the REC, membership should be seen to be broad; lay members should be persons of responsibility with relevant life experience, who will not be overawed by medical members.

2.67 The composition of the REC is laid down in GAfREC section 6. GAfREC emphasises the expertise of its 'expert' members, rather than their discipline. A committee of 12–18 should normally have one third medical members and one third members from other professional groups. The committee should include relevant and appropriate expertise, for example, in primary care, child health, mental health and epidemiology. Although this could be a general practitioner, a paediatrician, psychiatrist and epidemiologist, alternatives such as a practice nurse, clinical psychologist etc. might be considered. At least half of the 'expert' members should have some personal experience of research as evidenced by publications or a research degree. One of the six medical members could be a doctor in the training grades. In general, it is desirable if the medical members include those with a broad specialty experience, physiologically and scientifically literate across a wide spectrum of medicine.

2.68 GAfREC emphasises that members are not representatives of the groups from which they are drawn. They are appointed in their own right as equal individuals of sound judgement, relevant experience and adequate training in ethical review (GAfREC 6.8). They are not delegates taking instruction from other bodies or reporting to them.

2.69 Although GAfREC states that the chair and vice chair should be appointed by the appointing authority after consultation with the REC administrator and committee members, it is not clear what such consultation might mean. Both chair and vice chair must command the confidence of the REC members. We suggest that the REC should nominate one of its members to sit on the appointments committee. Such a nominee should not, of course, be a candidate for either post. Appointments should be made according to Nolan principles and after public advertisement.

2.70 An 'alternate vice chair' with the responsibility of chairing the REC in the absence of both the chair and vice-chair should be appointed from within the committee. The responsibilities are likely to be infrequent and a full appointments procedure by the appointing authority is both time consuming and expensive.

2.71 In general, it is not desirable for both the chair and vice chair to be lay members, but one should be lay.

2.72 The recommendations of GAfREC (6.15) with respect to deputies are noted.

2.73 The extent of 'chair's action' is not currently specified in either GAfREC or SOPs. In general 'chair's action' should be limited to authorising those amendments agreed by the REC. Major changes, for example to patient information leaflets, should require approval by the full committee or an executive subcommittee. The decision as to final approval should be taken by the REC at its initial consideration of a protocol.

2.74 GAfREC (7.17) states that REC meetings will normally be held in private to permit free discussion and minutes are not normally published. While there may be a case for confidentiality of some of its business, the requirement for such secrecy has been challenged[73] and seems at odds with the principles of open government.[74] An initial step might be a public version of the minutes, available on the Internet as currently practised by many government departments.

2.75 Members should declare any possible conflicts of interest in a study. The test should be anything that could be construed as influencing that member's opinion on the application. The range of possible responses is set out in the SOPs 2.60 from GAfREC (see also 10.22).

Duration of membership

2.76 Duration of membership should be prescribed (for example, 3 to 5 years) and should be renewable once, subject to a favourable assessment by the chair. A balance must be achieved between continuity, the input of new ideas, maintenance of expertise and excessively cosy working relationships. It is important not to lose a valuable and willing member simply because time has passed or to lose too much experience and expertise at any one time. In some circumstances, it may therefore be desirable to go beyond the general rule of two terms of office. Some overlap in membership may aid continuity.

All members should undergo training

2.77 All members should undergo training for their role. Members' needs will vary according to their background. Some understanding of research design, scientific method, NHS structures, research ethics governance and ethical principles is essential for all members. At least two days (or equivalent), of appropriate national or regional courses should be attended in the first year of membership, with half a day (or equivalent) for updating in subsequent years.

2.78 On appointment, all members should be supplied with a pack of appropriate guidance. We suggest this includes GAfREC, these guidelines and, for non-medical members, a medical dictionary and a copy of the British National Formulary.

Annual courses should be provided

2.79 We would strongly support the provision of annual courses of half or one day duration financially supported by NRES with advice from REC chairs in order to update members. These should always contain sessions on research and its ethical challenges, rather than being diverted into exclusively considering structural changes to the system or law.

2.80 We would also encourage programmes of professional development for REC members and investigators together. This would enable mutually beneficial discussion and understanding.

2.81 There should be regular circulation of relevant publications on research ethics to committee members. Some of these can be selected from the bulletin circulated by COREC/NRES and others identified by a REC member nominated and interested in taking on this role.

2.82 Methods of working are laid down in the *Standing operating procedures for research ethics committees* published by COREC/NRES and available online (www.nres.npsa.nhs.uk/docs/guidance/SOPs.pdf).

Applications are now made to the Research Ethics Service

2.83 Applications are now made to a research ethics service, rather than to a research ethics committee. Not all applications will be seen by the full committee. Those with no substantial ethical component may be approved by the research ethics adviser. However, all trials of investigational medicinal products will always be reviewed by the full committee.

2.84 We strongly encourage investigators to attend the REC meeting. This encourages cooperative working between the investigator and the REC, avoiding unnecessary misunderstanding. It also saves time.

2.85 We would encourage the attendance of observers, subject to those considerations set out in GAfREC 6.17. For example, a specialist registrar expressing an interest in research or an overseas visitor eager to see how the UK system works in practice should be welcomed.

2.86 Neither GAfREC nor the Standard Operating Procedures (SOPs) define what constitutes a committee 'opinion'. Decisions made by consensus are preferred if at all possible. On those occasions where this is not possible, a majority vote may be required but this should always include at least one lay member in favour. Prudence should guide the chair if, in a particular case, a majority decision would leave consciences with reasonable ground for serious misgiving.

2.87 RECs should make it known that investigators planning research may seek advice from the committee or from a member. The member should declare this at the subsequent meeting. Local research ethics advisers have a designated role to support the research ethics service locally.[75]

2.88 RECs have no direct sanctions, other than withdrawal of approval. If they discover that their advice is unheeded or that clinical investigations are being conducted without reference to them they should report the facts to their appointing authority, to the research sponsor, the research governance committee of the NHS organisation involved or even to a professional organisation such as royal colleges or the GMC. NHS employees and GPs are subject to guidelines from the UK health departments requiring that research is submitted to a REC. Where research is undertaken outside the NHS, RECs have a responsibility to make other employers/authorities aware of research not being conducted within this safeguard. Plainly, an investigator who bypasses or ignores the recommendations of a properly authorised REC could be subject to professional disciplinary or even legal proceedings.

RECs should publish an annual report

2.89 An annual report is a requirement for all RECs. This should be widely available and published on the appointing authority's website with paper copies in relevant places eg public libraries as well as circulation to NHS bodies. Annual reports should follow a standard format as laid down by GAfREC 7.19–21.

3 Medical research

Medical research defined

3.1 Medical research is a broad world-wide activity. Its two main objectives are to increase and refine the body of knowledge on which that part of the practice of medicine which is science-based depends and to explore the practical ways in which that knowledge can be applied in the prevention and treatment of disease. Increased knowledge can come from studies at all levels of biological organisation, from subcellular compounds and particles to whole organisms, both individual and grouped in defined populations. While the direct responsibility of RECs may be centred on the 'applied' component of medical research, including the numerous trials of the efficacy and safety of medicines, it should be appreciated that investigations on patients and on people in normal health have substantially contributed to basic medical knowledge and to the advantage of patients and the community.

3.2 Medical research may be conducted both on patients and on healthy people. In this document, medical research is considered to be all research involving patients, and some, but not all, research involving people who are not patients. For example, drug or physiological studies on healthy volunteers are considered as medical research whether conducted by doctors, nurses, psychologists or other allied health professionals. On the other hand, some psychological studies on normal individuals may not be considered as medical research. These guidelines are applicable to studies carried out by students in their professional education and some types of audit.

Research, audit and service development

3.3 The definition and classification of research remains controversial: in particular, the distinction between research, audit and service development. In our view, these categories may not be mutually exclusive. Studies such as the longstanding Confidential Inquiries into Maternal or Peri-operative Deaths, for example, may encompass all three: they lead to new knowledge that can be generalised (research), provide a highly effective audit of a service, and are essential for service development.

3.4 The distinction between medical research and innovative medical practice derives from the intent. In medical practice the sole intention is to benefit the individual patient consulting the clinician, not to gain knowledge of general benefit, though such knowledge may emerge from the clinical experience gained. For example, a randomised and blinded multiple crossover trial of one or two treatments for a single patient ('n of one trial') may appear initially to be research but is in fact medical practice.[76–80] In medical research the primary intention is to advance knowledge so that patients in general may benefit: the individual patient may or may not benefit directly.

3.5 When a clinician departs in a significant way from standard or accepted practice entirely for the benefit of a particular individual patient, and with the patient's consent, the innovation need not constitute research, though it may be described as an experiment in the sense that it is novel and unvalidated. (In this context, an 'experiment' is a procedure adopted on the chance of its succeeding. 'Research' is a systematic experiment or series of observations to establish

facts or principle and generalisable knowledge.) Clinicians should be prepared to justify their innovative therapy both ethically and scientifically if challenged.

Interventional procedures

3.6 If planning to undertake a new interventional procedure, medical practitioners are advised to seek approval from their NHS trust's clinical governance committee (Health Service Circular HSC 2003/011). The chair of the clinical governance committee should notify the procedure to the Interventional Procedures Programme at the National Institute for Health and Clinical Excellence (NICE) unless it is already listed there. In a case where the procedure has to be used in an emergency the procedure should be notified to the clinical governance committee within 72 hours.

3.7 Extension of such an experiment into wider use or general application should prima facie, be regarded as research.

Audit versus research

3.8 Clinical audit has been defined as: 'a quality improvement process that seeks to improve patient care and outcome through systematic review of care against explicit criteria and the implementation of change'.[81] Audit may involve the investigation of clinical practice or institutional systems. The distinction from research has been defined as follows: 'Research is finding out what you ought to be doing; audit is seeing whether you are doing what you ought to be doing'.

3.9 Research often creates additional administrative burdens. This is a deterrent, especially to small-scale studies that do not involve patients. There may be a reluctance to declare activity that lies in the grey areas. This creates problems for effective clinical and research governance. We therefore support the call for a systematic process for deciding how activities in grey areas should be dealt with, rather than relying on ad hoc responses.[82]

3.10 RECs should neither create nor foster a double standard for the regulation of audit versus observational research. Both should be judged according to the risks of disclosure, which should be proportionate to the expected benefits.

3.11 Further guidance on the ethics of audit and its distinction from research is available from the COREC ethics consultation E-group and from the United Bristol Healthcare NHS Trust.[83] These are shown in Appendix 1 (a and b).

Service evaluation

3.12 Service evaluation has been defined as: 'A set of procedures to judge a service's merit by providing a systematic assessment of its aims, objectives, activities, outputs, outcomes and costs'.[84]

3.13 Guidance from the NHS R&D Forum suggests that service evaluation which is relevant only to the population or setting upon which it is based would generally be low risk.[84]

3.14 Evaluation concerned with producing internal recommendations for improvements that are not intended to be generalised beyond the setting in which the evaluation took place should therefore not be managed within the Research Governance Framework, and other appropriate systems should be used. These might include for example authorisation and oversight by a clinical effectiveness manager or a senior person in the department/unit in which the evaluation is based (see 3.8).

3.15 We note that service evaluation may include audit, research or data management and that analysis

- may provide cost and/or benefit information on a service
- uses quantitative and qualitative data to explore activities and issues
- may identify strengths and weaknesses of services
- may include elements of research eg collecting additional data or changes to choices of treatment.

Role of research ethics adviser

3.16 The role of the research ethics adviser should include advice on the appropriateness of referral to a research ethics committee for issues of service evaluation. These issues may sometimes require referral to the research ethics committee itself.

Clinical ethics advice

3.17 The RCP has published a report about advice on clinical ethics,[58] including the role of the clinical ethics committee. Such a committee could include advice on the ethics of audit projects among its terms of reference for those trusts where committees exist.

Observational or experimental research

3.18 Research may be broadly categorised as observational or as experimental (or interventional). In observational research, participants are not asked to make any lifestyle, pharmacological or other changes for the sake of the study. In experimental research they are. Observations themselves, however, could be made by an intrusive method (eg an intra-arterial line to measure blood pressure). A paradigm example would be research using just medical records, but observational research also includes direct observations of patients. Examples might include patients with a specified disease whose doctors choose to give them one treatment compared with those given another or observations of healthy people measuring disease outcomes in people who choose to smoke or not to smoke. However, in the former example, the treatment is openly agreed between the professional and the patient and represents the standard therapy (the best available in the view of the clinician). In experimental studies, the participants may be randomly allocated to receive one of two or more interventions being tested with (of course) consent in competent individuals. The advantage of random allocation is that the comparison groups so generated will differ only by chance[85] (see also [86,87]), whereas in observational studies people who take a particular treatment may, for example, be of higher socioeconomic status and thereby be less likely to develop a disease for other reasons related to their higher socioeconomic status (so-called confounding factors).

3.19 This broad categorisation may be difficult in individual cases. A study may involve no intervention yet involve invasive measurements (a study based on liver biopsies in heavy drinkers for example) or they may be experimental but minimally intrusive (a study measuring blood pressure after moderate exercise for example).

3.20 Research may also be classed as that making no direct contact with the participant at all (non-intrusive) – again such as medical records research – and contrasted with that which does involve interference: psychological intrusion, including intrusion on privacy, or physical invasion. Such interference always raises ethical issues warranting referral to a research ethics service. A variation on this classification is to consider research as non-interventional or interventional.

Therapeutic and non-therapeutic research

3.21 Another way of classifying research has been to divide it into therapeutic and non-therapeutic. In therapeutic research there are interventions which may benefit the individual participant; in non-therapeutic research such interventions are not intended to yield benefit and any benefit is incidental. Phase 1 research or patho-physiological studies usually fall into the latter category. The distinction between therapeutic and non-therapeutic research has been rejected by American and Canadian policymaking agencies as unsatisfactory: for example, it has been argued that where a protocol includes comparison with a (non-therapeutic) placebo intervention, it should not be considered by the more permissive standards for therapeutic research.[88]

3.22 A study could involve randomisation of patients to several standard treatments. Even if care is taken to ensure that patients' personal or clinical preferences for one treatment over another are taken into account, such studies should still be referred for ethical review.

3.23 Analogous to biological taxonomy, a simple hierarchy can be used to categorise most studies[89] (Fig 1).

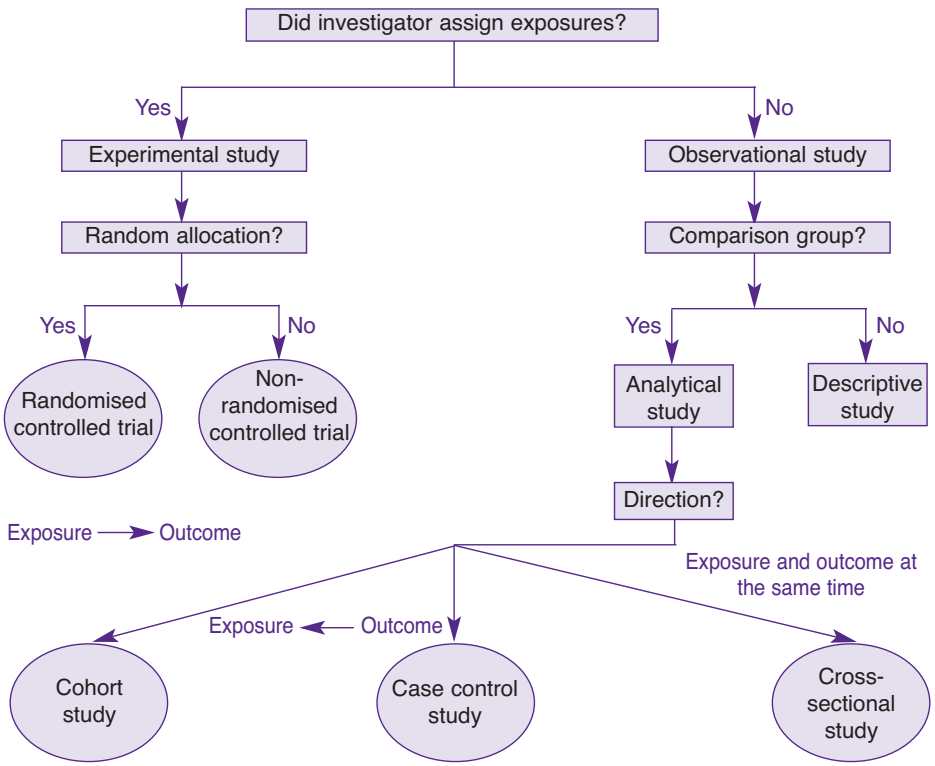


Fig 1 A simple hierarchy for categorising most studies. (Reproduced from Grimes and Schulz with kind permission of *The Lancet*).[89]

Design of trials

Experimental and observational research

3.24 Thus, in experimental research, the investigator assigns the exposure (eg the treatment), whereas in observational research usual clinical practice is usually observed. In the former, the exposure is best assigned by randomisation (with concealment of the upcoming assignment from those involved). Most trials randomise by individuals but some randomise by groups (eg by a general practice or an area) and are then termed cluster trials. In observational studies, there may be a simple description of the observed phenomena (descriptive). Descriptive studies may

- deal with individuals (case reports or case-series reports) or
- establish prevalence in a population or
- provide surveillance. Ecological studies describe associations between incidence or mortality of a disease (eg lung cancer) and an exposure (eg cigarette sales) across different populations (often different countries).

Observational studies with a comparison group are termed analytical:

- in a cross-sectional study a snapshot is taken at one time point
- in a cohort study a group of people, of whom some are known to have an exposure and others are known not to, are followed prospectively; the cohort may be identified at the present time or retrospectively from records.

By contrast, if the analytical study begins with an outcome and looks back for an exposure, the study is termed a case-control study.

3.25 An example may help to illustrate this. Suppose that it was proposed to examine the relationship of the oral contraceptive pill to deep venous thrombosis (DVT). Randomising women to either oral contraceptives or a non-hormonal form of birth control would represent an experimental study. Identifying a group of women who chose to take the oral contraceptive pill and a control group of women who chose not to, and following them for, say, five years and identifying those who developed a DVT would be a non-randomised prospective cohort study. Or one could go back in time to identify the cohort from general practice records – a non-randomised retrospective cohort study. Or the study could start with a group of women who developed a DVT (identifying them from hospital admissions) and a control group of age matched women who did not and determine whether the women with DVT were more likely to have taken the oral contraceptive than the controls – a case-control study.

Explanatory (exclusive) or pragmatic (inclusive) trials

3.26 Trials are often conducted under 'ideal' conditions in a homogenous group of participants (explanatory or exclusive trials). Concern is sometimes expressed that such results are not necessarily generalisable. Pragmatic (or inclusive) trials are advocated as reflecting routine clinical practice.[90] However, a relatively homogenous study population is not necessarily a disadvantage. The efficacy of many routine treatments has been demonstrated in clinical trials conducted mainly in white people for example, but there is usually no suggestion that the treatments may be ineffective in other groups (eg African or Chinese people). There are relatively few examples to the contrary – such as the varying response to some blood pressure lowering drugs between certain racial groups or differences between children and adults in the action of certain drugs (because of differences in drug metabolism). Most factors that cure or prevent disease are not selective: many treatments effective in humans are also used in veterinary medicine and many factors that cause human disease (eg tobacco smoke) do so in other mammals and in birds. A

treatment shown to be effective in one group of humans is likely to have similar efficacy in others in the absence of specific evidence to the contrary. A 'pragmatic' trial would need to be of enormous size to demonstrate statistically significant efficacy separately in several different ethnic or age groups. Nevertheless, both explanatory and pragmatic approaches can in principle create difficulties in their subsequent application. In the explanatory study, it may be uncertain how relevant the findings are to daily practice where patients are not well represented by the homogeneous population of the trial eg in age, gender[37] or co-morbidity. Similarly, in the pragmatic trial, there may be subgroups within the trial that may respond differently or not at all. Many trials represent a mixture of these features.[90]

Equivalence (non-inferiority) trials

3.27 In the classic, parallel group randomised trial, investigators hope to demonstrate a difference between two interventions – that one is better than the other. In doing so they reject the null hypothesis that there is no difference between the two. By contrast, an equivalence or non-inferiority trial seeks to demonstrate that a new intervention is similar to a reference intervention[91] – it would not really matter which intervention the patient received. A study cannot prove that no effect or no difference exists, because some uncertainty will always exist. Some threshold must therefore be decided, in advance, for what size of difference is clinically important.[92] What is the difference that would matter to the patient? Not: what tiny difference can be shown statistically? Or (conversely) not: what large difference can be failed to be demonstrated?

3.28 In practice, the selection of the non-inferiority margin is frequently an exclusively statistical one, whereas it should include clinical judgement. A difference between two interventions that is statistically significant may be too small to be of clinical importance. Alternatively non-inferiority margins may be too large to be clinically meaningful, ie the new intervention may indeed be inferior, so that the claim of equivalence becomes misleading. Claims of equivalence have been made on the basis of absolute differences as small as 1.5% and as large as 50%; or proportionate differences as small as 10% and as large as 400%.[93]

3.29 RECs must therefore ensure that clinical considerations have entered into the interpretation of significant difference.

3.30 Additionally, RECs should ensure that patients participating in an equivalence trial are informed that the trial is not expected to produce any real improvement in their health or the health of future patients. There may be risk of harm with little hope of an advantage and even if there were an advantage, the trial design may not detect it.[94] In equivalence trials, the hypothesis to be tested (and therefore refuted if equivalence is to be shown) is that one treatment is superior. If the trial is described in this way, it might be expected that only altruistic patients would participate because other patients may want to request the treatment that investigators assumed is better in their prior hypothesis.[95]

3.31 Equivalence studies may be used to compare medical protocols, surgical techniques or medical devices; to compare generic versions of innovator drugs or to show a new drug is as effective as a standard one but easier or cheaper to use (eg because of its more acceptable administration route or a lower cost to the public health budget). Equivalence testing may be entirely appropriate in such circumstances.

Qualitative research

3.32 Qualitative research or 'naturalistic inquiry' aims to study things in their natural setting, attempting to make sense of, or interpret, phenomena in terms of the meanings people bring to them. Examples include study of documentary accounts of events, analysis of narratives, passive observation, in depth interviews (one to one or in groups) to explore issues in detail, conversational analysis or focus groups. Qualitative research depends on the subjective experience of both the investigator and the research participant. It explores what needs to be explored.[96–101] Qualitative research is often hypothesis generating rather than hypothesis testing. In addition, understanding why people do what they do, rather than understanding only what they in fact do, can be crucial to good medical practice, eg a study on the reasons for non-adherence with medication can help to inform practice on prescribing.

3.33 The methodology of qualitative research is rooted in the social sciences and humanities, often in interdisciplinary fields. In the exploration of human experience there may be no single definitive truth and research questions are answered without numerical data.

3.34 Further guidance on qualitative research method is available from the Economic and Social Research Council (ESRC).[102] The ESRC Research Ethics Framework sets out the ethical standards expected by the Council and describes good ethical practice in social science research. Key principles of consent and confidentiality are essentially similar to other research areas, but many recommendations refer to non-NHS structures. At least one member of the REC should be familiar with these methodologies and the ESRC recommendations.

Patient preference trials

3.35 In some complex interventions, such as diet studies or behavioural therapies, the investigator may wish to compare interventions but cannot isolate the component that may be crucial to the anticipated difference in outcomes. Random allocation may only work if patients have no preferences for one particular intervention.[103–106] In such clinical trials participants may have a particularly active role.

3.36 In practice, patients may have strong preferences for one intervention.[107] They may participate because this is the only way to access it, or, alternatively, refuse participation to guarantee their choice of intervention outside the trial. The trial group may then not reflect the target population of all eligible patients.

3.37 Further, if selected for their preference, they may be educated or motivated to manage or adapt better. Any measured benefit may be unreliable due to psychosocial influences: patients may do better given treatments they prefer, compared with those who are unhappy about their allocation.

3.38 Such distortions may be increased by clinician preferences.[108] These may influence patient preferences and participation or impart enthusiasm for one intervention that leads to better compliance.

3.39 Preferences may vary in degree and with time.

3.40 There is no agreed consensus on how best to proceed when these issues arise.[104] One solution has been to establish patient preferences before randomisation, but, in contrast to Zelen designs (see 5.66), include those with clear preferences in the study. A detailed discussion

is beyond the scope of these guidelines, but RECs should be aware that trial design may be more complex in these circumstances.

Choice of research design

3.41 It is beyond the scope of these guidelines to describe the choice of research design, but some understanding of research design is essential in assessing the ethics of a study. The references quoted should guide the reader to a basic knowledge of why a study may be designed one way rather than another. Most guidelines state that all medical research, including the use of anonymous or confidentially kept records, must be subject to independent ethical review. This advice has implications for other groups such as non-medical bodies conducting research in, for example, nutrition and the social sciences. COREC/NRES has now (2007) introduced a scheme whereby tissue banks can apply for approval to supply tissue for research projects which comply with certain criteria and which would not then require further ethical review in addition to the tissue bank confirmation that they fit these criteria. See from section 7.36.

Confidentiality and consent

3.42 Data about the health of individuals should only be used for research under conditions of confidentiality that enjoy public support. Anxiety about public attitudes towards the use of health information in research has created disproportionate constraints on research, compromising its quality and validity.[109,110] However, evidence suggests that true refusal rates to inclusion in observational epidemiological studies are very low.[111,112] Similarly data suggest that while people want to control whether their samples are used for research, most are willing to contribute samples. Moreover most prefer one-time general consent to repeated approaches, on the understanding that a REC will review and approve future projects.[113]

Consent or anonymise

3.43 These issues have been the subject of a recent report from the Academy of Medical Sciences[114] as well as guidance from the Medical Research Council.[115] A policy of 'consent or anonymise' is not a legal requirement and can impede important research. Identifiable data may be used for medical research without consent provided that such use is necessary and is proportionate with respect to privacy and public interest benefits. Research with such identifiable data without consent falls under Section 60 of the Health and Social Care Act and advice should be sought from the Patient Information Advisory Group (PIAG) in England and Wales, but not in Scotland.

3.44 Seeking consent to use personal data may

1) be impractical, especially if individuals have moved or died
2) compromise effective population coverage
3) be perceived as likely to cause unnecessary distress or harm, especially if the research concerns a distressing condition or incident
4) lead to bias from self selection; and
5) prevent appropriately large studies.

Concerns around consent and confidentiality are dealt with elsewhere in these guidelines.

Information about research outcomes for participants and those responsible for their medical care

3.45 An investigator must inform others who may be responsible for the medical care of patients or healthy volunteers of their participation in experimental research (this may not be required in observational research). This will almost always require the investigator to notify the general practitioner when the patient is enrolled, with information about the possible medical implications of that involvement. We would consider it good practice to include the patient or participant information sheet in the information sent to the GP. Consent to transfer such information should normally be sought. In general, a patient's refusal to agree to notification of the GP may be a reason to compromise participation.

3.46 Wherever appropriate, of interest or practicable, the research participant should be informed of the progress and outcome of the research. Although sharing results may cause harm by creating anxiety or leading to unnecessary medical interventions, most participants find such information beneficial.

3.47 By sharing results, investigators are recognising people as participants rather than subjects and showing gratitude for voluntary participation.[116]

3.48 Information should be withheld if premature disclosure affects the scientific validity of the study or if it compromises the well-being of the participant or of a third party (eg information about paternity in a couple with a history of domestic violence).[117]

3.49 Results for the participant should always be disclosed, with consent, to a responsible individual such as the patient's GP or consultant so that appropriate action can be offered if risk to an individual is identified.

3.50 Participants should have the option of refusing information revealed in a study.[118,119] By contrast, investigators should not use informed consent procedures to request participants to waive rights to know results or to disclaim the investigators' ethical responsibilities. Information sheets should avoid such disclaimers without strong reasons. The onus is on the investigator to justify non-disclosure to the REC.

When non-disclosure is justifiable

3.51 If research data are difficult to interpret (eg a genetic marker with complex probabilistic interpretations), they may be of no clinical significance. Non-disclosure may be justifiable in this situation and should be advised in patient information materials. The results shared with patients may include both aggregate and individual results. The likely meaningful information should be identified by the investigator and the REC before the research starts.

Avoid unnecessary delays

3.52 Although the process of ethical review is independent of NHS trusts, it is desirable that ethical review is linked to trust research and development review to ensure unnecessary delays are avoided. Common application forms and the avoidance of duplication are, of course, desirable.

Patient perspectives

3.53 The role of lay people in the REC was recommended by the RCP in 1973, together with a definition of 'lay'. The RCP published an account of that role in its journal in 1991.[120] Since

then the lay role has expanded. Organisations such as medical charities not only fund much research but also play a role in its design.

3.54 This may be of value in many ways. Patients and the wider public have a role in helping to set the research agenda,[121–123] and may suggest highly productive lines of research not considered by professionals.[124] As the Research Governance Framework states 'participants or their representatives should be involved wherever possible in the design, conduct, analysis and reporting of research.'[125] Community-based participatory research[126] will demand particularly close strategies for academic and clinician engagement.

3.55 RECs may wish to inquire whether such input has been sought, particularly in the assessment of risk and in its description[127] in information materials. Risk is easily understated by investigators and may be inadequately understood by the REC.[128] Patient groups may have a valuable role here.

3.56 Familiarity with patient accounts[129,130] of research experience may lack a generalisable validity but emphasise the need for clear information. General information about the implications of research may be found in patient information leaflets in the JAMA patient page.[131–134]

3.57 INVOLVE is a publicly funded national advisory group promoting and supporting active research involvement. Its website (www.invo.org.uk) is a source of extensive information for the potential participant. Other consumer organisations include the National Cancer Research Network Consumer Liaison Group (www.ncrn.org.uk), the James Lind Alliance (www.lindalliance.org) and, in the USA, the Alliance for Human Research Protection (www.ahrp.org).

3.58 The REC should also be aware of the conflicting role when a clinician is involved in research as well as continuing clinical care.[45–47] The avoidance of all conflicts of roles between the clinician and an investigator would be ideal. In some cases (eg the collection of fetal material)[135] there is a mandatory separation between the clinicians caring for the patient who request their participation in research and the investigators. Patients can be vulnerable in their desire to please their doctors; there can be additional powerful psychological pressures on doctors to perform research. RECs should be aware of these conflicts of roles and, where possible, insist on separation and/or additional safeguards if the roles cannot be separated. These concerns may also be informed by lay involvement, not only on the REC but also in the research design.

3.59 To choose a patient's medication, or to alter, shorten or prolong it for the purpose of increasing enrolment in a study is unethical.

3.60 Apart from the potential conflict between research and clinical care roles, investigations in research studies may identify conditions or problems unrelated to the study. RECs should ensure that protocols address such issues and the extent, if any, of researchers' ancillary clinical care responsibilities[136] (see 2.25 and 3.36).

4 The legal background

RECs and legal opinion

4.1 The public will reasonably expect research involving human participants to be conducted in accordance with the law. It is not easy to envisage circumstances where an REC would approve a research project that infringed the law, eg EC Directive as implanted in the Medicines for Human Use (Clinical Trials) Regulations, Medicines Act, Mental Capacity Act, Data Protection Act, Human Tissue Act, Human Rights Act. (There are differences in Scotland with respect to the Human Tissue Act and Mental Capacity Act.)

4.2 RECs should avoid expressing a legal opinion and a protocol should not be given an unfavourable opinion on the grounds of its supposed illegality. Should a committee believe that a proposal contravenes the law, it should ask the principal investigator to seek further independent legal advice.

4.3 It should be made clear to investigators that the responsibility to ensure compliance with the law in each research project rests with them.

RECs are responsible to the UK Ethics Committee Authority

4.4 RECs are ultimately responsible to the UK Ethics Committee Authority (UKECA). UKECA consists of the four health ministers for the countries that make up the UK. Since 1 May 2004 the legal basis for the establishment of RECs is the EC Clinical Trials Directive (Medicines for Human Use (Clinical Trials) Regulations 2004). Before this there was no legal basis for RECs and their organisation was based on Department of Health guidance.

Harmonisation across Europe

4.5 A further measure to encourage harmonisation across Europe in the conduct of research has been the Council of Europe's 1997 Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine. This instrument lacks legal authority in the UK because it has not been ratified. It entered into force for signatory countries on 1 December 1999.

4.6 The appointing authority takes full responsibility for all the actions of members in the course of their duties as REC members other than those involving bad faith, wilful default or gross negligence (GAfREC 4.14). As RECs are not legally incorporated bodies, any action or claim is likely to be against members as individuals in respect of their own expertise.

Duty of care to research participants

4.7 RECs and the appointing authority almost certainly owe a duty of care to research participants that imposes upon them the obligation to take reasonable care to protect their interests. Failure to do so could lead to claims for negligence. Although no case has yet reached the courts in the UK, a case has been pursued in the USA.[137]

4.8 Under Regulation 16 of the Medicines for Human Use (Clinical Trials) Regulations 2004, the decisions of some RECs are open to review and appeal.

Indemnity for NHS employees

4.9 NHS employees serving on a REC are provided with indemnity for such work. Members who are not NHS employees should be issued with a form of indemnity on appointment (see SOPs 2.42). In the absence of such an undertaking, new members may wish to reconsider their participation.

4.10 Both sponsors and investigators must have insurance or indemnity cover to meet their potential liabilities arising from research.

Compensation

4.11 Under the Research Governance Framework, the research sponsor is responsible for ensuring that agreement has been reached about the provision of compensation for non-negligent harm. Any organisation, including the sponsor itself, offering such compensation must make the necessary financial arrangements and the sponsor should ensure that they are in place.[138]

4.12 The REC is required by the Clinical Trials Regulations to consider the provision for indemnity or compensation in the event of injury or death attributable to a Clinical Trial of an Investigational Medicinal Product (CTIMP), and any insurance or indemnity to cover the liability of the investigator and sponsor(s). This information is required in the REC application form.

Compensation following harm

4.13 If an accident occurs, the present legal position is that the individual (patient or healthy volunteer) who is injured is entitled to compensation if negligence on the part of the research worker or the team or a supplier of drugs or equipment can be shown (fault liability) or if it can be shown that the 'producer' has supplied a 'defective' product (strict liability under the Consumer Protection Act 1987). Since one of the purposes of medical research is to explore the unknown and to discover if there are any unforeseen or unforeseeable consequences of what is being investigated, accidents may occur despite the greatest care.

Ex gratia payment following injury

4.14 When an injury occurs, another means by which a participant or dependant might receive some compensation, whether or not negligence is alleged, would be by seeking an ex gratia payment from the sponsor of the research or the authority employing the researcher. The Consumer Protection Act 1987 reverses the burden of proof from the injured person to the manufacturer but is otherwise unlikely materially to alter the position in respect of research involving pharmaceutical products. This is because the manufacturer is allowed the 'development risk' or 'state of the art' defence, ie that the adverse effect was not predictable by currently known scientific tests. In addition, that a warning was given may also be taken into account in determining whether the product should be treated as 'defective' under the Act.

4.15 The situation regarding compensation for injury due to participation in research without legal proof of liability is currently unsatisfactory. Some issues await solution on a national basis and there is little that individual RECs can do about them. RECs should clarify whether indemnity arrangements cover negligent harm only or whether they extend to harm without admission of liability (non-negligent injury).

4.16 Arrangements for insurance and indemnity are addressed in SOPs (3.52–3.58).

4.17 Where research sponsored by an industrial company involves healthy volunteers or patients, clear guidelines exist and compensation is almost universally provided for both negligent and non-negligent injury.

4.18 The Association of the British Pharmaceutical Industry (ABPI) has published for its members guidelines on compensation for injury. These are advisory only and not all

pharmaceutical companies are members of the ABPI. In practice, however, these guidelines have always been honoured both by members and non-members.

4.19 In all studies in healthy volunteers sponsored by a pharmaceutical or other company, including those testing or sponsoring tests of industrial chemicals, cosmetics, instruments and appliances or devices, a contract which accepts liability regardless of fault should be used for each participant. A contract cannot be made without the agreement of both parties. The ABPI recommends a text for such a contract in its guidelines for medical experiments in non-patient human volunteers.

4.20 The ABPI provisions are satisfactory insofar as they provide for compensation by the sponsoring company for injury caused directly by participation in the study without the participant having to prove either negligence or that the product was defective in the sense that it did not fulfil a reasonable expectation of safety. These guidelines and contracts are also appropriate for use by non-pharmaceutical companies testing industrial or household chemicals or pesticides.

4.21 In studies involving healthy volunteers, the former Medicines Commission has recommended that there should be assurance in advance of adequate compensation without the need for the volunteer to show negligence. (In October 2005 the Medicines Commission was combined with the Committee on Safety of Medicines to form the Commission on Human Medicines.)

4.22 The legal situation for compensation for non-negligent injury in research funded by public sector bodies such as universities, NHS trusts or organisations such as the MRC, or originated by individual investigators, is much less satisfactory.

4.23 Public sector bodies may have difficulty in implementing a contract procedure or insurance policy for non-negligent injury compensation, although the MRC has stated that it will give sympathetic consideration to requests for ex gratia payments for non-negligent harm.

4.24 Most GPs are independent contractors with the primary care trust (or equivalent in devolved administrations). As such they must have their own personal indemnity. This also applies to many dentists, optometrists and community pharmacists. Staff employed by independent practitioners (eg practice nurses) will normally be covered by the practitioner's indemnity arrangements or through their own professional indemnity cover. Guidance on indemnity for GPs and other independent practitioners in primary care is available from the NRES website.

4.25 Detailed guidance has been issued by the NHS R&D Forum Primary Care Working Group and is available at www.rdforum.nhs.uk/workgroups/primary/indemnityarrangements.doc

4.26 NHS R&D Forum guidance recommends that the NHS care organisation will ensure appropriate indemnity arrangements are in place before giving management permission. RECs are not therefore required to seek separate evidence of insurance or indemnity cover for independent practitioners who are participating in research involving NHS patients. But where the research involves private patients, the REC is responsible for ensuring that appropriate indemnity arrangements are in place.

4.27 RECs should note that professional indemnity does not normally cover the responsibilities of chief investigators, where these go beyond normal care. Nor will it cover

clinical interventions, tests or investigations that are not accepted examples of normal care within the practitioner's clinical practice.

4.28 It is important that the situation regarding compensation for non-negligent injury is detailed in participant information materials.

EC Clinical Trials Directive (2001/20/EC)

4.29 European directives are legally binding in member states. The Clinical Trials Directive[139] defines a clinical trial as 'any investigation into human subjects:

- to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects
- and/or to identify any adverse reactions of one or more investigational medicinal products
- and/or to study absorption, distribution metabolism and excretion of one or more investigational medicinal products with the object of ascertaining its (their) safety and/or efficacy.'

As a result, all those involved in clinical trials now have their responsibilities, duties and functions governed by law. These responsibilities involve adherence to principles of good clinical practice.[140] The EC GCP Directive (2005/28/EC) was subsequent to the Clinical Trials Directive.

Mental incapacity; emergency research

4.30 The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) that implement the European Clinical Trials Directive permit research involving people lacking mental capacity in defined circumstances, with specific protections in place. The regulations set out the definitions and powers of personal legal representatives and professional legal representatives to enable consent to be given by an authorised proxy. In respect of emergency research, it was proposed[141] that initial entry into the trial should not be precluded by the lack of time for informed consent from a legal representative. Approval to this derogation from the letter of the Regulations (see MHRA, ref MLX326) has been authorised from 12 December 2006.[142]

4.31 In the Medicines for Human Use (Clinical Trials) Amendment (No.2) Regulations 2006 (SI 2006/2984), a clinical trial can take place in an incapacitated adult without the consent of a legal representative if

- treatment is required urgently
- and the nature of the trial also requires urgent action
- and it is not reasonably practicable to meet the conditions (eg obtaining consent)
- and an ethics committee has given approval to the procedure.

Regulation 3 amends the Adults with Incapacity (Scotland) Act 2000 consequentially. This was necessary as the EC Directive applies to the UK as a member state of the EU and not just to England, Wales and Northern Ireland.

Mental Capacity Act 2005

4.32 The Mental Capacity Act 2005 permits other (non CTIMP) research of an intrusive kind to be carried out on a person lacking mental capacity provided it is approved by an accredited REC. The Code of Practice to the Act contains a chapter on guidance on research.

4.33 The Act requires that the research must either have the potential for benefiting the patient without imposing a burden that is disproportionate to the potential benefits or be intended to provide knowledge of the causes or treatment of, or of the care of persons affected by, the same or similar condition.

4.34 This approach of balancing probabilities of benefits and risks, rather than assessing what is in the incapacitated person's 'best interests' is in keeping with the Adults with Incapacity (Scotland) Act 2000, which uses the word 'likely', while the European Clinical Trials Directive talks of expected benefits and risks. Where benefits are only likely to accrue to similarly situated patients, the excess risks to the research participant should be negligible, and there should be no significant intrusion into their privacy or freedom of action nor should the research be unduly invasive or restrictive.

4.35 Under the Mental Capacity Act, the investigator must consult with someone (other than in a professional or paid capacity) caring for or interested in the welfare of the prospective participant for advice on whether the incapacitated individual should take part. If the person consulted later advises that they believe that the individual would no longer wish to participate, then the participant should be withdrawn.

4.36 The requirement to consult described in 4.35 does not apply if treatment is urgent, but consultation should take place when conditions of urgency no longer apply.

Human Tissue Act 2004

4.37 The Human Tissue Act 2004 regulates removal, storage and use of human tissue – defined as material that has come from a human body and consists of, or includes, human cells. The Act extends to England, Wales and Northern Ireland. The criminal provisions in s.45 of the Act also extend to Scotland. Under the Act, the Human Tissue Authority, as part of its regulatory remit, issues practical guidance. This includes research guidance. Detailed information is available on its website (www.hta.gov.uk). (It has been proposed that the Human Tissue Authority is replaced by a regulatory authority for tissues and embryos.) See also section 7.

4.38 Where such tissue has been removed from a living person for the primary purpose of diagnosis or treatment, no licence is needed for research, but REC approval is required.

4.39 Where tissue is distributed to others (eg a tissue bank) or for a possible future project, a licence is required. No licence is required if a specific project is being undertaken, but in all cases REC approval is required unless the tissue is anonymous to the researcher and the bank has REC approval (see also 7.12).

4.40 A licence from the Authority is always required where tissue has been removed from the dead, along with REC approval.

4.41 The parallel legislation in Scotland is the Human Tissue (Scotland) Act 2006. The Scottish Act does not cover tissue removed from living people (other than for transplantation). The Scottish Act deliberately relies on 'authorisation' for removal and use rather than 'consent', the rationale being that only a person can consent or refuse on their own behalf. A relative or representative is merely giving authorisation for interference with the body.

Data Protection Acts, 1984 and 1998

4.42 The legal framework around the use of personal data in research involves UK legislation, especially the Data Protection Acts 1984 and 1998, case decisions, and European Directives (95/46/EC)[143,144] augmented by various guidance documents. The courts have not tested the legislation as it applies to medical research. This legal uncertainty has created difficulties for investigators.

4.43 The Data Protection Act established eight principles: see Box 1.

Box 1: the eight principles of the Data Protection Act 1998.

1 Personal data shall be processed fairly and, in particular, shall not be processed unless: at least one of the conditions in Schedule 2 is met, and in the case of sensitive personal data, at least one of the conditions in Schedule 3 is also met.

2 Personal data shall be obtained for one or more specified and lawful purposes, and shall not be further processed in any manner incompatible with that purpose or those purposes.

3 Personal data shall be adequate, relevant and not excessive in relation to the purposes for which they are processed.

4 Personal data shall be accurate and, where necessary, kept up to date.

5 Personal data processed for any purpose or purposes shall not be kept for longer than is necessary for that purpose or those purposes.

6 Personal data shall be processed in accordance with the rights of data subjects under this Act.

7 Appropriate technical and organisational measures shall be taken against unauthorised or unlawful processing of personal data and against accidental loss or destruction of, or damage to, personal data.

8 Personal data shall not be transferred to a country or territory outside the European Economic Area, unless that country or territory ensures an adequate level of protection for the rights and freedoms of data subjects in relation to the processing of personal data.

4.44 The Data Protection Act allows research using identifiable data that have been fairly obtained, provided those data are not used to make decisions about individual data subjects, their use would not cause substantial damage or distress, and they are not published in such a way as to enable identification of individuals. The relevant section concerning research is set out in Box 2.

Box 2: Data Protection Act 1998, Section 33 – research, history and statistics.

33 – (1) In this section:

'research purposes' includes statistical or historical purposes;

'the relevant conditions', in relation to any processing of personal data, means the conditions:

(a) that the data are not processed to support measures or decisions with respect to particular individuals, and

(b) that the data are not processed in such a way that substantial damage or substantial distress is, or is likely to be, caused to any data subject.

(2) For the purposes of the second data protection principle, the further processing of personal data only for research purposes in compliance with the relevant conditions is not to be regarded as incompatible with the purposes for which they were obtained.

(3) Personal data which are processed only for research purposes in compliance with the relevant conditions may, notwithstanding the fifth data protection principle, be kept indefinitely.

(4) Personal data which are processed only for research purposes are exempt from section 7 if:

(a) they are processed in compliance with the relevant conditions and

(b) the results of the research or any resulting statistics are not made available in a form which identifies data subjects or any of them.

(5) For the purposes of subsections (2) to (4) personal data are not to be treated as processed otherwise than for research purposes merely because the data are disclosed:

c) to any person, for research purposes only

d) to the data subject or a person acting on his behalf

e) at the request, or with the consent, of the data subject or a person acting on his behalf,

or in circumstances in which the person making the disclosure has reasonable grounds for believing that the disclosure falls within paragraph (a), (b) or (c).

4.45 Medical research using sensitive personal information without consent is allowed provided one condition in Schedule 2 of the Act is satisfied and one condition in Schedule 3.

4.46 The relevant condition in Schedule 2 is 'the processing is necessary for the purposes of legitimate interest pursued by the data controller or either party or parties to whom the data are disclosed, except where the processing is unwarranted in any particular case, by reason of prejudice to the rights and freedoms or legitimate interest of the data subject' (Condition 6(1)).

4.47 The condition in Schedule 3 is that 'the processing is necessary for medical purposes and is undertaken by (a) a health professional or (b) a person who in the circumstances owes a duty of confidentiality which is equivalent to that which would arise if the person were a health professional. In this paragraph 'medical purposes' includes the purposes of preventive medicine, medical diagnosis, medical research, the provision of care and treatment and the management of healthcare services (Condition 8).

4.48 The use of anonymised data for research is not regulated by the Act.

4.49 The Act does not relate to data on deceased persons.

Health and Social Care Act 2001

4.50 Section 60 of the Health and Social Care Act 2001 applies to England and Wales. It gives the Health Secretary powers to allow identifiable patient data to be used in specific circumstances without the patient's consent. These powers are specified by Statutory Instrument.

4.51 Under Section 61 a statutory body, the Patient Information Advisory Group (PIAG), drafts and administers regulations under Section 60. The Privacy Advisory Committee for Scotland serves a similar function to PIAG in considering and approving applications to use patient data for research purposes without specific consent. However, it is not established by statute and has no power to draft regulations.

Consent

Freedom of Information Act 2000

4.52 The Information Commissioner oversees the Freedom of Information Act 2000 and the Environmental Information Regulations 2004 in England and Wales, and the Data Protection Act 1998 for the whole of the United Kingdom. The Scottish Information Commissioner is responsible for enforcing and promoting the right to access public information created by the Freedom of Information (Scotland) Act 2002 and the Environmental Information (Scotland) Regulations 2004. The Information Commissioner has decided that, while obtaining consent for medical research involving identifiable personal health data is the default position, consent is not required where such access to the data is necessary (for example in a research protocol approved by an ethics committee), is considered proportionate and no more with respect to privacy and public interest, and where there is 'fair processing' (meaning that the patient should be informed of the data collection and have the right to opt out). Even informing the patient may be waived if the effort to do so is disproportionate, especially if the research is 'historical or statistical'.

4.53 There has been little case law with resulting uncertainty in the interpretation of data protection legislation. The first legal ruling on the interface between Freedom of Information and Data Protection was a Scottish case released on 1 December 2006. The Inner House of the Court of Session ruled in favour of the Scottish Information Commissioner's decision to allow a member of the Scottish Parliament access to 'perturbed' or 'barnadised' data about incidences of childhood leukaemia in southwest Scotland by age and census ward despite objections by the NHS Common Service Agency that the data remained 'personal data'.

4.54 The interpretation of these legal constraints on research is not the role of the REC, but of research governance structures. RECs should not overreact in ways that can stifle potentially valuable research by misinterpretation of the legal framework and presenting this as ethical objection.

Law on consent in adults and children

4.55 The law on consent in the competent adult requires voluntary agreement after the provision and comprehension of adequate information and is discussed from 5.21. The lawfulness of research in children has not been considered by the courts and is unclear. It has been held that a person with parental responsibility can consent to an intervention which, although not in the best interests of that child, is not against the interests of such a child. From

this has developed the idea that research which is not of direct benefit to such children may be lawful (with consent from a person with parental responsibility) if it is not against the interests of the child and imposes no greater than minimal burden. The Medicines for Human Use (Clinical Trials) Regulations, Schedule 1, part 4, lay out the conditions and principles which apply in relation to a minor. These are that:

- the minor has received information according to her/his capacity of understanding, regarding the trial, and its risks and its benefits
- the explicit wish of a minor who is capable of forming an opinion to refuse participation in, or to be withdrawn from, the clinical trial at any time is considered
- the clinical trial should relate directly to a clinical condition from which the minor suffers, or is of such a nature that it can only be carried out on minors, and
- there should be some direct benefit for the group of patients involved in the clinical trial.

Family Law Reform Act 1969; young people and consent

4.56 By virtue of section 8 of the Family Law Reform Act 1969 (England and Wales) people aged 16 or 17 are entitled to consent to their own medical treatment. Unlike adults, the refusal of a competent person aged 16–17 may be over-ridden by either a person with parental responsibility or a court. It should be noted that the Act concerns treatment and ancillary procedures, such as an anaesthetic, and not research.

The Gillick case

4.57 According to the ruling in the case of Gillick, children who have sufficient understanding and intelligence to enable them to understand fully what is involved in a proposed intervention will also have the capacity to consent to that intervention. As the understanding required for different interventions may vary considerably, a child under 16 may therefore have the capacity to consent to some interventions but not others. Again it is noted that this case law does not specifically concern research, although it might reasonably be applied, while acknowledging that threshold for understanding will vary according to the complexity of the research. Although 'Gillick competence' is now often referred to as 'Fraser competence' after judgement by Lord Fraser in the House of Lords, the two concepts are not identical.[145] Lord Fraser's guidance is narrower and relates only to contraception. See also section 8.11.

4.58 It would be unwise to include a child in a research project where the child agrees but the parents do not, notwithstanding the Gillick judgement.

4.59 In Scotland, the law is different and the Family Law Reform Act does not apply. Issues of consent are addressed in the Age of Legal Capacity (Scotland) Act 1991 and in the Children (Scotland) Act 1995. Children are considered mature at 16 and section 2(4) of the 1991 Act essentially embodies the ruling in Gillick for Scotland in respect of those under 16.

5 Ethical considerations

Validity and welfare

5.1 The dignity, rights, safety and well-being of actual or potential participants is the primary consideration in any research study. Their protection is the primary, though not exclusive, role of the REC (GAfREC 2.2; CIOMS guidelines p 25).

5.2 The initial considerations in the ethical review of research are those of *validity* and *welfare*. A study cannot be ethical if it is incapable of delivering a worthwhile result: at best it represents a waste of resources; at worst it creates an unjustifiable risk for participants. What counts as worthwhile is, of course, a social value – and hence the value of lay involvement in research planning. Invalid studies are unethical. As noted in 2.45–46, assessment of validity is not the primary responsibility of the REC.

Underpowered studies

5.3 Properly powered studies are ideal but too many underpowered studies may still be permitted.[146] Nevertheless, we believe that an underpowered study is not necessarily unethical. Pilot studies may be designed to assess practicalities, although using pilot studies in estimating effect size is likely to be unreliable; and in rare conditions,[147] an underpowered study may be better than no study at all. Low powered trials may contribute to a global effort when added to the results of others, especially if the trial is registered. Such meta-analyses require common methodologies for the studies. There is no harm to the patient provided these criteria can be met.[148] Underpowered trials do carry the obligation that prospective participants are informed that their participation may only indirectly contribute to future healthcare benefits. As noted above, student *projects* in particular may also often be underpowered. The REC should consider the prime purpose of such projects as being educational, although the concept of power should be understood and the student should appreciate why the sample size should be larger.

Equipoise and minimal risk

5.4 The welfare of participants is promoted by the application of two principles: firstly, depending on circumstances that of either *equipoise* or *minimal risk*; secondly, that of *consent*.

5.5 A more detailed exposition of what makes clinical research ethical has been proposed with seven requirements: value, scientific validity, fair selection of participants, favourable risk-benefit ratio, independent review, informed consent and respect for those enrolled.[149]

5.6 In clinical trials (*experimental* studies as defined in 3.18), each trial should begin with an honest null hypothesis, ie there is genuine uncertainty in the clinical community regarding the comparative merits of the intervention.[150] If an investigator *knows* that the interventions being tested are not equivalent for the individual participant, the superior treatment should be recommended. Equipoise implies that there is a balance of knowledge as to the outcome between the interventions being tested. If interim analysis or surveillance of adverse effects during a trial suggests that one intervention arm is superior, equipoise no longer exists. The trial may then need to be terminated and all patients offered the superior intervention. An independent data monitoring committee is helpful in making this judgement.

An ethical trial should aim to reduce or resolve uncertainty

5.7 We acknowledge that an individual investigator in a multi-centre study may have a strong opinion of the benefits of one intervention over another. In saying that 'we do not know' whether one intervention is better than another, it is not being suggested that 'no evidence leans either way'. The latter may create personal ethical difficulties for an individual investigator if a strongly held view is that one of the interventions is demonstrably superior. Theoretical equipoise, with expected benefits and harms identical, is overwhelmingly fragile,[151] perhaps more a theoretical concept than of practical help, disturbed by a slight accretion of evidence favouring one arm of the trial, when the odds that A is better than B differs from 50%.

5.8 Clinical equipoise is more complex,[150] as clinical choice rests on some combination of effectiveness, consistency, adverse effects, inconvenience etc. It exists where there is current or imminent uncertainty in the clinical community over what intervention should be preferred, ie there is an honest, professional disagreement among expert clinicians about the preferred intervention. An ethical trial should reduce or resolve this uncertainty. Progress in clinical medicine relies on progressive consensus within the medical and research communities, ie ethical medicine is social rather than individual in nature.

5.9 Some expert opinion prefers the term 'uncertainty' or 'justified uncertainty' or 'substantial uncertainty'[152] to that of equipoise. It has been objected that 'equipoise' implies that one can derive a measure of 'equality of effects', valid for every patient. On the other hand is the suggestion that 'uncertainty' is ambiguous in two respects. Firstly, knowledge comes in degrees and therefore uncertainty includes many possibilities; secondly, in circumstances where a known side-effect of treatment must be traded-off against possible benefits, uncertainty may relate, not only to the prior probabilities of these benefits but also to how they are valued. Uncertainty therefore means different things depending on context. Equipoise, on the other hand, implies that the expected size and probability of improvement balance the size and probability of side effects of comparator treatments. Equipoise provides a clear goal to aim at, in contrast to the ambiguous term 'uncertainty'.[153] Debate on this issue has been extensive.[154–159] Whichever term is used, the aim is to indicate that it is difficult to judge which intervention would be better for the individual patient.

Definition of risk

5.10 Equipoise implies some balance between the benefits and risks of participation in the study. In phase 1 studies in healthy volunteers or in patho-physiological studies of the effects of disease or perturbations in various physiological states, there can be no benefit. Similarly, in non-therapeutic, observational and qualitative research, many studies may create inconvenience such as answering questionnaires, and intrusive questions with no possibility of benefit. By definition, equipoise cannot exist in these situations. Ethical justification rests upon the alternative consideration of *minimal risk*.

5.11 Minimal risk has been defined as a risk for which 'the probability of harm or discomfort anticipated ... are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests'.[160] These risks vary enormously. In research, the risks to which people are allowed to subject others should be regulated, as opposed to those risks that people choose to take for themselves.[161]

5.12 Another definition is that 'a risk has ceased to be minimal where there is a risk that makes one stop and think'.[162]

5.13 The Council of Europe suggests that: *the research bears minimal risk if it is to be expected that it would result, at the most, in a very slight and temporary negative impact on the health of the person concerned.*[163] We believe that this is the most acceptable definition in practice.

5.14 The Royal College of Paediatrics and Child Health defines *minimal risk* for research involving children as procedures such as questioning, observing, and measuring children provided that procedures are carried out in a sensitive way, and that consent has been given.[164] They include collecting a single urine sample or using blood taken as part of treatment. *Low risk* refers to procedures that cause brief pain or tenderness, and small bruises or scars. The RCPCH notes that low rather than minimal risk may be incurred by injections and venepunctures for many children. An understanding of the reason for venepuncture, willingness by both child and parent/guardian and the use of local anaesthetic cream may allow a blood sample to be taken. *High risk* in children includes procedures such as organ biopsy, arterial puncture and catheterisation and should never be considered without a diagnostic or therapeutic purpose besides research.

Use of placebos

5.15 Placebo-controlled studies raise questions about both equipoise and minimal risk. Where there is no proven therapy for a disease, a trial with a placebo control may be in equipoise, but in other studies considerations of minimal risk will determine whether a study is ethical (see 6.9).

5.16 The nature of risk and its communication in routine practice, as opposed to research, has been the subject of much comment,[127] including a theme issue of the *BMJ* (27 September 2003). REC members may find the practical guidance offered there helpful in assessing whether the presentation of risk meets an acceptable ethical standard. A systematic review of publications on equipoise and risk in clinical trials has been published by the Health Technology Assessment programme.[165]

5.17 We acknowledge that risk may be underestimated by professionals and RECs should take care to assess the evidence that risk is indeed minimal.

Equipoise or minimal risk should be present

5.18 Equipoise (or minimal risk) is the first consideration in assessing the ethics of research for two reasons. Firstly, depending on the nature of the study, if either equipoise or minimal risk is not present, then there should be no invitation to the potential participant. Consent cannot make a trial ethical if criteria for either equipoise or minimal risk are not met. Secondly, in research studies involving incompetent individuals or in emergency research, the principle of equipoise (or minimal risk) may be the best or only principle according to which the participant is protected as consent may not be possible. Proxy consent is valuable but limited in its capacity to indentify the potential participant's best interests and even this protection may not exist in emergency research.

5.19 When a study is in equipoise, a participant may still be subject to a high *absolute* risk: for example, in a study of a new major surgical technique or of a new therapy for a life threatening condition. However, the *relative* risk of study participation should be low or non-existent. This may be expressed as an acceptable risk:benefit ratio.

5.20 When there is no possibility of benefit, absolute risk should always be low.

Consent

5.21 If the principle of equipoise (or minimal risk) is predicated upon the moral principles of beneficence and non-maleficence, then that of consent is based upon a doctrine of respect for persons or *autonomy*.

5.22 With few exceptions (eg in child abuse research), participants should always be made aware that they are involved in research, although to ensure this can sometimes be difficult or even impossible, eg in community projects or with children or people suffering from mental disability, or in medical emergencies.

5.23 The impracticability of giving full information has led to the saying 'there is no such thing as informed consent'. While sharing with the patient all that is known about a drug or the full rationale for a study would clearly take an impossible amount of time, this criticism is most easily rebutted by stressing that it is *adequate* or *sufficient* information that is required. The difficulties of what counts as adequate information are recognised in the various ways used to obtain consent.

5.24 Such information enables the patient to assess the complex factors that enter into choice and whether equipoise exists for them, ie personal, individual equipoise.

When disclosure of information might be unjustifiable

5.25 Where it is the investigator's medical opinion that disclosure of information that would be adequate for consent would be so *harmful* that it would be unjustifiable, this must only be a decision about *individual* patients in therapeutic research. In addition the option must be approved by the REC. Approval to withhold information can be justified only in exceptional circumstances.

Situations requiring deception

5.26 The need for significant deception arises infrequently in biomedical research but more often in psychological research as part of the experimental design. Such deception should carry no more than minimal risk of harm. Moreover the investigator must convince the REC that such a method is essential and that the deception would not inappropriately encourage participation of a reasonable person.

5.27 The British Psychological Society (BPS) suggests that there is a significant distinction between withholding some of the details of the hypothesis under test and deliberately falsely informing the participants of the purpose of the research, especially if the information given implied a more benign topic of study than was in fact the case.[166]

5.28 In order to be acceptable, it should be standard practice, after the experiment, to explain the reason for the deception. The BPS advises that in some circumstances the verbal description of the nature of the investigation would not be sufficient to eliminate all possibility of harmful after-effects. For example, an experiment in which negative mood was induced requires the induction of a happy mood state before the participant leaves the experimental setting.

Information to participants

5.29 In randomised trials, patients should be told 1) that a trial is in progress; 2) that they will, if they consent to participate, be given either the standard treatment or one which may prove to be better or worse, (or the standard treatment plus something new versus the standard treatment); and 3) that their treatment will be chosen by chance (random allocation). Studies have shown that the concept of randomisation is often poorly understood by research participants. Randomisation by the individual doctor does not occur in routine medical practice, so special care must be taken to explain this concept.[167–170] They must also be told of any risks inherent in their taking part.

5.30 For consent to be valid, it must be given voluntarily by an appropriately informed person (the research participant or where relevant someone with parental responsibility for a person under the age of 18) who has the capacity to consent to the intervention or observation in question.[171]

Adults or children who lack capacity

5.31 The Department of Health guidance notes that the 'lawfulness of medical research on adults or children who lack capacity has never been considered by an English court and therefore no definitive statement of the law can be made.' Nevertheless, the EC Clinical Trials Directive, as incorporated in the Medicines for Human Use (Clinical Trials) Regulations 2004, and the Mental Capacity Act 2005 Code of Practice give some statutory guidance for England and Wales. It is probably the case that the same would apply in Scotland.

5.32 Consent has information elements: a) disclosure of information in an appropriate form; and b) comprehension of information.

5.33 Consent also has purely consent elements: a) voluntariness; b) competence; and c) the ability to make a decision and communicate it

5.34 Consent is best considered as a process rather than an event. Individual judgements about information may change and participants should always be assured of the right to withdraw from a research study without personal detriment.

5.35 The same principles apply when seeking consent from patients for research purposes as when seeking consent for investigations or treatment. However, as research may not have direct benefits for patients involved, the GMC states that 'particular care' should be taken to ensure that potential participants have the fullest possible information about the proposed study and sufficient time to absorb it.[172] These issues are outlined in the Department of Health's *Reference guide to consent for examination or treatment.*[171]

5.36 Investigators are responsible for adequately counselling research participants by word of mouth and by written material approved by the REC. But there are areas of particular complexity and sensitivity, such as research in human reproduction, where it may sometimes be appropriate to appoint a special person to act as independent counsellor to the participant. The investigator or the committee may propose this.

5.37 Information may be given orally or in writing. This includes use of audio or video recordings.

5.38 In many studies, including all experimental studies, written information sheets should be made available to the potential participant. The standard for these is set out in guidance from COREC/NRES available online. Nevertheless, a study does not become unethical because the patient information sheet does not follow the COREC/NRES template. A shorter sheet may sometimes be more appropriate or an alternative layout may be equally acceptable ethically.

5.39 In emergency research (eg stroke or heart attack) there may sometimes be a very short window of opportunity in which to seek consent. A brief information sheet with four or five bullet points may then be helpful. The last of these should always refer to the definitive information sheet which should be supplied at the same time for later study.

5.40 Patient support groups may have a special role in reviewing and revising information sheets to ensure comprehensibility. It is unwise to submit an information sheet to the REC

that has not been assessed by lay opinion. We suggest that a panel of lay people to review information sheets before submission might avoid many delays occasioned by relatively minor changes currently requested by RECs. Professionals often use jargon or English that is unnecessarily complex or unreadable.[173,174]

When the investigator is not a member of the healthcare team involved in clinical care

5.41 Recruitment of research participants may create particular difficulties when the investigator is not a member of the healthcare team involved in clinical care. In such circumstances, it should be normal practice for the invitation to the potential participant to originate from a member of the healthcare team, seeking consent to pass details to the investigator. We acknowledge that using the current data controller may be unsatisfactory: for example, the general practitioner as a proxy to contact the patient and invite him or her to contact the investigator. However, it is necessary to show conclusively that it is impractical to obtain consent to release of identifiable information and that a high non-response rate will reduce the scientific validity of the study in order to obtain support by Section 60 of the Health and Social Care Act 2001[175] (see 7.23–7.24).

Avoiding causing distress

5.42 When contacting potential participants it is important to avoid inadvertently causing distress to them or their families. Checks should be made 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).[176]

Questionnaires

5.43 Questionnaires may be sent out with a simple introduction at the start of the questionnaire. Where a questionnaire is simple, its return may be adequate to indicate consent.

Protecting the privacy of family members and social contacts

5.44 Obligations to protect the confidentiality within the professional-patient relationship are well established, but additional considerations arise through family and social relationships. By providing personal health and family history information, a primary research participant may reveal sensitive information about family members or other social contacts. Such personal data may be retained without the consent or even knowledge of the individuals concerned. To this degree, readily identifiable family members could be considered secondary 'research subjects'.[177]

5.45 Although such information may be unreliable, if it is not generally available (eg family relationship) a breach of privacy is involved that could constitute more than minimal risk. Obtaining informed consent from numerous family members may be impractical and a hindrance to valuable research. In such circumstances, RECs should ensure that a risk of a breach of privacy is extremely small and that any health information disclosed can be addressed appropriately.

Information sheets

5.46 Information giving may present particular problems to children, and to those with sensory impairments or language difficulties.

Information for those with difficulties of comprehension

5.47 It has been estimated by the British Dyslexia Association that around 2 million (or approximately 4%) of the UK population are severely dyslexic (see: www.literacytrust.org.uk). In addition, those registered blind number 157,000 and those with significant visual difficulties over 200,000. Around a quarter of blind and partially sighted persons also have hearing loss.

5.48 Hearing impairment is also common. There are about 9 million deaf and hard of hearing people in the UK (55% of those aged over 60) with 698,000 people severely or profoundly deaf (www.rnid.org.uk).

5.49 Research participants with such sensory difficulties are often overlooked by RECs. These problems are more common than those of the non-English speaker. They can be addressed by use of visual or audio recordings and we would encourage these techniques to be more widely considered. In general, the outlay should be small and within the budget of most research projects.

Language

5.50 Apart from the special case of Welsh and the provisions of the Welsh Language Act, the ethically important issue with language is the failure to understand English, rather than the first language of the participant. Many professional translators, for example, may not speak English as a first language.

5.51 Estimates of the numbers of people in England who have difficulties with the English language vary widely from 400,000 to 1.7 million.[178] In the case of adult refugees, for example, the ability to understand spoken English is more often absent than present. This inability is a key barrier to citizenship under the British Nationality Act 1961, to employment, education, access to services and to a full role in society.[179] The latter includes participation in research.

5.52 Where translation is necessary for informed consent or other aspects of a research study, accredited translators should be used wherever possible, ideally trained to the Institute of Linguist's (www.iol.org.uk) Diploma in Public Service Interpreting (DPSI) standards or equivalent. [180]

5.53 Investigators working with interpreters may themselves need a short training course to achieve best practice.[181] For example, use of translators inevitably involves the disclosure of information to third parties. The investigator must therefore begin by assuring the patient of the confidential nature of the exchange and seeking consent to the use of the translator.[182]

5.54 Telephone interpreting interrupts flow and is not conducive to rapport; nor does it allow any checking on the quality of the translation. On the other hand, the anonymity of a telephone translator may be comforting in small or closely knit ethnic communities, where the presence of a potentially known third party may inhibit communication. Details are available from 'Language Line Services' (www.languageline.co.uk)

5.55 The use of family members raises similar concerns as the presence of a third party translator. Confidentiality is compromised and family members are often unprepared to deal with the complexity required by medical information. This may be compounded by the possibility that the translator may either persuade or dissuade participation rather than informing. The accuracy of the translation is one reason for using an accredited translator with DPSI qualification. (One study showed that between 23% and 52% of words and phrases were incorrectly translated by ad hoc interpreters.[183])

5.56 It is unreasonable to expect every research team to produce information in all languages spoken in multicultural Britain and, if necessary, to produce it on audiocassette where there is a chance that the potential participant may not be literate.[184] A counsel of perfection will

place an unrealistic burden on many research studies with limited resources. In particular, it is noted that many questionnaires may be validated in few languages or only in English. Demanding validation of such materials is not a realistic request for the REC to make and recruitment of participants may therefore need to be limited to those understanding English.

Ethnicity

5.57 Ethnicity and the ability to speak English are, of course, separate. Nevertheless, the exclusion of non-English speakers may bias the study population and the validity of outcomes in some studies – for example, in surveys of use of healthcare resources.

5.58 In summary, it is a principle of distributive justice that benefits and burdens should be shared. While the inability to speak English may create a vulnerability that may be difficult to overcome, RECs should encourage pragmatic solutions that encourage investigators to adopt inclusive strategies of recruitment wherever possible, while acknowledging that the ideal may sometimes be impractical.

Competence and capacity

5.59 Competence and capacity may be difficult to asess. Vulnerability in non-cognitive mental illnesses, for example, is typically a result of social stigma and threats to the ability to make a free and voluntary choice, more than to impairments in capacity.[185] Guidance on the assessment of capacity is available from the BMA/Law Society[186] and the Mental Welfare Commission for Scotland (see also 5.31). It is desirable that investigators check understanding and protocols may need to specify how this should be done.

5.60 Informed consent to participation in clinical studies should be the norm. New therapies may offer new benefits, but unknown hazards and inconveniences also face participants. Volunteers must therefore have accurate information about both potential risks and benefits of research. Our abilities to deliberate, to choose, and to plan for the future are the focus of the dignity and respect which we associate with being autonomous people, capable of participation in civic life.

5.61 It may be suggested that some patients may not want full disclosure of information, but still wish to be included in trials. Similarly some patients may not read the information materials which they have been given. In these situations, investigators must judge what constitutes adequate or sufficient information for consent. It would not be acceptable to proceed on the basis of no knowledge at all.

5.62 It must be recognised that how consent is sought may influence the choice that is recorded. Potential participants may agree or disagree to consent simply to end the interview or avoid reading a lengthy information leaflet. The REC will need to judge how best to structure information delivery to optimise participation in the consent process, eg use of summary sheets or breaking the process into discrete segments in complex studies.

Opt in/opt out consent

5.63 In 'opt in' consent, the potential participant must actively choose to take part; in 'opt out' consent, the individual becomes a participant unless they choose not to take part. In either case the potential participant is informed about the study. The use of 'opt out' consent may form part of observational studies in particular when it may be a more efficient method for participants and investigators.[187] Opt in recruitment strategies may result in lower response

rates and a biased sample.[188] Where opt out strategies are being used, a general notice should be displayed in the clinic or the surgery, where possible, indicating that research involving anonymised medical records or left over samples is being conducted unless you (= the patient) opt out.

5.64 Consent should normally be recorded in a consent form. Copies will be retained in the research record, in the patient's case notes (where applicable) and a copy given to the participant.

5.65 Where the participant has difficulty understanding or where there are special considerations such as vulnerability, the form is best counter-signed by a witness. The witness confirms that the signature is that of the participant and that it is made freely. The witness does not confirm that information has been understood. For this reason, a witness is best selected as someone who is independent of the study.

Consent after randomisation

5.66 In most RCTs, consent is sought before randomisation. In Zelen's design,[189–191] patients are randomised *before* consent has been sought. In the first (double) version (Z1), patients are initially offered the treatment to which they were randomised. If they decline the randomised treatment they can then be offered alternative therapies, including the experimental treatment. In the second (single) version (Z2), only patients offered the experimental treatment are told there is an alternative treatment (the control) available. Patients randomised to the control treatment are not allowed the experimental treatment.

5.67 Zelen's design has been chosen when it was considered preferable not to raise false hopes of a novel therapy only for the hope to be dashed by randomisation in half those approached eg in a trial of extracorporeal membrane oxygenation in infants.

5.68 The design may also be useful in population-based interventions such as screening if knowledge of the trial in the non-screened group induces changes in that group which may influence outcomes eg in a trial of bone density screening, this might have increased use of hormone replacement therapy in the control group without Zelen's design.

5.69 Although patients are randomised without consent, treatment consent will continue to be sought. Nevertheless, there are strongly expressed ethical (as well as statistical) objections to the Zelen design. Ethically, information is withheld for the sake of the trial and not for the sake of the patient. Statistically, unless no one refuses participation, more people must be recruited than in a conventional design to get the same result – a problem which worsens as refusals increase. Ethically this puts pressure on clinicians to keep refusal rates down.

5.70 We note the complexity of these debates. Pre-randomisation without consent is infrequently used, should never be used unless there are plausible harms to be avoided and the reasons should be explicitly examined by the REC.

Consent and cluster trials

5.71 In cluster (or group or community) randomised trials, clusters of people or intact social units, rather than individuals, are randomised to intervention and control groups. Outcomes are measured on individuals within those clusters.

5.72 Cluster randomisation may be used when the intervention has to be administered to and affects entire clusters of people as opposed to individuals within that cluster.[192] It is commonly used in trials of population screening (such as mammographic screening for breast cancer). With individual randomisation, people offered screening may talk it over with neighbours who are allocated no screening, who then feel resentment or seek out the screening themselves. As another example, people subjected to a health information package may talk it over with control participants, who may then adopt the experimental recommendation.

MRC guidance on cluster trials

5.73 The Medical Research Council has published guidance on *Cluster randomised trials: methodological and ethical considerations.*[193]

5.74 Some interventions in cluster randomised trials are received by the whole cluster. The decision is made by the investigator(s) and individual consent is not possible. For example, a study of fluoridation of the water supply or the showing of information videos in a practice waiting room. Even if an individual wished to refuse consent, the intervention might still be received.

5.75 Where individual consent is not possible, this places a particular responsibility on RECs to ensure that standards of equipoise are met.

5.76 In other cluster studies, individuals may not be able to avoid participation in the intervention, but may, for example, be able to consent to collection of samples or information.

Cluster representation mechanism

5.77 The MRC has suggested that a 'cluster representation mechanism' (CRM) is required to represent the interests of the cluster. Its role is envisaged as analogous to that of individuals for individual decisions. It would have, for example, the right to determine participation or to withdraw the cluster if the trial was no longer in the best interests of the community. Elsewhere this has been termed the 'guardian'.[192] A CRM might be the chief executive of a healthcare trust, a head teacher or the senior partner of a primary care practice or an appropriate representative group.

5.78 The CRM may have a scientific interest in the results as well as a benevolent concern for the welfare of the cluster. Like healthcare professionals in individual clinical trials there is the potential for conflicts of interest.

5.79 Procedural safeguards in cluster studies should be commensurate with perceived risks. For example, the protocol might include the possibility of consulting members of the cluster if the intervention is controversial or culturally sensitive.

5.80 If a reason for a cluster trial (where there is individual consent for active participation) is to avoid contamination, informing controls about randomisation may produce the effect that cluster randomisation was designed to avoid. One option is then to randomise to the control group without informing the participant – a group parallel to the Zelen design discussed above (5.66). The controls continue to receive routine care and do not know that they could have received experimental treatment. The acceptability of this should be determined by the REC according to the exact proposal.

5.81 The nature of the CRM will vary depending on the nature of both the cluster and the intervention, but the REC's approval would be contingent on the CRM confirming that the trial was in the interests of the cluster. On occasions, it may be appropriate for some form of

community consultation[194,195] to be organised to assess the acceptability of a study, even when this is observational in nature. Those consulted should be in a position to speak on behalf of the community or to reflect its views. Investigators should have adequate time and resources to discern how the study population is organised socially and politically and which groups can best speak with authority for the population.[196]

Consent and open-label extension studies

5.82 Open label extension studies should always be submitted to the research ethics service for review, and treated as a new submission if not detailed in the original protocol.

5.83 Patients finishing a double-blind, randomised trial are often requested to take part in an extension study.[197–199] This usually commences while the feeder study is still in progress or has not been analysed. Thus participants who took the new agent will continue to receive it, while those on placebo or standard therapy cross over to the new agent. Obviously, there will be continuing uncertainties about the efficacy or toxicity of the new study drug at this point.

5.84 Open label extension studies may provide information about longer term adverse effects. However, we note that most adverse drug effects tend to occur within the first three months of taking a drug, although a significant minority do occur later. Moreover establishing causality in an open label extension study may be difficult with no comparator group.

5.85 Open label extension studies may help to assess whether drug effects are cumulative or decline or whether those who cross over 'catch up'.

5.86 There may of course be commercial benefits in accustoming clinicians in the prescription and use of a drug ahead of licensing and normal availability. This is not a valid ethical justification for an open-label extension study.

5.87 While the possibility of an open label extension study may be described at the outset, consent to participation should always be sought independently towards the conclusion of the feeder study.

5.88 Whenever possible, it is preferable to unblind the patient before seeking such consent. We acknowledge that methodologically this may not be desirable.

Benefits may be from standard or placebo therapy

5.89 Where unblinding is not possible and as part of the consent process, it is therefore essential that patients are advised that their experience in the trial should not be used as a guide to their decision to participate in the extension study. Patients who have benefited in the trial may have done so from standard or placebo therapy; while those with adverse outcomes may have done so with the new agent or placebo through the mechanism of symptom suggestion during informed consent procedures. This must be clearly understood for valid consent.

5.90 Due to delay between trial completion and drug licensing, both patients and doctors may want to continue the drug outside the randomised trial. Prescribing a drug on these compassionate grounds is not primarily based on research considerations. The REC should not therefore approve the extension study on compassionate grounds as it has no authority, expertise or responsibility for decisions about clinical practice.

5.91 RECs should also be aware of the potential for extension studies to be confused with marketing. Open label extension studies that specify 'until licence approved', for example, may be more concerned with promoting the use of the study drug.[198,199]

5.92 RECs will also need to judge that standards of equipoise can be met for the longer period envisaged by the extension study.

Multinational research protocols

5.93 RECs may be asked to consider research protocols involving other countries. Care should be taken in trying to impose ethical normative frameworks developed within the UK on other cultures. It is sometimes said that where there is a disparity between the ethical review requirements of a UK REC compared with those (if they exist) in another country, the higher ethical standard should be imposed. The common implication is that the UK REC requirements represent the higher ethical standards. However, certain aspects of ethics review, such as consent and confidentiality, may be culturally dependent, and approaches in some countries which would be inappropriate in the UK may be morally acceptable in other countries. For example, in some less developed countries it would be the norm that a husband or a community leader must give consent for a woman to have treatment or to be approached to take part in research. However, CIOMS guidelines state that 'in no case…should the consent of a community leader or other authority substitute for individual informed consent'.

Research and HIV tests

5.94 In 2005, the Association of British Insurers implemented a new *Statement of best practice on HIV and insurance* (available from www.abi.org.uk). This guidance addresses the misconception that simply taking an HIV test will have a detrimental impact on insurance applications.

5.95 All life and protection insurance applicants are now asked a general HIV risk question: 'Within the last five years have you been exposed to the risk of HIV infection?' Many companies ask separate questions about risk-related behaviours (eg drug abuse) or include examples of increased risk in their question. However, the applicant 'will not be penalised by life insurance companies if they have taken an HIV test.' There is also no requirement to declare 'negative' HIV tests, nor are GPs required to inform insurers of negative tests that have been taken (see also 9.16).

5.95 Prospective research participants required to undergo HIV tests can therefore be reassured that participation in research does not affect insurance status.

6 The use of placebo in research

Descriptions of placebo interventions

6.1 This guidance addresses the use of placebos in research. It does not discuss their use in clinical practice. Use of placebo in clinical trials is sometimes controversial and has given rise to a substantial literature.[161,200–205]

6.2 The word 'placebo' comes from the Latin meaning 'I will please'. Its use is based on the observation that the administration of treatment, even without active properties, may have some beneficial effect. About a third of patients may show a positive response to treatment with a placebo. In conditions where there may be a significant psychological or emotional involvement, the response may be much higher.[206]

6.3 A placebo may be any kind of intervention as long as it is without intrinsic therapeutic effect. Examples include pills or injections containing some inert substance; a machine that has not been switched on, as in trials of trans-cutaneous electronic nerve stimulation (TENS); sham surgery, to the extent that incisions have been made, sutured and dressed but no operative procedure has taken place; or psychological interventions such as conversations that lack key counselling features. In every instance it is assumed that administering some intervention may alleviate a feature of the condition, either subjectively or objectively, such as the response of blood pressure.

6.4 The reality of the placebo effect has been questioned. A large Danish systematic review[207] analysing 114 studies has been reported as failing to find any significant difference between patients receiving no treatment and those receiving placebo. However, the paper divided outcomes into those with a binary distribution and those with a continuous distribution. For the binary distribution the meta-analysis showed that placebo was about 5% better than untreated controls – a difference that was almost, though admittedly not quite, statistically significant. Perhaps spontaneous recovery is underestimated: left untreated many people get better anyway. The placebo effect may sometimes be overestimated.

6.5 When there is genuine uncertainty in the clinical community about the superiority of a treatment over another treatment – or over no active treatment – the patient could ethically be randomised to either. This is the implication of equipoise (see 5.6–5.8).

6.6 In this situation use of a placebo is both ethically defensible and desirable in research. There is no proof that the new treatment is better or worse than placebo but there is an obligation to ensure that any apparent benefit from the new treatment is real and not just a placebo effect.

6.7 In general, when a standard treatment already exists, a new treatment should be compared with that treatment. Using placebo where a standard therapy exists implies risk to the patient's well-being in the pursuit of science. This may be unethical (see below).

6.8 However, it has been common practice to use placebo-controlled trials in conditions for which there are standard, effective treatments.

Declaration of Helsinki 2000

6.9 The debate regarding the use of placebo where active treatments already exist arose from placebo-controlled trials of anti-HIV agents in Africa. These debates led to a new draft of the Declaration of Helsinki in 2000. Paragraph 29 of the new draft stated that:

6.10 'The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.'

6.11 The implication was clearly that, where an effective treatment did exist, comparison against placebo should not be permitted. This provoked further debate and, in 2002, the World Medical Association (WMA) issued clarification:

Permissive clauses regarding the use of placebos

6.12 'The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm'.

First permissive clause

6.13 The first permissive clause (6.12) calls for 'compelling and scientifically sound methodological reasons'. As noted in 6.2, the placebo response may vary considerably in different conditions and populations. In headache research, for example, as many as 75% of recipients may show some placebo response.[208] When estimating the efficacy of a new treatment, it is important to know how much of the apparent success may be the result of placebo effects. If the comparison was with standard treatment, and in both arms there was a substantial placebo response, the therapeutic effect of the drug might account for a relatively small proportion of the effect, and an important difference could be overlooked.

Second permissive clause

6.14 Secondly comparison with placebo may require fewer participants. Detection of a small difference between two interventions requires a comparatively large number of outcomes to give the required level of confidence; a larger difference can be detected more easily and so needs fewer participants. An effective drug should show a clear advantage over placebo, but may show only a modest improvement over the standard treatment. In a placebo trial, a larger difference can be predicted, and the trial would require fewer participants. Ethically this has some benefits. Participation in a trial inevitably involves some cost and some risk, if only minimal, and it is desirable to recruit the smallest number of people necessary to give sound information. In addition to exposing a smaller number to risk and inconvenience, a smaller sample can be recruited more quickly. The results of the trial will be available sooner, so that any therapeutic advance can be introduced into practice faster and more patients will benefit. The financial and opportunity costs of the trial will also be less, so that resources will go further and more research can be done.

6.15 The second permissive clause (6.12) allows the use of placebo when the condition being investigated is 'a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm'. To return to the example of headache research, where there is a high placebo response, patients might be randomised to either active or placebo treatments. A protocol that required patients to wait two hours after the study medication before taking their usual medication if needed would expose the patient to, at worst, two hours of unrelieved headache. This constitutes inconvenience and discomfort but is unlikely to cause serious or irreversible harm. Participation would, of course, be consensual with freedom to withdraw at any point. We believe that this would be an ethical use of placebo in a condition for which effective treatments are available.

The placebo run-in

6.16 In many clinical trials, it is a common design feature to include a run-in period. This is one in which, prior to the use of the randomised treatments, the patient receives a non-randomised medication, often placebo, and is usually subject to most of the other trial procedures. The purpose of this single blind run-in is to identify adherers and non-adherers to treatment eg by returned pill counts.[209] Many information sheets have either not informed patients that all participants will receive placebo for some time during the trial or have used a form of words such as that suggested by Ramsay: 'During this study there will be one or more periods during which you will have inactive (placebo) treatment. It is important for the success of the study that you are unaware which study periods these are.'[210]

6.16 An intelligent patient might well ask why such a period is necessary or work out that the period is at the outset. Confidently blinding the patient to the assessment of their adherence may only be possible without consent ie by deceit.[211]

6.17 Research on the value and desirability of the run-in period is sparse.[212] In general, we believe that accustoming patients to the study in a run-in with assessment of adherence can and should be done with full information and consent. RECs should seek a detailed justification where such information is to be withheld.

6.18 Use of placebo controls has been proposed in studies in countries where an established effective intervention is not available, nor likely to be in the foreseeable future. CIOMS guidelines suggest that such protocols may be ethically acceptable if the purpose of the study is ultimately to make an effective alternative intervention available to the established effective one that is currently locally unavailable. The proposed investigational intervention must be responsive to the health needs of the population from which the research participants are recruited and there must be assurance that, if it proves safe and effective, it will be made available to that population. The REC would also need to be satisfied that the established effective intervention cannot be used as comparator because its use would not yield scientifically reliable results that would be relevant to the health needs of the study population.

Exceptional use of a placebo comparator

6.19 We note that RECs may have difficulty in confidently determining the likely availability of either an established effective intervention or, if successful, of the new alternative. Such difficulties may occur, of course, in rich as well as poor countries.

6.20 Protocols involving such exceptional use of placebo are rarely reviewed by RECs in the UK. We note the concerns that such use of placebo could result in the exploitation of poor

and disadvantaged populations. Any REC confronted by such proposals is directed to the more detailed guidance offered by CIOMS and by the Nuffield Council's report.

6.21 In summary, while the use of placebo is often uncontentious, its use in many protocols often creates controversy. RECs should consider carefully the justification and any risk, discomfort or inconvenience involved. As always the risk should be proportionate to the benefit, and competent patients should give valid consent.

7 Research involving use of human tissues or records and research presenting no material ethical issues

Consent and research on human tissues

Human Tissue Act 2004

7.1 The first part of the Human Tissue Act 2004 is concerned with consent. The Act makes consent the fundamental principle underpinning the lawful storage and use of human bodies, body parts, organs and tissues and the removal of material from the bodies of deceased persons. It is not the responsibility of the REC to give legal advice, but, in general, good ethical practice will follow the requirements of the Act (see also section 4.37).

7.2 Advice on interpretation of the Act can be sought from the Human Tissue Authority which has drawn up a series of Codes of Practice.[213] The Human Tissue Act 2004 (Persons who Lack Capacity to Consent and Transplants) Regulations 2006 gives additional guidance.

7.3 The proposed regulatory authority for tissues and embryos (RATE) to replace the Human Tissue Authority and the Human Embryology and Fertilisation Authority (as in 4.37) set out in a white paper in December 2006[214] will bring together the licensing roles of the HTA and the HFEA as modified by the implementation of the EU Tissue Directive (2004/23/EC). This merger has been strongly opposed by the Parliamentary Joint Committee (July 2007).

7.4 The Scottish Executive Health Department has produced guidance on the implications of the Act for Scotland.[215]

Imported tissues

7.5 There are exceptions to the general requirement for consent for imported bodies and material and to bodies, and material from bodies, of persons who died before the coming into force of the new regime where there is a gap of more than 100 years between the date of death and the activity concerned. This allows continued import of tissue for research and excludes archaeological specimens from the consent provisions. There is also an exception for health-related research on material from living people where the material is not linked to an identifiable individual and the research has been approved by a REC.

7.6 Although the default position in human tissue research is one of consent, there are situations where ethically this may not be necessary (see for example, paragraph 7.10)

7.7 Seeking individual consent may compromise the reliability of data due to incomplete and unrepresentative sample collection. However, knowing there is an unidentifiable person with a positive test does not invade that person's privacy or dignity; nor can there be a duty of care to someone unknown. Unlinked anonymised seroprevalence surveillance programmes, for example, comprise research studies designed to inform policy and practice. They are not screening for the purposes of individuals.

Code of practice

7.8 The Code of Practice from the Human Tissue Authority states that tissue may be 'used without consent provided that the tissue is anonymised', meaning that research is 'carried out

in circumstances such that the person carrying it out is not in possession, and not likely to come into possession, of information from which the person from whose body the material has come can be identified'.

Links to clinical records

7.9 It is noted that this does not mean that samples must be permanently and irrevocably unlinked, nor that the person holding the samples cannot themselves carry out the research. Links may be retained to the relevant clinical or patient records, but the investigator must not, in conducting the research, hold information from which he or she can identify the individual as a result of the research use of that sample.

Surplus tissue

7.10 We therefore believe that there is a continuing role for the non-consensual use of surplus tissue that is consensually removed as part of routine clinical care and which would otherwise be discarded. Such use is conditional upon anonymisation before commencement of research activity and REC approval. To be ethically acceptable, opt in consent should be impractical or would potentially damage epidemiological benefits.

7.11 The unlinked anonymised technique with irreversible anonymisation also remains legal under the Human Tissue Act. It has been used, for example, in studies of HIV and hepatitis prevalence; and in the national tonsil archive study.

Use in present and future projects

7.12 Patients may consent both to the use of tissues for specific projects and/or to the storage and use of tissues for future use within a category of research. Such future projects will require fresh research ethics approval but further patient consent may be neither practical nor necessary. Consent may be 'broad and durable' or 'limited in time and scope'. Consent could, for example, be sought for 'future medical research that has been approved by the research ethics service'. Empirical data indicate that this approach is acceptable to individuals.[113] Researchers are advised to consult the Code of Practice from the Human Tissue Authority and RECs should not obstruct research that fulfils the Code's requirements.

MRC recommendations regarding individual linkage

7.13 The MRC recommends that if samples are stored in a form that allows individual linkage, the possible future research should be explained in terms of the types of studies that may be done, the types of diseases that could be investigated and the possible impact of the research on the donor personally. Participants should be informed if future use will require research ethics approval (see 7.12).

7.14 As long as material is identifiable, donors should be offered the option of its removal from storage and destruction.

7.15 RECs should be especially cautious about use of tissues in areas of research likely to cause special concern to donors, even when unlinked and anonymised eg research on sexual orientation or abortion.

7.16 It should be noted that the Act does not apply to existing holdings (pre September 2006) or to cell lines.

7.17 There should always be explicit separation of consent to the treatment or diagnostic test from the use of the surplus tissue for research.

Guidance from RCPath and MRC websites

7.18 REC members are directed to further guidance and comment from the Royal College of Pathologists and the Medical Research Council websites.

Consent and personal information

7.19 Medical research based on records and surveys has led to important advances in understanding with enormous benefits to thousands of people. RECs must balance these benefits against the ideal of individual consent for every use of personal information.[216]

7.20 Personal information which is provided for healthcare must be regarded as confidential. Wherever possible people should know how information about them may be used. Consent is irrelevant to the statutory release of some information, but in research each individual's explicit consent should usually be sought to obtain, hold or use personal information.

Confidentiality issues

7.21 The common law on confidentiality is complex and the interpretation of the Data Protection Act is not based on a large body of case law. Issues of confidentiality are also subject to administrative law and the Human Rights Act 1998. In general, sound ethical judgement is likely to correspond with the law. Further guidance on ethical standards is available from the GMC,[217,218] the Department of Health and the MRC.

7.22 The ability to conduct some classes of research has been jeopardised by three factors:

- uncertainties about which classes of medical research using personal data can be exempt from the Data Protection Act's requirement for consent
- differences between professional organisations' interpretations of the law
- and an approach from regulatory bodies, including RECs that has erred strongly on the side of caution.

Difficulties have often stemmed from over-interpretation of regulations by RECs rather than from over-regulation itself.[109,175,176,187,219–221] Extensive debate has also taken place in the USA over the protection of privacy and its effects on research.[222,223]

Epidemiological research

7.23 Epidemiological research, in particular, requires representative samples and high response rates. Response rates matter: firstly, because if sample size is reduced, the study loses statistical power and true effects may not be identified; and secondly, because the restriction of observational research to only those who give consent is likely to result in 'participation bias'.

7.24 Personal information is often crucial to the conduct of the research in order to avoid counting the same person twice, to link records, to follow-up specific individuals. Some types of personal data are important determinants of health (for example, postcode as a surrogate marker of socioeconomic status). RECs must balance the requirements and benefits of research against the ideal of individual consent for every use of personal information.

7.25 RECs should examine proposals on their merits, and consider other factors such as research staff's competence in handling personal data and data security measures (such as processing and access policies, password protection of databases and servers, network security and data encryption). RECs should weigh the public interest (which should be important) against the interference with privacy involved in non-consensual data use (which should be low). That is to say, decisions should be based on proportionality.

Recruiting participants for study

7.26 In recruiting participants for any study, the initial approach should normally be made by the doctor or other health carer familiar with the patient. Patient details should not be disclosed to investigators with no clinical care responsibilities to the patient without that patient's consent. However, we acknowledge that in some situations the use of proxies such as the GP to initiate patient contact may be unsatisfactory.

7.27 Where even limited disclosure is possible (eg names and addressed of potential research participants with no clinical data), RECs will still need to be assured that obtaining consent is impractical and that a high non-response rate will reduce the scientific validity of the study.

Patient Information Advisory Group (PIAG)

7.28 The Patient Information Advisory Group (PIAG) was established under the Health and Social Care Act 2001. Its Secretariat will advise when identifiable information without consent is permitted for medical research. The Act applies to England and Wales. A similar function for Scotland is performed by the Privacy Advisory Committee established in 1990 to provide advice on requests for the release of patient identifiable information by the Information Services Division (ISD), part of NHS National Services Scotland (NSS), or by the General Register Office for Scotland (GROS).

Anonymisation

7.29 Since anonymised data are not about identifiable individuals, disclosure does not breach the duty of confidence to the patient. It may be good practice to inform patients if anonymised data are being used in research, eg by a notice in the clinic or surgery. Consent may still be sought if there are no major practical or logistical objections. Anonymisation at the earliest possible stage of research provides protection against disclosure even where consent has been given. PIAG advises that there *are occasionally circumstances when the use of patient-identifiable information is in the public interest but it is not possible or appropriate to gain consent from the patients involved. For example:*

- *In a historical study involving large numbers of patient records, it may be impossible to track down all the patients to ask for their consent or it would require disproportionate effort to do so. It may also be impossible to anonymise the data, especially if different records have to be linked.*
- *It may be inappropriate to ask for parental consent in a study of child abuse where the parent may be responsible for, or complicit in, the abuse.*

7.30 With a contentious diagnosis such as child abuse, this will include the collection of normal control data.

Deceased participants

7.31 The Department of Health and the GMC agree that, while there are no clear legal obligations of confidentiality that apply to the deceased, there is an ethical basis for requiring that confidentiality obligations should continue to apply and indeed codes such as the Hippocratic Oath demand them.

Market research

7.32 Doctors are commonly the subjects of market research questionnaires or interviews. Sometimes these will request details of patients and their responses to particular therapies. Market research primarily informs commercial policies rather than establishing scientific laws. Such surveys always involve anonymous information, often from memory. They have not been subject to REC review and are considered outside the remit of the REC.

Disclosure of identifiable data

7.33 In summary, in some exceptional circumstances, where the research is of such significance or a patient cannot be located in order to seek consent, the public interest may justify disclosure of identifiable data. In such circumstances the research project requires support under Section 60 of the Health and Social Care Act 2001 through PIAG or the equivalent Scottish arrangements (see 7.28).

Research presenting no material ethical issues

Role of research ethics adviser

7.34 In the recent consultation[224] and recommendations[225] arising from the *Report of the Ad Hoc Advisory Group on the Operation of NHS Research Ethics Committees*, it was recommended that ethical review should be proportionate to the level of risk provided by that study with assessment of applications by the research ethics adviser (REA). Research presenting no material ethical issues may be approved by the REA. The implementation document also indicates that NRES will continue to develop and refine this guidance.

7.35 We note that the examples given in the consultation document[224] include not only simple surveys, but also studies involving human tissue and medical records research.

Stored samples, medical record and database searches cause no harm or distress to patients if properly conducted

7.36 Performed in the right way, research using stored serum or other tissue samples or research using medical records or other medical databases causes no harm or distress to any individual. It is essential that such work is encouraged and not unnecessarily restricted. Conjectured hypotheses are commonly tested initially within large datasets. Such hypotheses are often speculative but such speculative ideas have resulted in important findings. We would support the development of a code of practice to maintain sound ethical practice, meet legal requirements, yet prevent large numbers of REC applications that may consume more time and money than conducting the work itself.

Data keyholder

7.37 One such proposal from the Wolfson Institute of Preventive Medicine[226] has suggested the appointment of a data keyholder not involved in the research itself. The keyholder anonymises the samples, linked anonymously to any relevant clinical data, and makes them available to investigators. Once in place, it is suggested that a REC would approve an application for a category of research in a particular institution or group of researchers, based on a particular set of samples for a specified period of time (perhaps five years). At the end of that time, an application would be needed to extend it.

7.38 The same ethical approval procedure could apply to the ongoing collection of blood or other tissues samples, provided the samples were originally collected for clinical purposes and the samples are no larger than necessary for such clinical purposes.

7.39 It has been suggested that a small additional amount of blood, with consent, could be covered by the same Code of Practice if it were part of the ongoing activity of a research group. The same could apply to urine samples obtained for research.

New approval conditions for tissue research

7.40 New procedures for ethics review of research tissue banks become operational in October 2007. NRES has issued a model set of research tissue bank approval conditions for use by RECs and issued guidance as Amendment no. 3 to version 3 of SOPs. These procedures fulfil many of the Wolfson Institute proposals.

7.41 Under these proposals, generic ethics approval for projects receiving tissue is possible. The research should be conducted by the establishment responsible for the tissue bank and/or by researchers and research institutions external to the bank receiving the tissue. Approval will be valid for five years and renewable on consideration of a new application. Such generic approval is subject to strict conditions set out at www.nres.npsa.uk/recs/index.htm#110107

7.42 For tissue banks where the applicant has not applied for generic ethics approval for projects receiving tissue or such approval has not been given by the REC, ethics approval for specific projects is still required.

7.43 As noted above the research use of computerised or paper health data carries no risk, provided the data are anonymised to the investigators. Such research could also be considered under an analogous Code of Practice to that proposed by the Wolfson Institute if it were an ongoing activity of a research group.

7.44 The research use of computerised or paper health data where identity of the patient cannot be concealed or individual projects using anonymised data that are not part of an ongoing activity of a research group, cannot fall under the arrangements proposed for class approval in association with a code of practice. Nevertheless such research should usually fall in the category of 'presenting no material ethical issues' with rapid review by the research ethics adviser. So too should many projects based on collection of additional blood samples.

Where an identification of patient is necessary

7.45 Should circumstances arise in which patient contact becomes necessary, perhaps because of an entirely unpredicted finding that they believe is in the interests of the patient to reveal, identification of the patient would be necessary through the keyholder to the general practitioner or consultant. Anonymity to the investigator would be maintained.

8 Research in special groups of participants

Children

8.1 Although not all RECs are involved in reviewing protocols exclusively devoted to research in children, many protocols involve some participants below the age of majority, for example asthma studies in those aged 12 to 20. All REC members should therefore be aware of the particular issues arising from research in children. RECs should obtain advice from those experienced in child health where they lack that competence or experience.

Guidelines from RCPCH and MRC

8.2 Guidelines for research in children have been published by the Royal College of Paediatrics and Child Health[227] and by the Medical Research Council.[228] We strongly recommend that these are consulted by RECs involved in the consideration of research in children. MRC guidance includes the key provisions for the protection of minors within the Medicines for Human Use (Clinical Trials) Regulations 2004. Additionally, an EC Regulation on research involving children, binding on all member states, became mandatory on 27 January 2007 and was effective immediately without the need for rewriting as a UK Act.[229,230] An EC draft document on ethical considerations arising in research involving children published in October 2006 outlined the guidelines that member states would be expected to follow.[231] A detailed discussion of the child as research subject may be found elsewhere.[232]

8.3 We endorse the importance of research in children which should be encouraged and conducted in an ethical manner.[233–235] The use of unlicensed medicines in children arising from the lack of research has been a particular concern.[236]

8.4 Research should only be done with children when comparable research could not be done in adults. In general, it is preferable to recruit older children rather than younger ones as participants where more understanding is likely but it must be remembered that younger children may react very differently to both illness and treatment compared with older children.

8.5 The MRC recommends that the knowledge obtained should be relevant to the health, well-being or healthcare needs of children.

8.6 Nevertheless, the beneficial results of research in adults should be validated in children if it is envisaged that the treatment will be useful in children.

8.7 As with other research, registration of projects should be encouraged. For example, for perinatal research this might include the planned database of all paediatric trials under the Medicines for Children Research Network based at the National Perinatal Epidemiology Unit.

Unique status of children

8.8 We note the unique status of children as a group on whose behalf others may give consent; and their vulnerability and difficulty in expressing their needs or defending their interests. Harms from research may be potentially longer lasting than in adults but so too may be the potential harm from using a medicine untested in children.

Role of parents

8.9 Those with parental responsibility should be involved in the decision to participate wherever possible and always where the child is not competent. The possible exception of emergency research outlined in the MRC guidance is noted (see 8.14). If the parents are themselves under age, they will only be able to give consent for their child if competent to take the decision in question, eg a study of child health in children of 14 year old mothers.

Consent

8.10 Seeking consent is not a single event but a process. The threshold for understanding will relate to the complexity of the research being undertaken. In long-term research, intermittent formal approaches to re-address consent may be necessary as the child matures and develops competence to make his or her own decisions. Children may achieve an understanding of a long-term condition in advance of their acquisition of competence in other areas. Such conditions might include cystic fibrosis, chronic inflammatory bowel disease and Duchenne muscular dystrophy.

8.11 The differing legal provisions for consent in English and Scottish law, outlined in the MRC guidance are noted. Larcher has published a short review of the issues surrounding consent, competence, and confidentiality in adolescence.[237] See also section 4.55–4.59.

Classification of risk

8.12 The classification of risk into high, low and minimal has been noted above (see section 5.14). We agree with the RCPCH that a study that is not intended directly to benefit the child is not necessarily unethical or illegal.

8.13 An articulated refusal of a child to participate or continue in research should always be respected. Evidence of significant upset should be accepted as a valid refusal.

Emergency research

8.14 Particular care should be taken in considering protocols for emergency research, especially in the neonatal period. The RCPCH provides detailed guidance relating to research involving babies. It is unwise for the REC to consider such protocols without a specialist paediatrician member. Indeed we would support the membership of every REC containing one member professionally involved with the care of children, besides the GP member.

8.15 RCPCH advice regarding skilled venepuncture is that all reasonable steps should be taken to minimise pain, eg by the use of local anaesthetic cream and by careful explanation.

8.16 In studies on children, information sheets should be appropriate for the age group being studied and, for example, should include appropriate illustrations (see COREC/NRES guidance). Consideration should be given to presenting data in innovative and non-traditional ways, eg narrative accounts of projects or cartoons, provided that the essential information is conveyed.

8.17 Although all investigators working directly with children should have a police check for crimes relating to children before starting such work, this is the responsibility of research governance and not the REC.

Learning disability

8.18 Many similar ethical considerations apply to people with severe learning disability as with children. They should not be subjects of research that might equally well be carried out in adults in full health (see also 5.31). Similarly, where research is necessary in children with

learning disabilities or mental illness, participants who are able to achieve a fuller understanding should be invited to participate, as above. Nevertheless, people with learning disabilities, whether adults or children, may be the only participants available for much research into the origins, nature and treatment of such disability or illness.

8.19 Less severe learning disability does not automatically imply incompetence to participate in research. People with learning disability have been unthinkingly excluded from many studies due to uncertainties about their ability to give consent. People with learning disabilities are more likely to be suggestible in their decision-making and may say what they feel is expected of them. Explanations should therefore be presented in simple language, augmented by pictures of other communication aids and not in uninterrupted text. It has been shown that most adults with moderate learning disabilities who have a research project explained twice understand what the research is about.[238]

8.20 Further guidance is available from the Royal College of Psychiatrists.[239]

Mental illness

8.21 Similarly, most people who suffer from mental illness are competent to understand the implications of research and to make up their own minds whether to take part. Careful explanation can sometimes help a patient with mental illness to achieve capacity. Even where it does not, it is good practice for investigators to help the patient to understand as much as possible of what is involved and to take a part in decision making. Nevertheless, many psychiatric patients should be considered vulnerable and research involving such patients should be limited to studying those conditions from which the patient suffers or those associated with the psychiatric illness (eg physical illness in a population of patients with schizophrenia).

8.22 It is ethically acceptable to proceed without the patient's consent, if the patient is incapable of giving consent, provided that the research is relevant to such psychiatric patients, that it cannot be undertaken in less vulnerable groups with the same disorder, assent has been given by the individual's closest relative or partner, the support of the patient's clinician has been secured, the opinion of an independent clinician has been sought, there are minimal risks and the approval of the REC has been given. However, the patient's refusal (whatever their capacity) should be accepted, irrespective of the above. The Mental Capacity Act is discussed above (see above 4.32).

8.23 Patients detained under the Mental Health Act should not necessarily be deemed to lack capacity. Especial care is needed to guard against perceived coercion and to ensure that informed consent is real. An independent professional opinion is essential in such circumstances. (Coercion is a credible or strong threat by one person that limits or adversely affects the option another person has available.) Treatment under the Mental Health Act is limited to the condition for which the patient is so detained. Treatment for other conditions requires consent.

8.24 The relevant legislation in Scotland is the Mental Health (Care and Treatment) (Scotland) Act 2003 which embodies the same principles as above and requires that a patient participate as fully as possible in all decisions affecting care.

8.25 The Royal College of Psychiatrists has laid down guidelines for research involving psychiatric patients.[240] RECs should consult these guidelines and seek relevant expert advice where needed (see also 5.31).

8.26 Competence to participate in research is discussed in the section on consent above (see 5.21). Difficulties arise where competence is in doubt or is clearly impaired. The use of validated assessment tools should be considered by the REC.[185,241] Refusal in such circumstances should normally be respected.

Students

8.27 The National Union of Students produced guidelines in consultation with the Association of Independent Clinical Research Contractors and the Association of the British Pharmaceutical Industry following the deaths of two students in the 1970s.

8.28 No student should undertake experiments for any investigator who acts as a personal tutor to that student without explicit justification to the REC. An anonymised questionnaire study, for example, might be justified, but the REC will wish to be reassured that no possibilities of coercion exist in research on students in an hierarchical relationship to the investigator. RECs should consider the relationships between student and academic staff carefully where teaching contact is considerable or there is involvement in academic assessment. Similar considerations apply to others in hierarchical relationships eg junior medical or nursing staff, members of the armed forces.

Inclusion of potentially fertile or pregnant women in pharmacological or radiological studies

Teratogenic risk

8.29 Since all contraceptive methods have a very small failure rate, the inclusion of potentially fertile women (ie all women of child bearing age) in pharmacological or radiological studies creates a teratogenic risk.

8.30 If research is not carried out in potentially fertile patients, then the use of drugs etc. in these groups must either be avoided or administered without adequate evidence of benefit or safety. A general policy of excluding potentially fertile patients from clinical trials would be unethical.

8.31 Although this issue is usually encountered in trials involving potentially fertile women, the possible effects of drugs on sperm in men may also need to be considered. The effects of medicinal products on male fertility have been less well studied. The limitations of knowledge may need to be openly recognised.

8.32 Ethical considerations include the frequency of the condition in this age group. A study of a disease that is rare in fertile patients (eg Alzheimer's disease, carcinoma of stomach) could be completed without the recruitment of such patients; a condition that is common in women of reproductive age (eg rheumatoid arthritis, type 1 diabetes) would be difficult without the recruitment of such patients.

8.33 Teratogenic risk may be high (eg a new cytotoxic agent) or low (eg a new formulation of an over-the-counter medication). Participants should be encouraged to discuss such risks with their sexual partner(s), possibly even asking for their partner's consent.

Avoiding pregnancy

8.34 A realistic assessment of the proposed method for avoiding pregnancy should be made. For example, an intra-uterine device may be acceptable with a low teratogenic risk, but the addition of barrier methods or the use of the oral contraceptive may be judged necessary where the risk is significant.

8.35 There should be advice about the duration of contraceptive precautions and about the possibility of emergency contraception if precautions have been omitted.

8.36 Abstinence from sexual activity is, of course, the best method of avoiding pregnancy. If this is the patient's choice or if the patient is not heterosexually active, inclusion in a study may be acceptable.

Pregnancy testing

8.37 Pregnancy tests will normally be required before any study with potential teratogenic risk. The reason for this should be set out in the information sheet. It should be emphasised that this is a general rule for all participants and does not imply the participant is actually sexually active. Similarly, the study may require further pregnancy tests during its conduct, especially if there is any possibility of an interaction between study medication and oral contraception.

8.38 This may be particularly sensitive in studies involving those under 16 years of age: it is a criminal offence for a male to have sexual intercourse with a female under 16 years of age, even with consent. When a female is 14 or under she is deemed unable to consent to sexual intercourse in law, ie it is a more serious offence. The REC should ensure that nothing in the protocol could be construed as encouraging under age and illegal sexual activity.

Research in pregnant and nursing women

8.39 Pregnant or nursing women should not participate in non-therapeutic research that carries more than minimal risk to the fetus or neonate, unless this is intended to elucidate problems of pregnancy or lactation

8.40 As a general rule, therapeutic research should only be undertaken in pregnant or nursing women with a view

- to improving the health of the mother without prejudice to that of the fetus or breast-fed baby, or
- to enhancing the viability of the fetus, or
- to aiding the baby's healthy development, or
- to improving the ability of the mother to nourish it adequately.

8.41 Good evidence of efficacy and safety in the non-pregnant state is mandatory when studying a drug for a medical condition occurring in pregnancy (eg for hypertension or epilepsy). Without studies in pregnancy possible pharmacokinetic differences will not be recognised or women may be denied the benefits of new therapies entirely or required to revert to older, possibly more hazardous therapies when pregnant. Often observational studies may be the most practical option rather than randomised trials.

8.42 Women in labour are particularly vulnerable. They may be coping with painful contractions, receiving medication or anxious about outcomes. It has been suggested that

wherever practical, women should therefore be given information well in advance of being asked for their consent to participation in research.[242] It is therefore argued that a woman who is about to be induced, have a caesarian section or is newly delivered should not be asked to consent to research unless she has been given prior information during her pregnancy. Such an ideal is neither realistic nor necessary for research into many interventions or conditions. Some research, such as that involving collection of placental material, amniotic fluid, myometrium, cervical cells etc during a Caesarean section is low risk and most women would be able to give consent without prior information. Even in higher risk studies, it may be impractical to seek advance consent from all pregnant women for a rare condition of mother or neonate.

8.43 We consider that there can be legitimate research directed at benefiting the mother in which the possibility of fetal loss cannot be excluded. That is, there may be trade-offs between maternal welfare and fetal risk. For example, exceptions to the general rule in 8.40 might include studies of epilepsy or psychosis in pregnancy.

Cultural considerations

8.44 CIOMS guidelines acknowledge that in some cultures women are vulnerable to neglect or harm in research because of their social conditioning to submit to authority, to ask no questions, and to tolerate pain and suffering. If a study has the potential to include such participants, the REC should exercise special care in examining the proposed consent process to ensure adequate time and a proper environment in which a decision to participate can be made.

8.45 In no case is it acceptable for the permission of spouse or partner to replace the individual informed consent of the woman herself. A strict requirement of authorisation of spouse or partner violates the principle of respect for persons. Nevertheless, if a woman wishes to consult with husband or partner or voluntarily seek their permission before deciding to enrol in research, that is not only ethically permissible but in some contexts highly desirable.

Prisoners

8.46 Consideration of the ethics of research in prisons is currently limited to a small number of RECs. This enables those RECs to gain experience in the special considerations that may apply to prison research.

8.47 Research that can be conducted on patients or healthy volunteers who are not in prison should not be conducted on prisoners. Incarceration in prison creates a constraint which could affect the ability of prisoners to make truly voluntary decisions without coercion to participate in research.[243] Accusations of exploitation or violation of human rights could easily arise. Additional safeguards are therefore warranted.

8.48 Research studies in prisons should normally be limited to:

- Studies of the possible causes, effects, and processes of incarceration, and of criminal behaviour, provided that the study presents no more than minimal risk and no more than inconvenience to the participants.
- Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults).

- Research on practices, both innovative and accepted, which have the intent and reasonable probability of improving the health or well-being of a prisoner.
- Studies of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the participants.

Follow-up for long-term research may be impossible

8.49 Where there may be a need for follow-up examination or care of participants after the end of their participation, the REC should ensure that adequate provision has been made for such examination or care, taking into account that long-term follow-up studies are rarely feasible because of the varying lengths of individual prison sentences, and the frequent movement of prisoners from one prison to another. The REC should ensure that participants are informed of this fact.

8.50 Members of the REC should have no connection with the prison in which research is being conducted.

Concept of prisoner representative

8.51 The Office for Human Research Protections in the USA has recommended that a prisoner or prison representative with appropriate experience should participate in the Institutional Review Board (the American equivalent of the REC) in considering research projects in prison.[244] We acknowledge this may not be currently practical in the UK but could be considered in future developments.

8.52 Any possible advantages accruing to the prisoner through participation in the research, when compared with the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, should not be of such magnitude that the ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired.

8.53 Procedures for the selection of participants within the prison should be fair and immune from arbitrary intervention by prison authorities or other prisoners. Unless the principal investigator provides to the REC justification in writing for following some other procedures, controls should be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project.

8.54 Adequate assurance should exist that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner should be informed in advance that participation in the research will have no effect on parole entitlement.

Older people

8.55 The RCP recognises that the greatest burden of disease in the developed world falls upon older people and that research activity should reflect this.

8.56 There is compelling evidence that older people are under-represented in research.[245] Age has often been an exclusion criterion in clinical trials.[246] Without inclusion of older participants, the generalisability of research to them may be seriously compromised.

8.57 We acknowledge that old age is associated with co-morbidities, multiple medications, increasing mortality and higher drop-out rates. However, protocol restrictions create a tension

between the generalisability (external validity) and accuracy (internal validity) of research findings.

8.58 The assumption that older people are more vulnerable undermines autonomy. Evidence suggests that older people may be more willing to participate in research. Transport and mobility problems, social isolation and communication difficulties secondary to visual or hearing impairments are all problems that may need to be surmounted. RECs should therefore examine protocols to ensure that applications address such practical difficulties and should regard exclusion on arbitrary and unjustified age restrictions as unethical.

Refugees

8.59 Research on people who may be desperately poor and frightened raises huge ethical concerns. Refugees are vulnerable in political status with fewer rights than those who can claim citizenship status within stable national frontiers. In collapsed or collapsing states their status is even more ill defined. Refugee flows may occur during complex emergencies with flagrant human rights abuses.

8.60 There is a need both to acquire better knowledge about refugees arriving in secure host countries such as the UK, and to establish better science about what should be done in those places where the disaster is taking place, such as refugee camps. There is unlikely to be a framework for ethical review for studies of the latter sort. We would encourage UK teams engaged in such studies to submit them to RECs in the UK.

8.61 Language, culture, educational background and social norms create particular difficulties with consent and confidentiality. Moreover the mobility of many refugee populations may make it difficult to design studies with realistic prospects of benefit for the participant.

8.62 Given the difficulties in practice, yet the urgency in establishing answers to practical management of disease in these often grave situations, the certainty of achieving standards of consent applicable in ordinary clinical practice may have to be compromised. Basic guidelines and discussion of these complex and challenging issues may be found elsewhere.[247,248]

Other vulnerable groups

8.62 Besides refugees, there are many other vulnerable groups deserving special consideration by RECs. These include migrant workers, the homeless, employees (in the context of occupational health research) and asylum seekers (an asylum seeker is defined as someone who, outside their country of origin, is unable or unwilling to avail themselves of their country's protection as a result of being in genuine fear of persecution; some may achieve refugee status but others may have more limited leave to remain in the UK).

Research on patients at the end of life

8.64 While the eradication of premature death is a legitimate goal of medicine, death comes to us all. The relief of suffering at the end of life is one of medicine's most important goals.

8.65 Research into end-of-life care presents additional challenges, yet better research is needed both on patient views on dying as well as on techniques of palliative care.[249,250] Better data on how people die, as opposed to what they die of, is required.[251]

8.66 Potential research participants constitute a vulnerable group. Firstly, there may be a tendency to grasp at any therapeutic possibility. Secondly there may be a particularly close relationship with healthcare professionals that makes refusal difficult. Thirdly, consent may be difficult to obtain due to the effects of drugs or disease. Fourthly, patient wishes may be filtered through the views of anxious family members.

8.67 From the professional perspective, there may be difficulties in balancing the research and clinical care roles. It may also be harder to determine the balance of risk and benefit.[252]

8.68 These difficulties should not prevent such research. RECs should review such proposals sympathetically including innovative methods of consent, such as the use of advance directives.

8.69 Phase 1 research in terminally ill patients in the assessment of new chemotherapeutic agents may offer relatively few benefits yet create substantial risks (it is because of these risks that healthy volunteers are not used). There are also concerns about the quality of informed consent. However, patients with advanced cancer who participate in phase 1 studies have a different set of values from many critics and are not coerced by virtue of participation. Even if vulnerable they do not lack capacity. We note that claims of coercion are projections and not empirically substantiated facts.[253]

Letting a patient choose the poisons (under professional guidance) adds something to the will to struggle. We who are struggling to escape cancer do not, obviously, want to die of it … The enemy is not pain, or even death, which will come for us in any eventuality. The enemy is the cancer and we want it defeated and destroyed … This is how I wanted to die – not a suicide and not a passively accepting victim but eagerly in the struggle.[254]

Fetuses and fetal material

8.70 The *Review of the guidance on the research use of fetuses and fetal material* (the Polkinghorne Report)[135] was published in 1989 and remains extant. The Department of Health has published guidance on this (1995). All RECs should have access to the Polkinghorne Report whenever the use of fetuses or fetal material is proposed.

8.71 Item 6 of the Code of Practice proposed by the Polkinghorne Committee states:

> 'All research, or therapy of an innovative character, involving the fetus or fetal tissue should be described in a protocol and be examined by an ethics committee. Projects should be subject to review until the validity of the procedure has been recognised by the committee as part of routine medical practice.'

8.72 We note that research using fetuses or fetal material is now regulated by the Human Tissue Act (see sections 4 and 7).

In vitro fertilisation and embryos

8.73 The Polkinghorne Committee recommended that protocols for treatment as well as research should be submitted to a research ethics committee. However, treatment protocols are outside the terms of reference of the REC and would normally be considered by a clinical ethics committee.

8.74 For research involving *in vitro* fertilisation, other methods of assisted reproduction, gene, embryo, fetal and transplant research, RECs should refer to the guidelines issued by the Human Embryology and Fertilisation Authority (see 4.37 and 7.3) or other authorities where applicable. While reproductive cloning is unlawful under the Human Reproductive Cloning Act 2001, the government proposes to ease research in therapeutic cloning by permitting replacement of the nucleus of an embryo (somatic cell nuclear transfer – SCNT). Regulation of cloning for basic research will also be eased. Specialist opinion should be consulted or co-opted where necessary.

Gene therapy

8.75 Trials involving gene therapy are outside the remit of the REC and should be referred to the Gene Therapy Advisory Committee (GTAC). UKECA recognises GTAC is the UK national research ethics committee for gene therapy trials according to the Medicine for Human Use (Clinical Trials) Regulations 2004. It is the only UK ethics committee empowered to approve clinical trials of gene therapy products. GTAC is also the relevant REC for approval of clinical trials and research in humans using genetically modified animal cells (but not solid organs).

Xenotransplantation

8.76 The UK Xenotransplantation Interim Regulatory Authority (XIRA) was formed in response to the Habgood Report of 1997. Because xenotransplantation is now fully embedded in UK regulations on medicinal products, UKXIRA completed its work in December 2006. Any proposal for a clinical trial of a xenogenic product must go to a UKECA recognised REC. If the xenogenic product is genetically modified, investigators should apply to GTAC for ethical approval. For trials of other xenogenic medicinal, investigators should contact COREC/NRES who will ensure the proposal is reviewed appropriately. Any REC considering a trial of a xenogenic product can seek further specialist advice and to allow for this the regulations do not apply a time limit for the process. Home Office approval is also required.

9 Special classes of research

Research in genetics

9.1 Genetic diagnosis can result from analysis of DNA. It may also be possible from the family history, clinical examination, biochemical tests, anatomical features etc. DNA testing should not be treated differently from other types of genetic diagnosis without good reason.

9.2 Normal standards of consent and confidentiality are applicable to large research studies such as epidemiological studies to determine population genetic variations or pharmacogenetic studies.

Potential adverse effects

9.3 Where results from research are intended to be, or may be, disclosed to the participant, the information provided before the study must inform the participant of potential adverse implications of the results eg for employment, for insurance or for other family members.[177] The 'right not to know' is as important for some as the 'right to know' is for others.

9.4 Wherever practical, a clear distinction should be maintained between genetic diagnostic testing and testing as part of a research study. If a later diagnostic test is required, normal practice should be to request a fresh sample or consent for use of a previously taken sample and this should be explained to the research participant. It should be noted that this distinction cannot always be maintained. Where this is the case it should be made clear to the participant.

9.5 RECs should ensure that protocols address the nature of disclosure of results, with prior specific consent.

9.6 Genetic testing should not be added to any existing research study without REC consent or vice versa. If new tests are proposed for other disorders/diseases, then fresh consent and a new protocol application are required.

9.7 RECs should ensure that the investigator and the referring clinician (if different) have considered their duty of care to any individuals who may find themselves or their relatives affected or at risk as a result of participation in research. Such situations are frequent in normal service delivery and should be approached in a similar manner.

9.8 Genetic research involving patients with rare diseases differs from other genetic research studies in the implication it has for close blood relatives. Knowledge of an inherited disorder carries with it a risk which cannot be reduced or eliminated by actions of the affected patient.[255,256]

9.9 In rare disorders, anonymisation may be difficult because of the small number of people affected; small sample size has certain methodological requirements; and there is a closer relationship between clinical practice and research than in most other genetic research studies. This problem is not specific to genetic research, but is perhaps more common.

9.10 Genetic research may necessitate evaluating large numbers of genetic markers, which may take months or even years. Also in rare disorders collecting sufficient samples may take

much time and involve large geographical areas. In addition, the participants are not born within a narrow time frame. Consent should therefore be open ended with regard to gene markers/genes which require to be analysed. (This does not mean that any research is acceptable on the sample, of course.)

9.11 RECs should ensure that potential participants are not under undue family pressure to opt in or opt out of a study. Participation (or refusal) should be truly voluntary.

Difficulties with anonymity

9.12 Given the long-standing links that many investigators have with families or through patient support groups, anonymisation may be impossible to guarantee. It may also be undesirable where it is necessary to track back to the families providing the original sample in order to test genetic markers and genes etc. This will involve other family members, for example when checking a mutation in the family to determine if other family members are at risk because they carry the mutation. This can be important clinically as those at risk will require genetic counselling. RECs should not require anonymity to be preserved if this is unrealistic, undesirable or contrary to the research participant's expressed wish.

9.13 Families with rare diseases are often highly motivated to support research, sometimes assisting in its funding. RECs should be aware of the negative impact on morale if reasonable research proposals are delayed or obstructed. They should also note that new developments and technology may permit reanalysis of old samples which may result in the identification of a genetic defect which will benefit the individual and family. Linkage to an identifiable donor may then be required for individual or family benefit – another contrast with epidemiological genetic research.

9.14 Children whose participation in the research study was subject to parental consent, will become adult. Where contact with the family is still possible it would be appropriate to obtain consent from the individuals themselves when able to provide it. RECs should consider these issues at the initial review of the protocol.

Genetic Interest Group and partnerships

9.15 We note that the Genetic Interest Group[257] recommends a partnership in which researchers, funders and patient groups explicitly work together in the design of research projects. We endorse these aspirations.

Implications for insurance

9.16 The anxieties expressed by some RECs over the possible effects of participation in genetic research on insurance have been addressed in a joint statement announced at the Royal Society in 2001 by the Association of British Insurers,[258] the UK Forum for Genetics and Insurance[259] and the British Society for Human Genetics.[260] The ABI stated: 'It has been suggested that people will be put off taking part in genetic research because they fear that insurers will use the results of any test they undergo in that context in the underwriting process. This is not the case … ABI hopes that this statement of its members' position will reassure people who are asked to take part in genetic research and encourage them to participate'. We endorse the response of the British Society for Human Genetics: 'We welcome the ABI's confirmation that genetic research results will not affect any insurance proposal and do not need to be declared in any insurance application'.

Intellectual property rights and patents

9.17 Patient information sheets and consent should clearly set out in the proposal implications for intellectual property rights or patents if appropriate – as for all research.

9.18 The Joint Committee on Medical Genetics of the Royal College of Physicians, the Royal College of Pathologists and the British Society for Human Genetics has published valuable guidance (see Appendix 4).

Research in practical procedures: surgery and other modalities

9.19 Hitherto surgical procedures have generally been introduced without rigorous evaluation.

9.20 Similar considerations apply to other invasive modalities such as interventional radiology or endoscopic therapies carried out in other specialties.

9.21 Assessment of established surgical procedures can raise particular difficulties in the assessment and implications of equipoise.[261]

Sham (placebo) surgery

9.22 In trials of medicinal agents under conditions of equipoise, participants do not incur direct risks by taking placebo, whereas in surgery or with other interventional therapies placebo ('sham surgery') may involve risks such as general anaesthesia that are certainly greater than minimal. Sham surgery has been used[262] to the extent that incisions have been made, sutured and dressed but no operative procedure has taken place.

9.23 It has been suggested that some risks in placebo surgery may not exceed the risks of other generally accepted research interventions, such as muscle biopsy, bronchoscopy and phase 1 testing in healthy volunteers.[263] A small skin incision may also be considered as a minimal risk procedure.

9.24 On this basis, surgical trials with sham surgery controls have been carried out – for example in arthroscopic surgery for osteoarthritis.[264] Many would consider this example an acceptable one. Another example was the comparison of prophylactic sclerotherapy for oesophageal varices with endoscopy and sham injection in the control group.[265]

9.25 Rather more controversially there have also been placebo controlled trials in surgical treatment of angina and in Parkinson's disease. In the former case, a trial of internal mammary artery ligation versus a sham procedure for the treatment of angina, participants consented to participate in an evaluation of the operation, but were not told that it was a blinded trial involving a sham procedure.[266] The more recent trials comparing a sham neurosurgical procedure against an intracerebral fetal cell implant for the treatment of Parkinson's disease[267] were crucial to the important discovery that fetal implants are ineffective and even dangerous. Both raised important ethical concerns.[268]

9.26 Methodologically, placebo controls (sham surgery) may be required particularly when the primary outcome is subjective, such as pain or quality of life.

9.27 In some research designs the participants randomised to a sham procedure are offered 'real' surgery if at the end of the trial it is found to be effective and still indicated.[269]

9.28 While placebo (sham) surgery will always be controversial,[270] an absolute prohibition on its use seems unwise. It is unlikely to be ethical where there is an objective outcome measure that is free from any reasonable possibility of observer bias (eg mortality). The risks of a sham surgical procedure should be proportionate to the public interest of conducting the trial, be

methodologically essential and always with full consent. Low recruitment rates are likely to discourage such designs unless important information cannot be found by alternative methods.

Comparison of two surgical techniques

9.29 Randomised trials in surgery may still be double blind (ie blind to the patient and to the outcome assessor) when two surgical techniques are being compared but it is vital that assessments are unbiased and that those taking part are appropriately blinded to which procedure has been done.[262]

9.30 Methodological techniques may help to reduce observer bias, eg in comparing operations through different incisions, patients and nursing staff have been (single) blinded by the use of identical blood or iodine stained opaque dressings irrespective of which operation was performed.

Comparison of surgical and non-surgical techniques

9.31 In comparing surgery with non-surgical treatment it is impossible to blind the carers or patients at the time. It is therefore essential that assessment is performed by someone who is unaware of the procedure and that patients do not divulge details to the assessor.

Effects of skills of individual practitioners

9.32 Further difficulties arise in trials of surgery along with those of other disciplines requiring practical skills (eg physiotherapy). Equipoise may need to take into account not only the relative merits of two treatments but also the skills of the practitioner. This has led to a call for expertise-based randomised controlled trials in surgery and other practical disciplines[271] as well as an awareness of the possible effects of clustering by health professionals.[272]

9.33 RECs should apply the same principles in assessing research in surgery while being aware of the particular difficulties that invasive treatment poses.

Use of audio/video recordings

9.34 Audio or video recordings present special problems in relation to consent. At the time of agreeing to take part, the participant will not know the content of the recording.

9.35 Consent should include a specific description of the uses (eg for teaching) that will be made of the material, and the audience or research staff to whom it will become available.

9.36 There should be provision for removal of consent after the recording has been made and an offer to review the recording if wished. Material can then be destroyed if wished.

9.37 Many audio and video recordings represent a valuable store of data. REC approval should not normally be contingent upon destruction of data on completion of the project.

9.38 If data storage is planned, the REC should assess the security, access and possible future uses of the data. Any future project should be the subject of further research ethics approval.

9.39 Consent should always be requested from patients for all medical photography and for subsequent use of their images, whether or not they can be identified.[273] Further guidance is available from the GMC.[274] The GMC advises that consent is not required for images taken from pathology slides, x-rays, laparoscopic images, images of internal organs or ultrasound images.

Medical devices

9.40 A medical device is defined *as any instrument, apparatus, appliance or other article whether used alone or in combination including the software necessary for its proper application by the manufacturer to be used for human beings for the purpose of: diagnosis, prevention, monitoring, treatment or alleviation of human disease; diagnosis, monitoring or alleviation of or compensation for an injury or handicap; investigation, replacement or modification of the anatomy or a physiological process; control of conception; and which does not achieve its principal intended action in or on the body by pharmaceutical, immunological or metabolic means but which may be assisted in its function by such means* (MHRA).

9.41 The variety of devices is wide – from robotics and pacemakers to basic surgical instruments or diagnostic equipment. In contrast to drugs they have short market lives. They may also malfunction, break or cause injury because of error in use.[275]

Device Directive (Medical Devices Directive 93/42/EEC, 2002)

9.42 Drug/device combinations are common (eg drug eluting stents, aerosol preparations, pre-filled syringes). If the device has an ancillary action to that of the medicine, the product is controlled as a medicine but the device component still has to meet the requirements set out in the Device Directive (Medical Devices Directive 93/42/EEC, 2002). Products meeting all essential safety and administrative requirements display the 'CE mark' (the letters CE do not stand for any specific words). Without the CE mark no device can be used to treat a patient unless it is part of an approved clinical investigation. UK investigations require review and approval from the MHRA.

9.43 Despite the differences in regulation between devices and medicines, there should be no essential difference in ethical review. However, given the specialised and variable nature of device regulation, review of protocols is being limited to a small number of RECs designated by COREC/NRES.

Research and the Internet

9.44 Proposals to use the Internet in research are growing and most RECs are likely to encounter such proposals.

9.45 In recruitment, internet advertisements may appear on the web page of a research sponsor or contract research organisation or on the website of a patient organisation. Such advertisements have the potential to reach a larger population than traditional methods. However, such an approach may be considered as a natural extension of the advertising used in many studies, whether by poster, press or radio.

9.46 The advertisement should be submitted to the REC in the usual way as part of the protocol for approval.

9.47 The Internet has also been used to treat patients, mainly using counselling techniques in emotional or psychiatric conditions. This raises wider issues. There is the potential for the patient to be recruited with no personal contact with the investigator at all and across national boundaries. There are also security issues of confidentiality.

9.48 RECs in the UK are likely to have little influence on internet research initiated abroad yet recruiting in the UK. Experience of such studies is currently small. We would expect that a UK-based study would be submitted to the REC with the usual standards applicable to any other protocol.

9.49 In particular, registration forms and questionnaires with personal identifiers should receive a high degree of security. Passwords and the best available technology, such as encryption, should be used in order to make sure that only authorised persons are able to read the data. With no face-to-face contact, agreement to participate should be based on a clear disclosure of the purposes for which data are being collected and who (investigator and institution) is collecting or accessing them.[276]

Complementary and alternative medicine

9.50 Complementary and alternative medicine (CAM) refers to a number of diverse medical systems, each with its own philosophy, diagnostic criteria and therapeutic modalities. Other terms include 'unorthodox', 'fringe', 'holistic' or 'sectarian' medicine. At one end of the spectrum, CAM overlaps with orthodox practice; at the other extreme, CAM involves practices that many (including CAM practitioners) would consider very strange. Use of CAM is growing throughout the Western world and practised by many orthodox practitioners.[277,278]

9.51 Research on CAM has increased[279,280] although still accounting for under 0.2% of UK research spending.[281]

9.52 Many CAM therapies are described by their practitioners as scientific, albeit science by a 'different paradigm'.[277]

Evidence of efficacy

9.53 Evidence for the efficacy of some CAM therapies has grown and their widespread use makes research desirable,[282] despite their unorthodox theoretical basis. Respect for cultural diversity mandates tolerance of the beliefs and practices of others, provided this does not harm patients.

Herbal products

9.54 We note that there may be special issues in relation to herbal products which may fall between regulation as dietary supplements and regulation as medicines.[283]

9.55 The ethical requirements underlying all research are universal. There are no valid reasons for exempting CAM from these. CAM research should have validity both in terms of social value and be conducted with sufficiently rigorous methods so that findings have scientific validity.[278] Considerations of consent and confidentiality are similar.

9.56 The application of traditional concepts of clinical equipoise may be difficult. Investigators must negotiate the justification to conduct the trial, as well as criteria for informed consent on a case-by-case basis. Relevant considerations will be whether the CAM treatment is being compared with conventional treatment as a supplement or, where no effective conventional treatment is available, with an inactive control (with whatever preliminary evidence concerning safety and efficacy is available).[284]

The need for placebo controls

9.57 It is sometimes claimed that techniques of treatment protocols, randomisation, double blind conditions and placebo controls distort the personal attention, individual treatment selection and the use of healing rituals that characterise much CAM. Without placebo controls the efficacy of many CAM therapies will remain uncertain. Difficulties of this sort are also found in conventional medicine eg studies of psychotherapy and surgery.

9.58 Recruitment into CAM studies should focus recruitment on patients who are at least open to the possibilities of CAM practices. As most CAM patients pay privately for their treatment, waiving fees in return for participation may need to be considered.[285] The REC may need to consider the potential for improper inducement, as in other areas of research.

9.59 As with clinical use of CAM, so too in research the possibility arises of conflicts between doctors and patients. RECs should be aware of these possibilities.[286,287]

9.60 Where possible, placebo-controlled comparative studies with randomisation and blinding should be carried out, but other research designs may still be desirable as in other areas of medicine.

10 Financial considerations

Payments to investigators or departments

Relationship with sponsoring companies must be declared

10.1 Any pecuniary relationship of an investigator with a sponsoring company has ethical implications[288] and should be declared to the REC, with details of both the amount and nature (money, gifts, travel etc) of payments to investigators. Such relationships constitute a conflict of interest.[289–296]

10.2 Similarly, payments to departments and to institutions by a pharmaceutical company or contract research organisation should be declared.

10.3 Even where ethically permissible economic arrangements exist, safeguards are needed to protect against the appearance of impropriety. Clinical investigators should therefore disclose any ancillary ties to companies whose products they are investigating, such as participation in educational activities or in other projects supported by the company or any other conflicts of interest.

10.4 Money is the most tangible motivating factor for many people. Excessive payments may induce investigators to exploit research participants or participants to take unacceptable risks (eg by not declaring excluding factors for a study).[297]

10.5 Personal or departmental involvement in a company or direct ownership of its shares (excepting ownership where decided by a fund manager) are interests that should be declared.

GMC and the ethics of payments

10.6 The General Medical Council advises that doctors must not ask for or accept any inducement, gift or hospitality, which may affect or be seen to affect their judgment. 'You should not offer such inducements to colleagues.' [298] The GMC also states that 'It is unethical to accept payment unless it has been specified in a protocol, reviewed by a REC'.

10.7 The RCP gives advice to investigators in its report, *The relationship between physicians and the biomedical industry*.[49]

10.8 The RCP recognises that per capita payments are widely used in recruitment to clinical trials and that such payments relate work done to reward. Nevertheless, it draws attention to the possible conflict of interest between the reward and the temptation to investigators to recruit inappropriate patients to studies or to retain them improperly when recruited. These temptations may be stronger in trials with competitive recruitment of participants.

10.9 Doctors may be asked to recruit patients to a study in which they are not personally involved. Financial reward for such recruitment should only be proportionate to the work done and to cover costs.

10.10 Council of the RCGP has recommended that 'full details of any payments made to doctors or other clinicians who recruit patients into trials should be included in the information given to patients, including details of the amounts involved and an explanation of those amounts'.[299] While such transparency is admirable, we acknowledge that further information

is required to explain why payments are being made eg for setting up the study or for administrative work. Without such explanation, payments may seem excessive to many participants and deter their recruitment. In general, potential participants are less concerned about high levels of payment to departments than to individuals.[300]

Payments to individuals should reflect work carried out

10.11 Rates of payment should reflect work actually carried out with personnel costs reflecting normal rates for the professional involved where payments to individuals are made. Estimates of the time required for trial activities should be justified and RECs should review estimates. Sometimes such payments are additional to the investigators' regular incomes and can result either in overwork or in displacing other more pressing clinical activity. Payments should always be made into a trust or practice account and never into a personal investigator's bank account. Patient information leaflets should make patients aware when trusts or practices or doctors and other health professionals who recruit patients into trials are being paid for the work undertaken, as well as for the facilities required to enable the work to be done. Participants have a right to see further details regarding these payments if they so wish.

Payments to research participants

10.12 Payment to research participants, both healthy volunteers and especially patients, is controversial. Inducements that would ordinarily be acceptable may become undue influences if the participant is especially vulnerable. The shift to a commercial ethos (investigator as buyer, participant as seller) challenges the professional ethos of concern for the welfare of participants, which is the research participant's most important safeguard against harm.[301] American institutional policies vary widely on the basis for payment,[302] whether market model, a wage payment model or a reimbursement model.

Considerations regarding payment to research participants

10.13 We believe that payment to patients is acceptable in some cases.[303] Whether patients or healthy volunteers, some worry that payment may target economically vulnerable persons or compromise scientific integrity by altering the makeup of the population taking part. The reverse may also be true. The burdens of research may fall disproportionately on the poor if payment levels are too low.[304] Lower levels discourage the wealthy and higher payments may achieve a more representative sample. Money may also compromise the voluntary nature of the participant's decision. Empirical data are sparse but one American study found no evidence that commonly used payment levels represent undue or unjust inducements.[305] We note that payments may be variably made for time, inconvenience, travel or incurring risk. Given that risks should be minimal for the study to be ethical in non-therapeutic studies, it should not be necessary to pay for taking significant risks. Payments should not be so high as to induce people to incur a risk which is perceived as high. We acknowledge that even where the risk is low, the hazard may be high (ie a low probability of a serious adverse event).

10.14 Paying research participants is essential for recruitment to phase I studies in healthy volunteers. Most contract research organisations provide incentives to healthy volunteers to compensate for the amount of time spent participating in a trial, and reimburse for inconvenience and travel expenses incurred. plus costs of child care, meals, and accommodation.[306] RECs should ensure that payments levels will not interfere with the benefits that unemployed people or those classed as incapable of work may receive, or should ensure that they are advised accordingly.

10.15 In phase I studies, study-related medical care and study medication(s) or treatment(s) are generally provided free of charge. Although the trial sponsor and investigator jointly make the decision about the amount volunteers are paid, this must be reviewed by the REC to ensure it is appropriate. The amount received for participation should be in proportion to the amount of time required in the trial. As some trials may require a site visit for just two hours, while others require an overnight stay or live in for two weeks, the total amount received as a healthy volunteer could vary widely. Practical guidance is available from INVOLVE.[306]

RECs should be given information regarding payments and compensation

10.16 The responsibility of the REC is also specified in ICH GCP guidance which advises that the REC 'should obtain ... information about payments and compensation available to subjects (3.1.2)' and 'should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject' (3.1.8). In 3.1.9 it suggests that the REC 'should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified'. 'Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following: The anticipated prorated payment, if any, to the subject for participating in the trial.' (4.8.10).

10.17 Payments are not normally made to patients but may be considered under certain circumstances. Partial payment based on the amount of time or procedures actually finished should be offered rather than payment only on completion of the study. Completion bonuses are unethical. The sums offered in phase 1 studies provide a guide to reasonable levels of payment in those occasional cases of payment to patients. Payment may help patients distinguish procedures that are done purely for research purposes from those done for their benefit, thus minimising vulnerability due to 'therapeutic misconception'.

10.18 Such payments should always be detailed in patient information sheets.

Small payments may be made in recruiting individuals for research

10.19 The offer of small payments in kind (eg entry into a prize draw or a voucher for a small amount) may be considered acceptable in recruiting individuals into some studies, eg focus groups where the participant receives no therapeutic benefit.

10.20 Where there are additional visits, payment for travel or for time lost from work or other legitimate expenses should always be offered to patients.

Financial arrangements in commercial research

10.21 Financial governance in NHS trusts should explicitly address financial arrangements in commercial research. Without standard policies for paying research participants, there are uncertain safeguards against unfair or coercive payment. We would encourage organisations to develop mechanisms for tracking studies that pay participants, as well as written guidance about participant payment to guide both investigators and RECs.

REC members

10.22 REC members should also declare financial relationships with industry as these constitute conflicts of interest.[307]

Appendix 1a

Differentiating research, audit and service evaluation/development: a guide from COREC/NRES

September 2006

The Ad Hoc Review recommended COREC should develop guidelines to aid researchers and committees in deciding what is appropriate or inappropriate for submission to RECs, and COREC (now NRES) (with the health departments and with advice from REC members) has prepared the guidelines in the form of the attached table.

Research	Clinical audit	Service evaluation
The attempt to derive generalisable new knowledge including studies that aim to generate hypotheses as well as studies that aim to test them.	Designed and conducted to produce information to inform delivery of best care.	Designed and conducted solely to define or judge current care.
Quantitative research – designed to test a hypothesis. Qualitative research – identifies/explores themes following established methodology.	Designed to answer the question: 'Does this service reach a predetermined standard?'	Designed to answer the question: 'What standard does this service achieve?'
Addresses clearly defined questions, aims and objectives.	Measures against a standard.	Measures current service without reference to a standard.
Quantitative research –may involve evaluating or comparing interventions, particularly new ones. Qualitative research – usually involves studying how interventions and relationships are experienced.	Involves an intervention in use **only**. (The choice of treatment is that of the clinician and patient according to guidance, professional standards and/or patient preference.)	Involves an intervention in use **only**. (The choice of treatment is that of the clinician and patient according to guidance, professional standards and/or patient preference.)
Usually involves collecting data that are additional to those for routine care but may include data collected routinely. May involve treatments, samples or investigations additional to routine care.	Usually involves analysis of existing data but may include administration of simple interview or questionnaire.	Usually involves analysis of existing data but may include administration of simple interview or questionnaire.
Quantitative research – study design may involve allocating patients to intervention groups. Qualitative research uses a clearly defined sampling framework underpinned by conceptual or theoretical justifications.	No allocation to intervention groups: the healthcare professional and patient have chosen intervention before clinical audit.	No allocation to intervention groups: the healthcare professional and patient have chosen intervention before service evaluation.

continued over

Research	Clinical audit	Service evaluation
May involve randomisation	No randomisation	No randomisation
Although any of these three may raise ethical issues, under current guidance:		
Research requires REC review	**Audit does not require REC review**	**Service evaluation does not require REC review**

Source: COREC Ethics Consultation E-group (www.nres.npsa.nhs.uk).

Appendix 1b

Differentiating research, audit and service evaluation/development: a guide from United Bristol Healthcare NHS Trust

This guide is one of a series of How to guides produced by United Bristol Healthcare NHS Trust's (UBHT) Clinical Audit Central Office (CACO). (What is clinical audit? Bristol: UBHT/CACO, 1995.)

> 'Research is concerned with discovering the right thing to do; audit with ensuring that it is done right' (Smith R. Audit and Research. *BMJ* 1992;305:905–6)

Research is about creating new knowledge about what works and what doesn't. It provides the foundations for national and/or local agreement about the kind of clinical treatment and care we *should* be providing; ie helps to answer the question **'what is best practice?'**

Clinical audit asks whether we are doing the things we have agreed we *should* be doing or achieving the outcomes we have agreed we should be achieving; ie it answers the question **'are we following agreed best practice?'**

Research and audit projects may look very similar: what differentiates them is **purpose**. For example, a piece of research may examine outcomes of a particular form of surgery in order to arrive at a conclusion about what represents best practice. A clinical audit project might look the same, but the purpose would be to see if a recommended surgical method was producing the expected outcomes.

Clinical audit is not research. Research is about obtaining new knowledge; about finding out what is best practice. Clinical audit is about quality; about finding out if best practice is being followed.

The similarities

- audit and research involve answering a specific question relating to quality of care
- both can be carried out either retrospectively or prospectively
- both involve careful sampling, questionnaire design and analysis of findings
- both activities should be professionally led

The differences

Research	Clinical Audit
Creates new knowledge about what works and what doesn't	Answers the question 'are we following best practice?'
Is based on a hypothesis	Measures against standards
Is *usually* carried out on a large scale over a prolonged period	Is *usually* carried out on a relatively small population over a short time span
May involve patients receiving a completely new treatment	**Never** involves a completely new treatment
May involve experiments on patients	**Never** involves anything being done to patients beyond their normal clinical management *
May involve patients being allocated to different treatment groups	**Never** involves allocation of patients to different treatment groups
Is based on a scientifically valid sample size (although this may not apply to pilot studies)	Depending on circumstances, may be pragmatically based on a sample size which is acceptable to senior clinicians
Extensive statistical analysis of data is routine	Some statistical analysis may be useful
Results are generalisable and hence publishable	Results are only relevant within local settings (although audit processes may be of interest to wider audiences and hence audits are also published)
Responsibility to act on findings is unclear	Responsibility to act on findings rests with clinical directorate/s
Findings influence the activities of clinical practice as a whole	Findings influence activities of local clinicians and teams
Always requires ethics approval	Does not require ethics approval†

*Patient surveys could be construed as doing something to patients 'beyond normal clinical management'. Surveys should be designed in such a manner as to cause minimum possible disruption to patients and may require specific ethics approval.

†Simple statistical analysis eg measures of central tendency (mean, median, mode) and dispersion (ranges of data) is a routine part of clinical audit; however, more complex analysis (eg t-tests, correlations) is not always necessary. Healthcare professionals may consider results to be 'clinically significant' even if they are not 'statistically significant' (and vice versa).

The interface between audit and research

The NHS Clinical Effectiveness initiative explicitly links clinical audit and research: without research we won't know what clinically effective practice is; without audit we won't know whether it is being practised. More specifically:

- Clinical audit can be legitimately viewed as the final stage of a good clinical research programme
- Alternatively research could be viewed as a precursor to the clinical audit process
- Research can identify areas for audit
- Audit can pinpoint areas where the research evidence is lacking
- The audit process assists with the dissemination of evidence-based practice

For example, research might ask:
'What is the most effective way of treating pressure sores?'

Audit would then ask:
'How are we treating pressure sores and how does this compare with accepted best practice?'

The piece of research would involve measuring outcomes as a way of finding out what the best treatment is. The audit would measure process (are we doing the things we should do?) but might also look at outcomes, in this instance to **monitor** the success of a treatment which is known to work, rather than to find out *whether* it works (a subtle but important difference).

Grey areas

Even with this guidance, you may still find yourself struggling to decide whether your proposed project is audit or research. Indeed it is possible that larger projects may contain elements of both audit and research, in which case both clinical audit and the RDSU should be informed (although you are not expected to complete two proposal forms).

However, it is possible to get so bogged down in trying to categorise your project that you lose sight of your objectives. Use common sense and concentrate on three key questions:

1. Is the purpose of the proposed project to try to improve the quality of patient care in the local setting?
2. Will the project involve measuring practice against standards?
3. Does the project involve anything being done to patients which would not have been part of their normal routine management?

If you can answer 'yes' to the first two questions and 'no' to the third, it is safe to say that your project conforms to the requirements of clinical audit. If it doesn't, you're probably doing research.

This guide has been produced by the UBHT Clinical Audit Central Office and is available on the UBHT Clinical Audit website (www.ubht.nhs.uk/clinicalaudit). It is reproduced with kind permission.

See also references 346–350.

Appendix 2

Websites

Websites change and a long list is likely to be incorrect in detail after a short time. Almost all the websites referred to in these guidelines can be accessed either through an internet search engine such as Google or via links on the following sites:

National Research Ethics Service: www.nres.npsa.nhs.uk (formerly Central Office for Research Ethics Committee (COREC))

Department of Health: www.dh.gov.uk

Ethics Research Information Catalogue: www.eric-on-line.co.uk

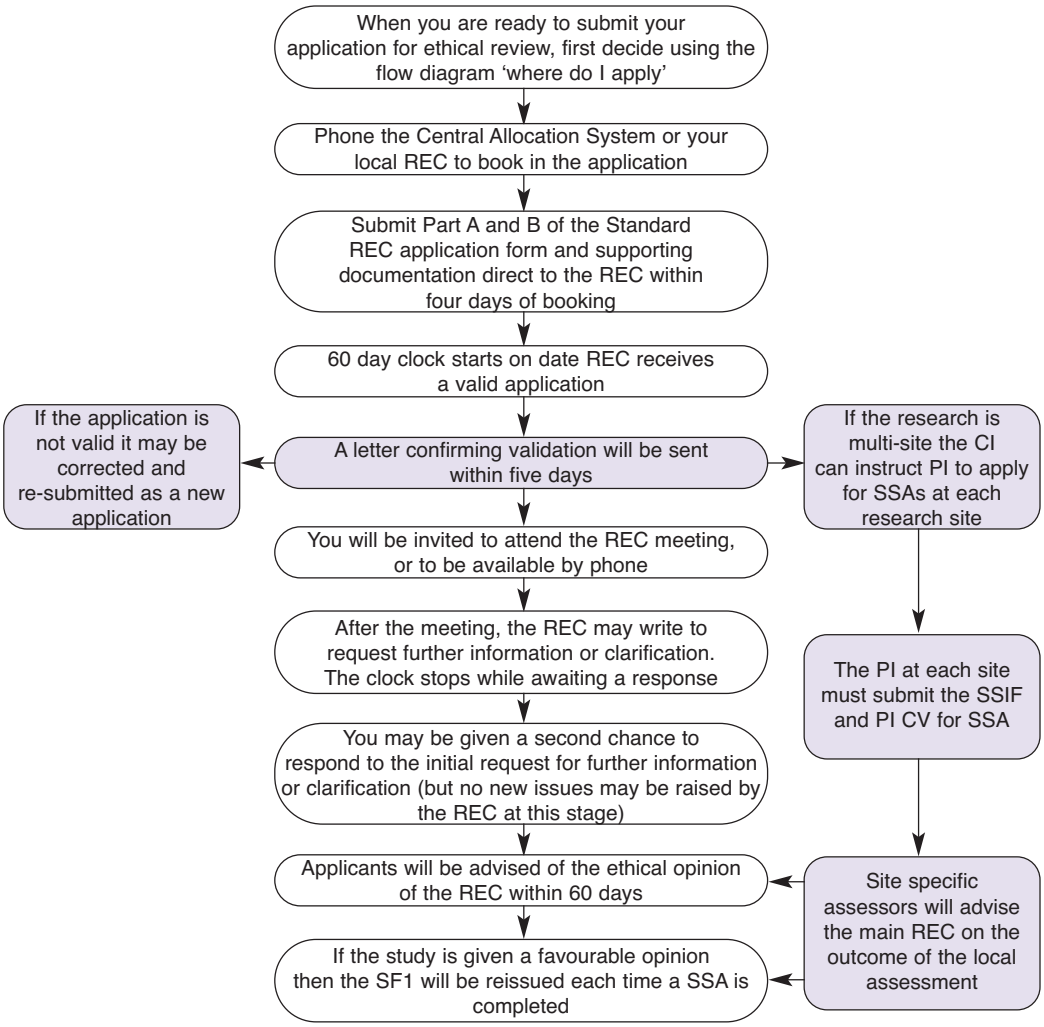
Medical Research Council: www.mrc.ac.uk

The Wellcome Trust: www.wellcome.ac.uk

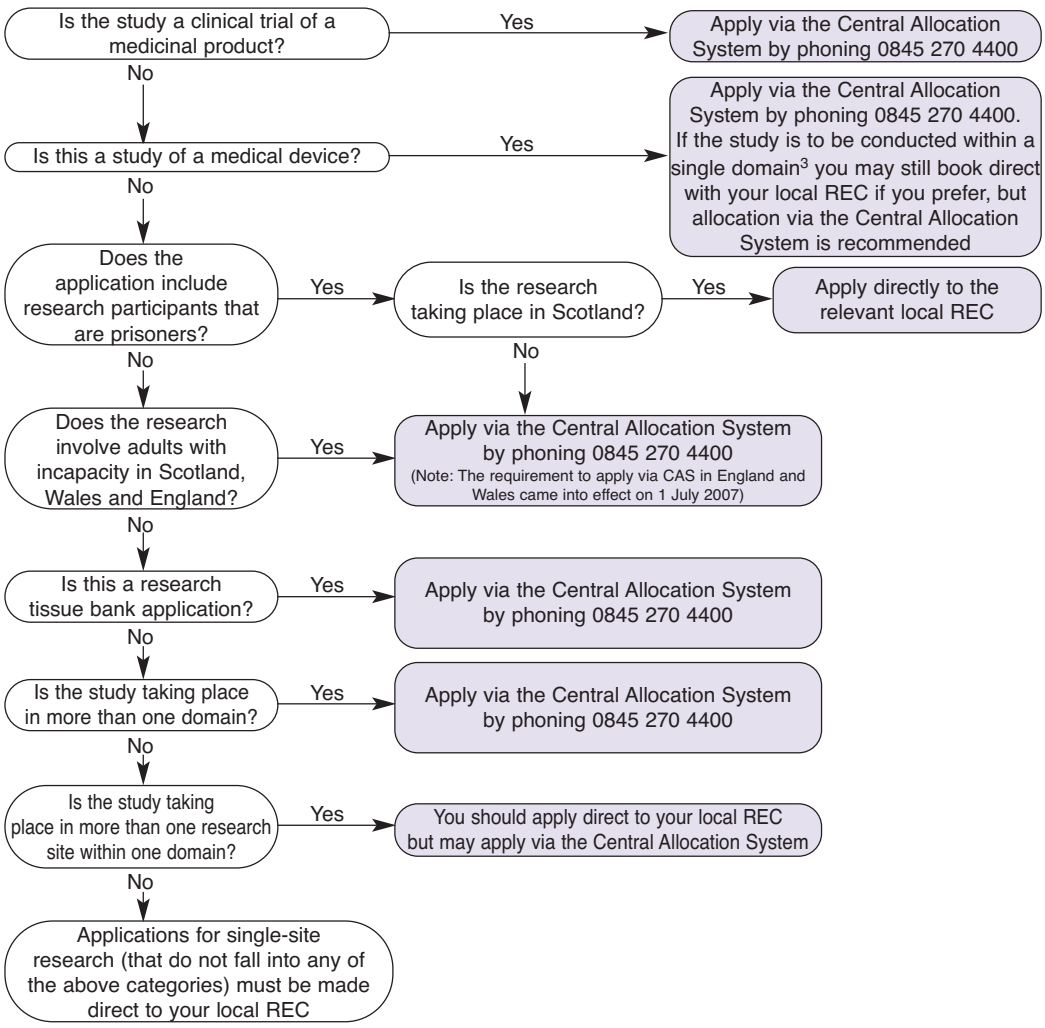
Appendix 3

Guidance from the National Research Ethics Service on applying for ethical review

How to apply

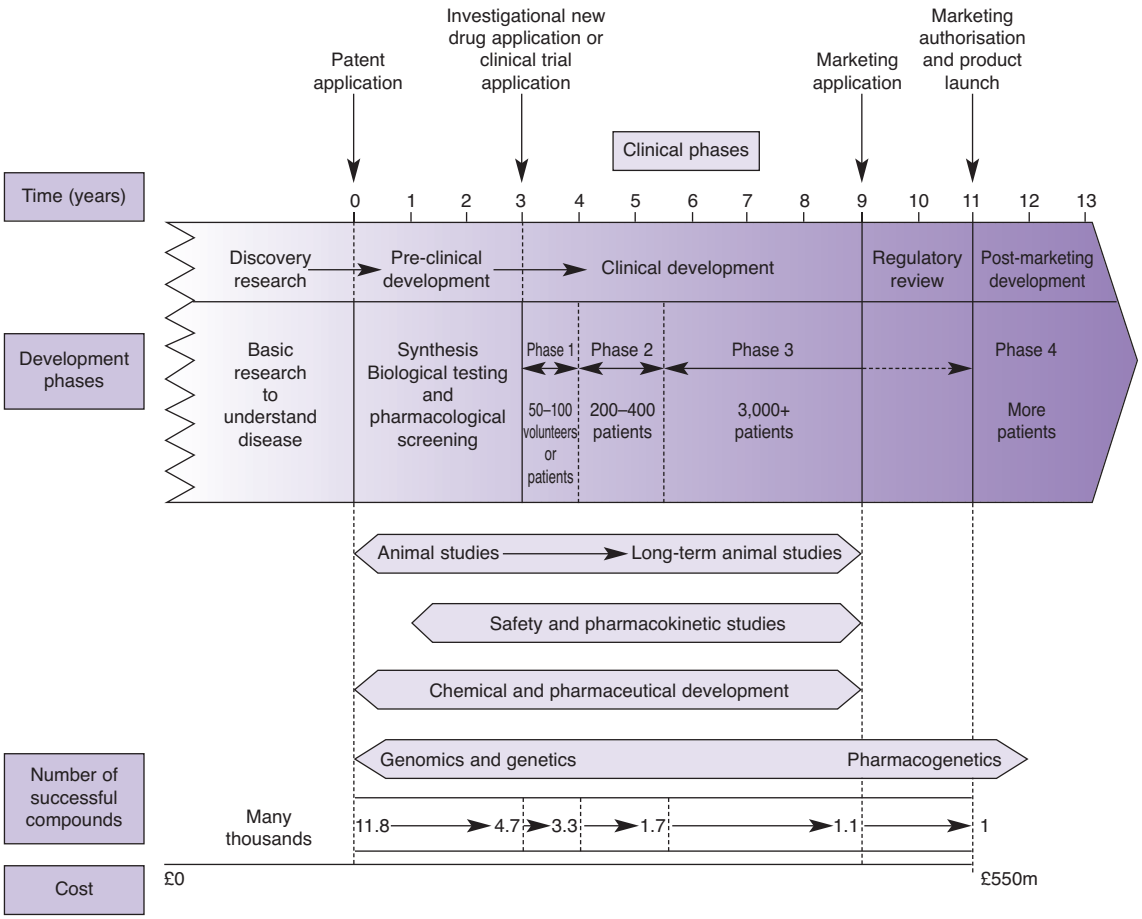


Where do I apply?



Appendix 4

Drug development (from Goggins,[56] reproduced with kind permission)



Appendix 5

Glossary

This short glossary is not a substitute for a medical dictionary, nor for the detailed glossary provided in the Standard Operating Procedures, available on the NRES website (www.nres.npsa.nhs.uk/docs/guidance/SOPs.pdf).

ABHI: Association of British Healthcare Industries. An organisation to represent manufacturers and suppliers of medical devices.

ABI: Association of British Insurers. The association has issued helpful guidance on HIV testing and on genetic risk in the context of research (www.abi.org.uk).

ABPI: Association of the British Pharmaceutical Industry. A voluntary trade association of about 100 drug companies, supplying over 90% of NHS drugs. Responsible for industry policy, relations with government, standards, codes of practice etc; but not a research sponsor (www.abpi.org.uk).

Academy of Royal Colleges: A body that represents all the medical royal colleges – there are now over a dozen (www.aomrc.org.uk).

Amendments: A change to the protocol of a study after the study has started. The definition is laid down by the EC Directive. See also 'revisions'.

AREC: The Association of Research Ethics Committees. An independent association with a focus on training and the interchange of ideas. Membership open to all RECs and their members (www.arec.org.uk).

ARSAC: Administration of Radioactive Substances Advisory Committee. Investigators need an ARSAC certificate for all clinical research involving the use of radioactive substances. The application for such a certificate should usually be made at the same time as the protocol is submitted to the REC.

ATC: Anatomical therapeutic chemical code. An international coding system for all drugs in use worldwide. You can look up codes at www.whocc.no/atcddd

BAN: British approved name. Most drugs have a name approved by the British Pharmaceutical Commission (BPC) and a trade name – for example, paracetamol is a BAN but Panadol is a trade name used exclusively by its manufacturer.

BNF: British National Formulary. A publication from the BMA and Royal Pharmaceutical Society listing drugs prescribable in the UK with indications etc. Ask any doctor for a copy – most get one twice yearly.

BMA: British Medical Association. Although it has scientific and professional interests, it may be seen as the doctors' trade union. Has an influential ethics committee (www.bma.org.uk).

BP: British Pharmacopoeia. A compendium of medicines. BP is also an abbreviation for blood pressure (and British Petroleum).

CA: Competent authority. A body which has the authority to act on behalf of the government of an EU member state to ensure the requirements of the EU Directive are carried out in that state.

CAM: Complementary and alternative medicine. More CAM practitioners exist than UK GPs. Research details on the Prince's Foundation for Integrated Health's website (www.fih.org.uk).

CAS: Central Allocation System. All trials of CTIMPs must be centrally allocated to a REC. This is done by booking in the application with NRES. Non-CTIMP studies taking place in two or more domains (see below) must also be centrally allocated. Also an abbreviation for Chemical Abstracts Service Registry Number: a code assigned to every known chemical, even water (see: www.chemfinder.com).

CCRA: Clinical Contract Research Association. A voice for all organisations which provide clinical contract development services for the pharmaceutical and biotechnology industries. As the Association of Independent Clinical Research Contractors was responsible for the organisation of the first national training conferences for REC members in association with the University of Wales (www.ccra.org.uk).

Centre for Philosophy, Humanities and Law in Healthcare, University of Wales Swansea: The first centre to set up a master's programme in bioethics and to organise a national training meeting for REC members (www.swan.ac.uk).

Centre of Medical Law and Ethics, King's College London: Active in courses for REC members and other aspects of bioethics (www.kcl.ac.uk/schools/law/research/cmle/). There are now several other academic centres eg Preston, Oxford, Glasgow, Manchester, Keele.

CERES: Consumers for Ethics in Research. A consumer organisation that produced leaflets to advise patients on both general and genetic research. CERES was formally dissolved on December 31 2007, with its website open until July 2007.

CHM: Commission on Human Medicines. A body set up in 2005 combining the former responsibilities of the Medicines Control Agency and the Medicines Commission. Responsibilities include advising ministers on human medicines and collecting information on adverse reactions. Full details including minutes are available on the MHRA website (www.mhra.gov.uk).

CI: Chief investigator. The CI has overall responsibility and all applications must be submitted by him/her. Not to be confused with PI (see below).

CIOMS: Council for International Organisations of Medical Science: Best known for its guidelines for conduct of research ethics committees, currently being updated (www.who.int/ina-ngo/ngo/ngo011.htm).

Coercion: A much overused word in research ethics circles. Coercion is a credible or strong threat by one person that limits or adversely affects the options that another person has available – not just a suggestion that one course of action is to be preferred or recommended.

Confidence interval: The variation about which a genuine difference is thought to exist.

Cohort study: A specific group is followed long term, eg all children born in a given month.

Consent: See the DH's excellent booklet, available free or on its website (www.dh.gov.uk/consent). Consent implies agreement given without coercion after receiving information and understanding it. The adjectives 'informed' and 'valid' are superfluous and should be avoided. ('Informed consent' is a term of legal significance in the USA, hence its frequent use in American literature.)

COREC: Central Office for Research Ethics Committees. Although formally an organisation with responsibilities for England only, COREC has had a coordinating role, assisting developments in Scotland, Wales and Northern Ireland. See section 1.11. Now the National Research Ethics Service (NRES).

Council for Professions Supplementary to Medicine: Established as a gatekeeper between the boards representing individual professional groups (eg paramedics, physiotherapists) and the Privy Council. This has now become the Health Professions Council. (www.hpc.org.uk), and includes many familiar professional groups but not others (eg hospital photographers/illustrators, hospital chaplains).

Council of Europe: Not to be confused with the EU; an association of 26 European states. Published the Convention on Human Rights and Biomedicine on Biomedical Research – which may pass into UK law (www.coe.int, also: www.coe.int/T/e/Communication_and_Research/Press/Topics/Bioethic.asp).

Cross-over trial: Patients cross over from one therapy to another, so both groups receive the drug. See: Sibbald B, Roberts C. Understanding controlled trials: Crossover trials. *BMJ* 1998;316:1719–20.

Cross-sectional study: A study across a population at a given time.

CRO: Contract research organisation. An independent private company that may organise clinical trials for a pharmaceutical company – a sort of middle man between the company making the product and the clinical investigator.

CSD: Committee on Safety of Medical Devices. A standing committee of the MHRA concerned with medical devices. Minutes of its meetings are posted on the web (www.mhra.gov.uk).

CSM: Committee on Safety of Medicines. A standing committee responsible to the MHRA for monitoring and advising on drug safety. Since 1964 the CSM and its predecessor committee have received over 400,000 notifications of possible reactions via the Yellow Card scheme.

CTA: Clinical trials authorisation. A trial sponsor must make an application to a competent authority in order to carry out the clinical trial of an investigational product. Regulations governing this are set out on the MHRA website.

CTIMP: Clinical Trial of an Investigational Medicinal Product (any other study is a non-CTIMP).

DES: Device evaluating service

DNA: **Deoxyribonucleic acid** – which everyone's heard of, but not all can pronounce. The chemical in chromosomes and genes in which genetic information is stored.

Domain: The area covered by a SHA (England), a health board (Scotland), a regional office of the Welsh Assembly Government R&D office (Wales) or the whole of Northern Ireland.

EFGCP: European Forum for Good Clinical Practice. A Brussels-based organisation with both individual and organisational membership dedicated to promoting the interests of patients in clinical research through the development of European ethical and scientific standards. The EFGCP provides a common meeting ground for the many disciplines and organisations affected by GCP (www.efgcp.be).

EMEA: European Medicines Evaluation Agency. A European Union agency for assessing medicinal/licensing products in the EU, located in London. Various reports are on its website (www.emea.eu.int).

English not a first language: Not to be confused with 'unable to speak English' (consider, eg North Wales).

ERIC: Ethics Research Information Catalogue. An online resource of information on research ethics, publications, news, issues and arguments etc (www.eric-on-line.co.uk).

Ethics: A branch of morals or moral philosophy. Exploring the meaning of words like 'good' and 'right' would be termed 'meta-ethics'. Also used to mean the definition of acceptable conduct for a profession or professional, often set out in a code. In research ethics, both dimensions apply.

EudraCT: The European Clinical Trials Database

FDA: Food and Drugs Administration. Enormously influential American body responsible for drug licensing in the USA (www.fda.gov/default.htm).

GMC: General Medical Council. The body responsible for regulating doctors. Entirely funded by doctors, but with a part-lay membership. Maintains the medical register. Publishes guidance on research, confidentiality, consent (all available free of charge or on the website, see: www.gmc-uk.org).

GMP: Good manufacturing practice – a recognised standard for manufacturing and processing.

GTAC: Gene Therapy Advisory Committee. Set up after the report of the 1992 Clothier committee to advise ministers on proposals for gene therapy research and related developments (www.advisorybodies.doh.gov.uk/genetics/gtac/).

HPC: Health Professions Council. The regulatory body for 13 professions including physiotherapists, dietitians and radiographers (www.hpc-uk.org).

HEFA: Human Embryology and Fertilisation Authority. A statutory body set up under the Act to collect data, license and regulate practice and research in fertility treatment and embryo research (www.hfea.gov.uk). Planned to be merged with the HTA as RATE.

HITF: Health Industries Task Force

HPA: Health Protection Agency. Established to provide an integrated approach to protecting the public health (www.hpa.org.uk).

HSE: Health and Safety Executive. An enforcing agency of the Health and Safety Commission that is responsible for health and safety regulation in Great Britain. Looks after these in hospitals (among other places). Relates to the Department of Work and Pensions (www.hse.gov.uk).

HTA: Human Tissue Authority. Set up under the Human Tissue Act to oversee its implementation and has issued valuable guidance (www.hta.gov.uk). Planned to be merged with HEFA as RATE.

HTC: Health Technology Cooperatives

Human Genetics Commission: An independent advisory body to government on social and ethical issues in human genetics. Recent (2003) report on sale of genetic tests to the public, for example (www.hgc.gov.uk).

ICD: ***International statistical classification of diseases and related health problems.*** Now in its 10th edition. Sometimes quoted in protocols, perhaps especially in those involving more contentious diagnostic entities (www.who.int/classifications/icd/en).

ICH GCP: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Harmonised Tripartite Guideline of Good Clinical Practice. The 'tripartite' refers to the regulatory bodies of the European Union, Japan and the USA. All UK ethics committees are supposed to be compliant with these guidelines in so far as they advise on pharmaceutical research. You should have a copy. The European Forum for Good Clinical Practice is on www.efgcp.be

IM, IV, SC: Professional jargon! Intra-muscular, intravenous, subcutaneous. Refers to the route of administration of drugs and fluids.

INVOLVE: A national advisory group. Originally named the Consumers in NHS Research Support Unit, funded by the National Institute for Health Research to promote and support active involvement in NHS, public health and social care research. Links on its site will direct you to other consumer, advisory and research bodies (www.conres.co.uk).

IRB: Institutional Review Board. The American equivalent of the REC – with similar controversies!

ISRCTN: International standard randomised controlled trial number – which can be obtained from www.controlled-trials.com. Registration is (still) optional. Not a job for the REC.

Licensing: All drugs are licensed by the MHRA (see below) for specific indications. Many drugs are routinely used outside their licensed indications especially in paediatric practice. But no drug can be promoted for an unlicensed use.

MA: Master of Arts, of course (or Magister Artium or Magister in Artibus if you will). But more prosaically, marketing authorisation also. A code given to manufacturers when marketing of a drug is approved. Can be found on the SPC (see below), the product packaging or on the datasheet on www.medicines.org.uk

Main REC: The REC undertaking the ethics review for a multi-site study, whether 'recognised' or not.

MHRA: **Medicines and Healthcare products Regulation Agency**. An executive agency of the DH created by a merger of the former Medicines Control Agency and the Medical Devices Agency. The Agency is responsible for ensuring that medicines and devices work and are safe (www.mhra.gov.uk).

MB/BM: Bachelor of Medicine. The main university qualifying degree in medicine in the UK. Only a small minority of doctors hold the MD degree. 'Doctor' is a courtesy title in the UK as most doctors do not hold doctorates. The BCh or BS stands for bachelor of surgery and is usually part of the same degree. Some also award the BAO – bachelor of the art of obstetrics.

MD/DM: A research degree in the UK (and many Commonwealth countries), roughly equivalent (in the UK) to a PhD in medical sciences. In other countries a qualifying degree only for medical practitioners.

Mr/Mrs (etc): Courtesy title in the UK for doctors in surgical specialties. A throw-back to the days when surgeons were barbers and did not hold doctorates from the universities. A courtesy title only – there is no qualification that entitles it.

MRC: Medical Research Council. A government quango that both sponsors research through its grants and runs specific research units. MRC research is generally of the highest standards (www.mrc.ac.uk). Also excellent guidance on research ethics eg tissue samples.

NEAT: New and Emerging Applications of Technology

NHS: National Health Service. Of course – although some would say there are now four services, as health is a devolved function. The result of one of the finest pieces of UK legislation in the 20th century and to be treasured. RECs are part of the NHS and not independent as some members used to think.

Northern Ireland Office of Research and Development: The R&D Office is a directorate of the Northern Ireland Health and Social Services Central Services Agency and was established to promote, coordinate and support R&D within the field of health and social care.

NPSA: National Patient Safety Agency. A government agency responsible for ensuring and promoting quality of care. One of its arms is COREC (now NRES).

NRES: National Research Ethics Service. The new name for COREC following the Warner Report, reflecting its changing functions.

Nuffield Council on Bioethics: An independent council jointly funded by the Nuffield Foundation, the MRC and the Wellcome Trust to consider bioethical issues. Reports such as *Human tissue, ethical and legal issues* have been highly influential (www.nuffieldfoundation.org/bioethics).

Observational study: No experimental intervention, the population is simply observed.

Open label extension study: After the double-blind phase of a trial the drug is offered to all participants – usually before analysis of the first part. Used to gain further information on safety and efficacy.

OREC: A network of offices for RECs. OREC managers were based regionally and had a role in the supervision, support, training of RECs. Reorganisation has led to a structure with two heads of operations and one head of quality assurance, with NRES managers reporting to them and with ORECs becoming part of National Research Ethics Centres.

Parallel group study: Two or more groups studied in parallel. See also: Sibbald B and Roland M. Understanding controlled trials: why are randomised controlled trials important? *BMJ* 1998;316:201.

Partially-randomised patient preference trials: When blinding is impossible and interventions may require active patient participation, partial randomisation may be a solution. See text and: Torgerson D, and Sibbald B. Understanding controlled trials: what is a patient preference trial? *BMJ* 1998;316:360.

Peer reviewed publication: The best sign of good science. The world's leading general journals are: *New Engl J Med, The Lancet, JAMA, BMJ.*

PI: Principal investigator. The person responsible for the research at a particular site. Not to be confused with CI (see above).

Pragmatic trial: One in which all patients likely to benefit from the drug are included (also called an 'inclusive' trial). Needs lots of patient to rule out effects of particular sub-groups. See: Roland M, Torgerson DJ. What are pragmatic trials *BMJ* 1998;316:285.

Phase I study/trial: New drug given to humans for the first time: generally healthy volunteers, but patient volunteers where toxicity may prevent administration to healthy volunteers (eg cancer drugs). To investigate pharmacokinetics, dosing, safety.

Phase II study/trial: Early therapeutic trials in small numbers of closely monitored patients for information on efficacy, dose and safety.

Phase III study/trial: Performed when drug has good initial safety profile and likely to be useful. Usually randomised controlled trials. Essential for licensing.

Phase IV study/trial: Carried out on licensed drugs to compare efficacy and safety with established agents or investigate long-term effects.

Physician: In American usage, a medical practitioner; in the UK when used without qualification as in 'consultant physician', a specialist in internal medicine, equivalent to the US 'internist'.

POM: Prescription only medicine. As opposed to OTC (over the counter) medicine which can be bought without prescription. Most POMs attract a prescription charge, unless exempt; some are charged at full cost except for certain categories of patient (eg sildenafil, better known as Viagra).

Power: A study has adequate power if there are enough observations to detect the differences predicted between the treatments being studied with statistical confidence.

RATE: Regulatory Authority for Tissues and Embryos. A proposed government 'arms length body' representing a merger between the Human Tissue Authority and the Human Fertilisation and Embryology Authority, along with some functions of the Medicines and Healthcare products Regulatory Agency. It will be responsible for the regulation and inspection of all functions relating to human tissues – cells, gametes, tissues, embryos, organs; plus the procurement, testing, storage and distribution of blood and blood products. Proposal not supported by Parliamentary Joint Committee (July 2007).

RCGP: Royal College of General Practitioners (www.rcgp.org.uk). Other medical royal colleges' websites can be found at www. followed by the initials then either 'org' or 'ac'.uk

RCN: Royal College of Nursing. The nursing and midwifery equivalent to the BMA and medical royal colleges (www.rcn.org.uk).

RCP: Royal College of Physicians. The London college is the oldest of the medical royal colleges and was responsible for producing the first guidance on research ethics committees. Maintains a special interest in this area. Last edition of its guidelines was published in 1996 (www.rcplondon.ac.uk).

Recognition: Under the Regulations implementing the EC Directive, UKECA 'recognises' certain RECs to review CTIMPs.

Revisions: Changes to the protocol made before the study starts (compare 'amendments' above).

SAE: Serious adverse event. These are notified to the MHRA and also to ethics committees under ICH GCP. SAEs are not necessarily caused by the drug. See also SUSAR.

SHA: Strategic health authority

SMO: Site management organisation: a multi-site organisation whose primary activity is the conduct of clinical trials using owned sites or sites with which a pre-existing, permanent contractual undertaking exist. A SMO offers consistency of management of trial conduct and sensitive, professional management of the patient/investigator interface. There are different types of SMOs eg GP networks (eg Profiad), Owned Site Organisations (eg Synexus, see for example: www.synexus.co.uk).

SOP: Standard operating procedure. As set out by NRES, the SOPs are a necessary, but lengthy (over 200 pages), bureaucratic document to meet the obligations of the UK under the EC Directive. They are designed to apply to review of all research by RECs and to the review on a voluntary basis of research outside the NHS in the fields of health and social care where the opinion of a NHS REC is sought. See NRES website.

SSA: Site-specific assessment. A check that local facilities, investigators, support staff etc are suitable to undertake the research. The REC may use local research governance structures to assess this.

Statistically significant: An expression of how likely an event is to be due to chance alone. If less likely than 1 in 20 (ie 5%), it is conventionally labelled statistically significant or $p<0.05$. See: Greenhalgh T. How to read a paper: statistics for the non-statistician. *BMJ* 1997;315:364 and 422. (If you find statistics impossibly difficult, this article gives a checklist of preliminary questions to help you appraise validity.)

SUSAR: Suspected unexpected serious adverse reaction. A specific term arising from the Clinical Trial Directive. In contrast to SAE, the term SUSAR should only be used for reactions occurring in studies.

UKCC: United Kingdom Council for Nursing, Midwifery and Health Visiting. The regulatory body for nurses, midwives and health visitors. In April 2002 it became the Nursing and Midwifery Council (www.ukcc.org.uk).

UKCRC: UK Clinical Research Collaboration. A partnership of organisations aiming to promote research in the UK (www.ukcrc.org).

UKECA: United Kingdom Ethics Committee Authority. Consists of the health ministers of the four UK constituent countries and set up to fulfil requirements of the EC Clinical Trials Directive (see section 1.10).

Validation: An administrative check to ensure an application for ethics review is complete – a job for the REC administrator rather than the REC member.

The Wellcome Trust: The biggest single sponsor of research in the UK. Also library and other academic resources (www.wellcome.ac.uk) Its museum collection is now housed in the Science Museum. The website has one of the best guides to bioethics on the Internet including academic units.

WHO: World Health Organization. An agency for health of the United Nations, established in 1948 and governed by 193 member states through the World Health Assembly (www.who.int).

WMA: An association of national medical associations. The WMA is responsible for the Declaration of Helsinki. It also publishes an International Code of Medical Ethics and the Declaration of Geneva, a sort of updated Hippocratic Oath with a series of declarations to be made upon becoming a doctor (www.wma.net/e/).

WORD: **Wales Office of Research and Development for Health and Social Care**. The department of the Welsh Assembly Government that funds research in Wales and provides admin support to MREC for Wales whose annual report is published on its site (www.word.wales.gov.uk).

XIRA: Xenotransplantation Interim Regulatory Authority. Formed in response to the Habgood report of 1997. Advised the minister on xenotransplantation research, except where xenotransplants involve gene therapy (see GTAC). Dissolved December 2006.

Appendix 6

Guidelines and reports from professional and government bodies

Academy of Medical Sciences. *Personal data for public good: using health information in medical research.* London: Academy of Medical Sciences, 2006.

Academy of Medical Sciences. *Strengthening clinical research.* London: Academy of Medical Sciences, 2003.

Academy of Medical Sciences. *Safer medicines.* London: Academy of Medical Sciences, 2005.

Advisory Committee on Genetic Testing. *Advice to research ethics committees*, London: DH, 1998.

Association for Improvements in Maternity Services/National Childbirth Trust. *A charter for ethical research in maternity care.* Taunton: AIMS, 2006.

Association of the British Pharmaceutical Industry. *Advertising for subjects for clinical trials.* London: ABPI, 2001.

Association of the British Pharmaceutical Industry. *Clinical trial compensation guidelines.* London: ABPI, 1991.

Association of the British Pharmaceutical Industry. *Facilities for non-patient volunteer studies.* London: ABPI, 1989.

Association of the British Pharmaceutical Industry. *Guidelines for medical experiments in non-patient human volunteers.* London: ABPI, 1998, revised 1990.

Association of the British Pharmaceutical Industry. *Guidelines for company sponsored safety assessment of marketed medicines.* London: ABPI, 1994.

Association of the British Pharmaceutical Industry. *Relationships between the medical profession and the pharmaceutical industry.* London: ABPI, 1994.

British Medical Association, the Law Society. *Assessment of mental capacity: guidance for doctors and lawyers.* London: BMA, 1995.

British Psychological Society. *Good practice guidelines for the conduct of psychological research within the NHS.* Leicester: British Psychological Society, 2004.

British Psychological Society. *Ethical principles for conducting research with human participants*, Leicester: British Psychological Society, 2004.

British Sociological Association. *Statement of ethical practice.* Durham: British Sociological Association, 2002.

Central Office for Research Ethics Committees. *Multi-centre research in the NHS – the process of ethical review when there is no local researcher. Supplementary operational guidelines for NHS research ethics committees.* London: COREC, 2000.

Central Office for Research Ethics Committees/National Patient Safety Agency. *Implementing the recommendations of the report of the Ad Hoc Advisory Group on the Operation of NHS Research Ethics Committees: a consultation.* London: COREC, Jan 2006.

Central Office for Research Ethics Committees/National Patient Safety Agency. *Building on improvement: Implementing the recommendations of the report of the ad hoc advisory group on the operation of NHS research ethics committees.* London: COREC, August 2006.

Central Office for Research Ethics Committees/National Patient Safety Agency. *Governance arrangements for NHS research ethics committees.* London: COREC, 2001.

Central Office for Research Ethics Committees/National Patient Safety Agency. *Guidelines for researchers. Patient information sheets and consent forms.* London: COREC, 2006.

Chartered Society of Physiotherapy. *Research ethics and ethics committees.* London: Chartered Society of Physiotherapy, 2001.

College of Emergency Medicine. *Position statement on consent in emergency care research.* London: College of Emergency Medicine, 2006.

College of Emergency Medicine. *Acting as a professional legal representative – guidance from the CEM Research Committee.* London: College of Emergency Medicine, 2006.

Consumers for Ethics in Research. *Medical research and you.* London: CERES, 1993.

Consumers for Ethics in Research. *Spreading the word on research or patient information; how can we get it better?* London: CERES, 1995. These valuable resources may no longer be available following the dissolution of CERES in December 2006.

Council for International Organizations of Medical Sciences (CIOMS). *International Ethical Guidelines for Biomedical Research Involving Human Subjects.* Geneva: CIOMS, 2002.

Council for International Organizations of Medical Sciences (CIOMS). *Special considerations for epidemiological research: draft guidelines.* Geneva: CIOMS, 2007.

Council of Europe. Committee of Ministers. *Convention on Human Rights and Biomedicine, on Biomedical Research.* Strasbourg: Council of Europe, 1997.

Council of Europe (Susan Venables). Steering Committee on Bioethics. Working Party on Biomedical Research. *Survey of the procedures for ethical review in the Council of Europe member states.* Strasbourg: Council of Europe, 1998.

Council of Europe (Povl Riis). Steering Committee on Bioethics. Working Party on Biomedical Research. *Ethical review of biomedical research in Europe: suggestions for best national practices.* Strasbourg: Council of Europe, 1998.

Council of Europe. Steering Committee on Bioethics. *Draft additional protocol to the Convention on Human Rights and Biomedicine, on Biomedical Research.* Strasbourg: Council of Europe, 2001.

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Department of Health. *Good practice in consent implementation guide: consent to examination or treatment.* London: DH, 2001.

Department of Health. *Confidentiality: NHS Code of Practice.* London: DH, 2003 (www.dh.gov.uk/assetRoot/04/06/92/54/04069254.pdf).

Department of Health Research and Development Forum. *Guidance on defining research with the Research Governance Framework for Health and Social Care.* London: DH, 2004.

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European Forum for Good Clinical Practice/Council for International Organisations of Medical Sciences. International Guidelines on Bioethics. An informal listing of selected international codes, declarations, guidelines etc. Published in *The EFGCP News.* Brussels: EFGCP, Autumn 2000.

European Forum for Good Clinical Practice Ethics Working Party Subgroup on Ethics Committees Reviewing Investigational Medicinal Products within the European Union. The procedure for the ethical review of protocols for clinical research projects in the European Union: a report on the structure and function of research ethics committees across Europe. *Int J Pharm Medicine* 2007;21:1–113.

General Medical Council: *Seeking consent: the ethical implications.* London: GMC, 1998.

General Medical Council. *Research: the role and responsibilities of doctors.* London: GMC, 2002.

General Medical Council: *Making and using visual and audio recordings of patients.* London: GMC, 2002.

General Medical Council: *Confidentiality: protecting and providing information.* London: GMC, 2004 (www.gmc-uk.org/guidance/current/library/confidentiality.asp).

General Medical Council: *Confidentiality FAQs.* London: GMC, 2004.

General Medical Council: *Good medical practice.* London: GMC, 2006.

General Medical Council: *Conflicts of interest.* London: GMC, 2006.

General Medical Council. *Children and young people: doctors' roles and responsibilities.* General Medical Council. London: GMC, 2007 (draft).

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Joint Committee on Medical Genetics. *Consent and confidentiality in genetic practice. Guidance on genetic testing and sharing genetic information.* London: Joint Committee on Medical Genetics, 2006.

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Medical Research Council: *Ethical conduct of research on the mentally incapacitated.* London: MRC, 1993.

Medical Research Council: *Personal information in medical research.* London: MRC, 2000.

Medical Research Council: *Human tissue and biological samples for use in research: operational and ethical guidelines.* London: MRC, 2001.

Medical Research Council: *Cluster randomised trials: methodological and ethical considerations.* London: MRC, 2002.

Medical Research Council: *Medical research involving children.* London: MRC, 2004.

Medical Research Council: *Human tissue and biological samples for use in research: clarification following the Human Tissue Act 2004.* London: MRC, 2005.

Medical Research Council: *Position statement on research regulation and ethics.* London: MRC, 2005.

Medical Research Council: *Good research practice.* London: MRC, 2005 (www.mrc.ac.uk/PolicyGuidance/EthicsAndGovernance/GoodResearchPractice/index.htm).

National Union of Students. *NUS guidelines for students participating in medical experiments.*

National Council for Hospice and Specialist Palliative Care Services. *Knowledge to care: research and development in hospice and specialist palliative care.* London: National Council for Hospice and Specialist Palliative Care Services, 1999.

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Royal College of Psychiatrists. *Guidelines for researchers and for research ethics committees on psychiatric research involving human particpants.* CR82, London: RCPsych, 2000.

United Nations Development Programme/WHO special program for research and training in tropical disease. *Operational guidelines for ethics committees that review biomedical research.* Geneva: UNDP/WHO, 2000.

UK Xenotransplantation Interim Regulatory Authority. *Guidance on making proposals to conduct xenotransplantation on human subjects* (Habgood Report), London: UK Xenotransplantation Interim Regulatory Authority, 1998.

World Medical Association. *Declaration of Helsinki* 1964, latest revision 2000. (Note: it is the 1996 version that is referred to in the Medicines for Human Use (Clinical Trials) Regulations 2004, laid down in UK law.)

Appendix 7

Other sources

A compendium of guidance has been produced by the King's College London Centre of Medical Law and Ethics containing either complete guidelines or extracts together with background essays. See: Eckstein (ed) *Manual for research ethics committees,* 6th edition. Cambridge: Cambridge University Press, 2003.

Dated but still valuable and witty is: Evans D, Evans M. *A decent proposal: ethical review of clinical research.* Chichester: John Wiley and Sons, 1996.

More recently we recommend: Evans I, Thornton H, Chalmers I. *Testing treatments: better research for better healthcare*, London: British Library, 2006. This is a short and pithy introduction to the issues surrounding research in healthcare, intended as much for the lay as the professional reader.

For research design, see: Schulz K, Grimes DA. *The Lancet handbook of essential concepts in clinical research.* London: Elsevier, 2006.

The *Induction guide for new members essential reading* is available on the National Research Ethics Service website and is particularly valuable on research ethics organisation and terminology (www.corec.org.uk/recs/training/docs/Members'_Induction_Guide_3 Essential_Reading_and_National_Information.doc).

A number of relevant theme issues of the *British Medical Journal* are easily available in most medical libraries or their contents are online:

Risk. September 27, 2003.

Nuremberg doctors' trials: 50 years on. December 7, 1996.

The randomised controlled trial at 50. October 31, 1998.

Evidence based medicine: does it make a difference? October 30, 2004.

What is a good death? July 26, 2003.

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