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GUIDELINES ON THE PRACTICE OF ETHICS COMMITTEES IN MEDICAL RESEARCH

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This report was approved by the College at the meeting held on 26 July 1984, subject to minor amendment arising from discussion and the final approval of The President.

The College wishes to record its appreciation to Dr. DR Laurence for preparing the report.

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September 1984

GUIDELINES ON THE PRACTICE OF ETHICS COMMITTEES

IN MEDICAL RESEARCH

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THE ORIGINS OF THIS DOCUMENT

This document has been prepared by Dr D.R. Laurence at the request of a Steering Committee set up by the President of the Royal College of Physicians at the behest of a meeting of Chairmen of Ethics Committees, and others, held at the College on 21st September 1982.

The document was initially drafted with advice from Drs. D.A.J. Tyrrell and D.W. Vere. It has since been circulated for comment to the 31 people present at the above meeting and has been seen by specialists in a variety of subjects including paediatrics; it has been reviewed by some Ethics Committees. The views of all these as well as of the Council and the General Meeting of the College have contributed to the document, which has also been reviewed by Aubrey Diamond, Professor of Law and Director of the Institute of Advanced Legal Studies, University of London, who is a member of an Ethics Committee.

The document is offered as a source of information and opinion on a range of matters concerning the procedures of Ethics Committees. The detail given on some topics, eg consent, liability, is the result of experience of enquiries from other Ethics Committees to the author. Relevant quotations from documents which, though published, never seem to be at hand when wanted, are also included. It has seemed desirable that practice in the UK should be in accord with international guidelines as far as possible.

ACKNOWLEDGMENT

The College would like to thank the Council for International Organisations of Medical Sciences and the World Health Organisation for permission to quote passages from their Proposed International Guidelines for Biomedical Research Involving Human Subjects (WHO/CIOMS) (Ref 1).

INTRODUCTION

It is now generally agreed that research investigations on human beings should be governed by codes such as those of the World Medical Association (Declaration of Helsinki and its Tokyo Revision) (Ref 1), and of the Medical Research Council of this country. But these are general statements and do not provide detailed guidance on how the principles which they proclaim should be applied to individual research proposals, nor how best to organise the consideration of such proposals by Ethics Committees.

Ethics Committees in this country developed when the Royal College of Physicians, in 1967, recommended that clinical research investigations should be subject to ethical review. Its report was widely circulated by the Department of Health and Social Security (DHSS).

In 1970 the College sent out a questionnaire to find out to what extent clinical investigations were then supervised (345 questionnaires, 201 replies).

In 1973 the Chief Medical Officer of the DHSS accepted the role of the College by formally seeking advice. He put to the President some questions on the composition and scope of research ethics review committees to which the College replied.

The College has continued to be concerned with the subject, and, by convening meetings of chairmen of Committees, has recognised the value of discussion and exchange of experience to promote optimal function of Committees.

The Medical Research Council requires ethical review of projects prior to making a grant as do some learned societies, and some scientific journals require it as a condition of publication. The DHSS has refrained from requiring that all institutions where clinical research is done should set up such a Committee, though it is plainly in favour of this, and its conduct so far has implied that it prefers to leave the organisation and conduct of the Committees to the profession. It has given advice (1975) based on the College's deliberations (see footnote to 5).

Such information as the College has implies that the practice of Committees is extremely variable, not only due to natural differences of opinion, but due to disagreement about, and sometimes even unawareness of, what issues fall within the scope of ethical review; in particular there may be discrepancies between institutions where research is an occasional or minor activity and those where research is a major activity.

The College considers that the time has come when it would be useful to summarise aspects of the practice of and the problems faced by Ethics Committees.

It is not to be expected that answers will be found to all the problems that beset Committees, indeed in this field there often is no single correct answer. However, it is hoped that many of the issues are usefully discussed.

GUIDELINES ON THE PRACTICE OF ETHICS COMMITTEES IN MEDICAL RESEARCH

1. The objectives of Ethics Committees. The objectives are to facilitate medical research in the interest of society, to protect subjects of research from possible harm, to preserve their rights, and to provide reassurance to the public that this is being done. Committees also protect research workers from unjustified attack. The proposed international guidelines of the World Health Organisation (WHO) and the Council for International Organisations of Medical Sciences (CIOMS) on biomedical research advise that an Ethics Committee should consider the following points :

" - the objectives of research are directed to a justifiable advancement* in biomedical knowledge that is consonant with prevailing community interests and priorities.

" - the interventions are justifiable in terms of these objectives; the required information cannot be obtained from animal models; and the study has been designed with a view to obtaining this information from as few subjects as possible who will be exposed to a minimum of risk and inconvenience.

" - the responsible investigator is appropriately qualified and experienced, and commands facilities to ensure that all aspects of the work will be undertaken with due discretion and precaution to protect the safety of the subjects.

" - adequate preliminary literature research and experimental studies have been undertaken to define, as far as practicable, the risks inherent in participation.

" - every effort will be made to inform prospective subjects of the objectives and consequences of their involvement, and particularly of identifiable risks and inconvenience.

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* Research directed to a "justifiable advancement" may be defined as an intention to increase the understanding of some of the fundamental aspects of human structure or function in disease, but also in health, as well as to test the effectiveness of various forms of diagnostic technique or the prevention or treatment of disease.

" - any arrangement to delegate consent has adequate justification, and appropriate safeguards will be instituted to ensure that the rights of the subjects will in no way be abused.

" - appropriate measures will be adopted to ensure the confidentiality of data generated in the course of the research." (Note: this refers to personal clinical details and to any fact which could be attributed to an individual subject).

In undertaking the above functions it is important to be continuously aware of the need to avoid impeding good medical research. The Committee should indeed seek to facilitate good research.

2. The nature of the decision that the Committee has to make is largely defined by 1. above. But the question of the extent to which scientific quality, design and conduct should be considered continues to cause difficulty. It has been pointed out that badly planned, poorly designed research that causes inconvenience to subjects and may carry risk without producing useful or valid results, is unethical. Plainly, full scientific evaluation is beyond the capacity of the great majority of Ethics Committees and few will be in a position to set up a scientific Advisory Group as has the Committee at the Medical Research Council Clinical Research Centre at Northwick Park Hospital. Nonetheless, Committees should approve only studies which are of good quality. Most Committees will do their best in this area, using their own knowledge and knowledge of their colleagues, but they should not hesitate to make use of external advisers for difficult problems, particularly in the areas of design and statistical evaluation of protocols (see also 18). A committee should feel free to refuse an application on grounds of inadequate scientific quality.

Where a Committee is doubtful of the scientific quality (eg whether a therapeutic trial is so small as to be incapable of giving a useful result) it may tell the applicant to obtain expert advice. This is preferable to enlarging the Committee in an attempt to obtain a full range of scientific expertise.

3. Mandatory review. The institution setting up an Ethics Committee (see 5) should provide that all research projects affecting human subjects, including fetal material and the recently dead, come before it. Optional submission, which is said to occur in some institutions, cannot be justified since it leaves the decision as to what research raises ethical problems to

an interested party, the investigator. The legitimate concern of the public and the profession that led to the setting up of Ethics Committees cannot be satisfied by anything less than mandatory review.

4. (a) Definition of a research project that should be put before an Ethics Committee continues to present difficulties. Any investigation in man designed to develop or contribute to knowledge raises ethical issues, though these may sometimes be quite small. Since any such study may involve subordination of at least the immediate interest of the individual participant to the objective of the advancement of knowledge, all should be subject to ethical review. There are two major classes of research, that which involves making observations without any interference with the subject (non-experimental), eg use of case records, and investigations that involve interference (experimental). Both raise ethical issues, sometimes large but sometimes very small, and both should be subject to review for the reason that optional submission (3 above) is no longer acceptable.

Research may also be classed as (a) research which may benefit the individual participant (therapeutic research) and (b) research that will not or is unlikely to benefit the individual participant (non-therapeutic research). Ethics Committees will naturally give close attention to non-therapeutic research.

Where two treatments are to be compared it is often decided to allocate them at random, and in order to obtain unbiased recording of the patient's progress, to conduct the study double blind, ie without either the clinical observer or the patient knowing which treatment is being used. Such studies always require ethical review, for the main problem is not the use of the randomised blind procedures but whether there is a consensus that there really is no other means of knowing whether one treatment is better than the other. Normally a placebo is used if no known treatment is effective and the best available treatment is used if several effective measures are available, but a placebo is also sometimes needed to test the discriminatory capacity of an experimental design. In general, patients should be told that a trial is in progress and that they are being given the best available treatment or one which may be better or worse. Only under exceptional circumstances when it would cause more distress to reveal the nature of the experiment is there an argument for not telling the patients; however, this should be a deliberate decision taken as part of the ethical review (see also 8h). Where a placebo is to be used as a control device in temporary substitution for effective

treatment then the ethical issues require special consideration (see also 19a).

It has been suggested that a randomised controlled comparison of two or more standard treatments in current use does not raise ethical issues provided the investigator himself is satisfied that he genuinely has no reason to prefer one to another (the null hypothesis); and that in these circumstances he may legitimately conduct such a study without informing the patients of what is being done and without taking advice. Even where so precise a balance of advantage exists and even if the investigator has made provision for excluding from the random allocation any patients in whom there are particular factors that imply a preference for one treatment over another, such studies do present ethical issues and should be subject to review by an Ethics Committee. The doctor-patient relationship is based on the belief that the doctor is concerned to put the interest of the individual patient first. Patients believe this and it is essential that their confidence should not be impaired. Secret use of random allocation to treatments, however strong the investigator's belief in the null hypothesis, may impair such confidence and therefore all studies involving random allocation should be subject to ethical review.

(b) The introduction of a novel procedure with the intention of using it on a certain category of patient (eg a new invasive diagnostic technique), even though unplanned, may constitute research and raise ethical issues that should be put before a Committee.

(c) Novel medical intervention in diagnosis or therapy that is solely inspired by the intention of immediately benefiting an individual patient can arise as part of the normal process of medical practice. It is plainly subject to the ethics of the doctor-patient relationship; it would not ordinarily require review by an Ethics Committee, eg the use of a novel drug in a particular individual with advanced cancer, other treatments having been exhausted, or the use of a novel drug for cardiac arrhythmia in similar circumstances.

5. Membership and appointment of Ethics Committees

The WHO/CIOMS Guidelines advise two principles in determining membership of Ethics Committees:

" - committees must command the technical competence and judgment to attempt to reconcile the physical and psychological consequences of

participation with both the welfare of the subjects and the objectives of the investigation.

" - they may also, with advantage, accommodate respected lay opinion in a manner that provides effective representation of community as well as medical interests."

It is not necessary that those who become members of the Committee are experts in moral philosophy or particular scientific disciplines; they need to be people of goodwill, with a high regard for the human personality, for truthfulness and for the continued advance of medical science. Those who are totally opposed to any experimentation on man should be left to attack the system from outside and not invited on to the Committee. On the other hand, individuals who are acquiescent and may be thought likely to give automatic approval are not suitable members. Of the medical members there should be a majority of those who are mainly employed in providing clinical care. It is important that there be individuals who will look at applications critically from the patient's point of view, but this role may be taken by a number of different individuals ranging from general practitioners or nurses, to lay members.

Membership should comprise at least * :-

(a) medical, both those occupied chiefly with clinical care as well as experienced clinical investigators; a general practitioner should be included whether or not the Committee reviews projects in general practice.

(b) nursing: a nurse who is in active practice with patients.

(c) lay: ie one, or perhaps better, two persons not trained in or practising any medical or paramedical discipline.

The Committee should elect its own Chairman.

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* The Department of Health and Social Security has given advice (HSC (15) 153: 1975), as has the British Medical Association (Revised recommendations 1984: copies from BMA, also British Medical Journal 1981. 282. 1010) which proposes broader membership, ie representatives of community medicine and junior hospital doctors.

The Committee should be of manageable size, eg less than twelve. A busy Committee may find it useful to have alternates for members to ensure a valid quorum (see 7(i)) is always available.

It is important that the community should have confidence in Ethics Committees and provided that the membership is seen to be broad and not exclusively medical and the lay members to be persons of responsibility and standing who will not be overawed by medical members such confidence should be forthcoming.

Experience has shown that lay members, though they may not grasp some of the niceties of some research projects (nor do some of the medical members), are invaluable particularly on issues of consent and information to subjects. A lay member with legal training can be of great value and his/her role should be a general one, not simply to answer questions of law. Both sexes should be represented.

It is not appropriate to use an unmodified hospital medical committee as an Ethics Committee.

The nominations should be made by a responsible authority, District Health Authority, Hospital Committee or Academic Executive, and the Committee will report to this Authority, though details of its considerations of applications will be confidential. An established Committee, knowing its own needs, may propose names where this is appropriate. The appointment of lay members may need wider consultation than the appointment of professional members.

It is essential that members should serve on the Committee as individuals and not as delegates taking instruction from other bodies. Some members especially perhaps some lay members, may feel that they should report back to an outside body that nominated them. This is acceptable provided it is done in general terms and confidentiality (see 7g) on the applications is preserved.

Scope. Ethics Committees are increasingly constituted to serve a National Health Service (NHS) District rather than a single institution. This means they may cover several institutions as well as general practice. It also carries the disadvantage that the Committee will be less familiar with the applicants, their departments and their facilities; such familiarity can be a valuable asset when judging projects. On the other hand there is value in the

additional experience of dealing with a larger number and wider range of applications.

In some centres there is a single Ethics Committee for all research on man, set up jointly, where appropriate, by Health and University authorities. In other centres there is a Committee of the Health Authority that reviews research on patients and a Committee of the University or Medical School that reviews research on healthy volunteers. There is no reason of principle to prefer one arrangement before the other.

6. Format of applications. Although research projects are extremely various, there are some questions that must always be answered. A standard format, though not always appropriate, can save much time since it ensures that applicants do not omit essential matter. An example follows:-

(a) (i) State the title of the proposed project.

(ii) Give an outline of the proposed project.

(b) State the question to be answered, the measurements to be made and how the data will be analysed.

(c) Specify the number and type of patients or other subjects likely to be involved.

(d) State the likely duration of the project and where it will be undertaken.

(e) Specify the procedures to be involved.

(f) State the potential hazards to subjects, if any, and the precautions to be taken to meet them.

(g) State the procedures which may cause discomfort or distress to subjects and the degree of discomfort or distress likely to be entailed.

(h). State the personal experience of the applicant in the field of investigation concerned.

(i) State the manner in which the subject's consent will be obtained (if written, include a copy) (see 8).

(j) Any other relevant matter: for instance, letters or information sheets to subjects, payments to subjects (see 19c), copies of advertisements for volunteers, etc.

(k) If the project involves the use of a drug or appliance, state its exact regulatory status, ie whether it has a Clinical Trial Certificate (CTC) or Exemption (CTX), or a Product Licence (PL) or none of these. Is the study sponsored or initiated by an industrial company? What arrangements, if any, for compensation in the event of injury to subjects (where there is no fault) have been made? (If it is not sponsored by industry, see 16).

In the case of a pre-marketing study of a drug initiated or sponsored by an industrial company, the company should provide a written statement that it accepts the Guidelines : Clinical trials - compensation for medicine-induced injury, of the Association of the British Pharmaceutical Industry (ABPI) (1983) or the Association's code of practice for research on healthy volunteers, as appropriate (see 16) (copies of these Guidelines can be obtained from the ABPI, 12 Whitehall, London SW1A 2DY).

Where a study is undertaken on patients of a marketed drug (having a Product Licence) for a licensed indication, whether or not it is sponsored by an industrial company, it is not usual to require the company to accept liability for injury (any change in this policy will probably have to await a change in the law).

(l) Is there any 'interest', ie of profit, personal or departmental, financial or otherwise, relating to the study? (see 19c).

Note (i) The Committee should be notified of any adverse or unforeseen circumstances arising out of this study and should be sent any abstracts and reprints of publications arising from the work.

(ii) Nursing staff should be made aware that research in progress on patients with whom they are concerned has been approved

by an Ethics Committee.

For Paediatric projects the following additional information is required:-

(a) In what way, if any, can the proposed investigation be expected to benefit the individual patient on whom it is to be performed? (because non-therapeutic research is unacceptable except as stated in 9 and (b) below).

(b) In the case of an investigation which cannot be expected to benefit the individual patient:

(i) Are the hazards judged to be negligible?

(ii) Is parental agreement to be obtained and if so, in what form?

(iii) Is the child capable of giving assent? *

For all studies on patients the approval of the consultant responsible for their overall care is required (see 7f).

Where fetal material is employed slightly different information is required to comply with the regulations (see 19d).

It can be useful for the applicant to review his application with an experienced clinical scientist or with a Scientific Advisory Group appointed by the main Committee (see 2). They can identify obvious errors or inadequacies and make sure that the presentation is clear.

The Committee may also issue general guidelines to applicants with the object of minimising difficulties and delays resulting from the excessive use of technical terminology, confusion over the regulatory status of a new drug, product liability, consent, etc.

It is worth stressing that applications must be in language that can be understood by all members of the Committee.

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* Assent is used here to imply a willingness that does not necessarily carry the greater understanding generally understood by consent (see 9).

7. Mode of working

(a) Committees may work entirely at meetings, which should normally be open to the applicant, but a proportion of applications may raise only minor ethical issues and some Committees arrange for applications to be circulated so that these can be approved quickly without convening an unnecessary meeting. The size of the workload is obviously relevant to these choices. A disadvantage of working by post is that Committee meetings may become so rare that the valuable mutual exchanges between members are lost, and lay members particularly will feel isolated. For these reasons it is inappropriate to seek to conduct all business without meetings. Alternatively, the Chairman may deal with minor applications immediately by "Chairman's action", these decisions being reviewed later at a regular meeting of the Committee.

An accurate record of decisions should be kept.

(b) It is useful to circulate to the Committee relevant publications on general policy, or particular aspects such as consent, or research in paediatrics, that appear from time to time.

(c) Adverse decisions. Experience has shown that it is rare for a project to be found totally unacceptable, but common for projects to be modified in discussion with a Committee. This is how it should be. If an adverse decision is made, the reasons should be given to the applicant in writing. Review of an adverse decision should be available to an investigator. There can be few cases where this is necessary and experience in practice is lacking. The Ethics Committee might, on request of an investigator, appoint referees by mutual agreement, or in cases of special difficulty ask the appropriate Royal College to appoint referees, who would consider the views of both investigator(s) and the Ethics Committee in the presence of both. (see 19b).

(d) Plainly it is impracticable, even if it were desirable, for an Ethics Committee to monitor in detail the conduct of ongoing investigations, but it is desirable that Committees should not entirely lose contact with investigations that they have approved. Some form of follow-up seems desirable, if only an annual circular to those who have made applications: it should establish whether the project has been completed, abandoned (the reason should be given) or is still in progress in the original or in other form; information on any adverse events should be sought. Applicants should

be told in any guidelines or forms issued that adverse events should be reported and reprints of publications arising from work sent to the Committee. Alternatively a more detailed follow-up of selected projects may be preferred. Experience in this area appears to be small.

(e) Ethics Committees have no direct sanctions, but in the event of their discovering that their advice is unheeded or that clinical investigations are being conducted without reference to them, then they should report the facts to the body that set them up, eg an NHS district or hospital authority or a university board. Plainly, an investigator who bypasses or ignores the recommendations of a properly authorised Ethics Committee creates a potentially serious situation.

(f) Clinical responsibility for all patients in the NHS falls on a consultant or consultants (and their junior staff) or on a general practitioner; they should be clearly seen to accept responsibility not only for their own research but also for that conducted on their patients 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.

(g) Confidentiality should be preserved because the issues considered are often complicated and delicate and uninformed or unbalanced publicity could rouse emotions that are damaging to all concerned, especially the patients; also some investigators who have had an original idea fear that this may be passed to others who are in competition with them.

(h) Co-option. In areas of particular difficulty or sensitivity, eg research involving the fetus, neonates, breast cancer, it may be useful to co-opt additional lay or professional advisers for an individual application.

(i) Quorum. It is undesirable to take important decisions in the absence, for example, of a lay member, and it is prudent to define the range of a quorum as well as its number.

(j) Declaration of interest by Committee members. Just as applicants should declare any interest (see 61) so members of an Ethics Committee should declare their interests, eg where an application relates to testing a product of a company to which the member is an adviser. The Chairman will

decide whether the interest disqualifies the member from the discussion. Where the Chairman has an interest, a Vice-Chairman should take his place.

8. Consent. Obtaining true (or informed or understanding) consent is central to the ethical conduct of clinical investigation. The terms "true" and "informed" imply that the subject has all the information, in a form that is comprehensible, to enable him or her to make a proper judgment. The obvious impracticability of this in many cases has led to the saying "there is no such thing as informed consent", which is less than fair. The difficulties are recognised in the various ways that are in practice used to obtain consent. There is no single preferred mode of consent. Written consent is not always required. Modes of consent include:-

(a) trivial or minimal risk procedures: eg questionnaires, a blood sample, may be done with a simple verbal explanation and verbal response.

(b) more substantial procedures should be the subject of an explanatory document setting out the purpose of the investigations, the procedures, the risks, the benefits, a statement that the subject will be free to withdraw at any time without giving a reason and without in any way impairing his/her management or incurring displeasure, and an invitation to ask questions. The subject may study this and then sign a paper that states that the document has been studied and discussed with the investigator and that the subject agrees to participate.

Any fears of the subject that refusal to participate may lead to adverse consequences for himself must be allayed. He must be assured that refusal to participate will be accepted without questioning and he will be treated as though the matter had not arisen; it is often appropriate that this be written into the explanatory document.

(c) An alternative, especially useful in the old and those who have intellectual or cultural difficulties in speech or understanding, is witnessed consent, where an independent person, eg a senior nurse, signs a document stating that the witness was present when the investigator explained the project to the potential subject and that in the witness's opinion consent was given freely and with understanding.

(d) Healthy volunteers and patient volunteers engaging in non-therapeutic research should ordinarily give written consent to all but trivial procedures.

(e) Classes of subjects where capacity to give consent is impaired, eg children, mentally retarded and some psychiatric patients require special consideration (see 9 - 15).

(f) There are various opinions on the value of written evidence of consent in the event of a legal action arising out of a clinical investigation. The likelihood is that a court would look at any such document in the context of the whole investigation and might at best regard it as evidence that the investigator had seriously endeavoured to meet his responsibilities, and at worst dismiss it as meaningless or misleading. Formal consent in no way reduces the responsibilities of an investigator and does not remove the ordinary rights of the subject.

(g) Copies of consent documents should be kept in patient medical case records.

(h) The question remains whether there are some undoubted research activities that can be carried out <u>without consent</u> of the patient, eg

(i) <u>minor procedures</u> that entail no, or negligible, discomfort to a patient and where to ask for consent would be more likely to cause distress than to proceed without it. In such cases the criterion has been proposed that the procedures should not cause appreciably more discomfort than would be experienced by a patient undergoing routine diagnostic procedures for patient care, eg collection of urine and faeces, nasal and throat swabs and the withdrawal of a small extra volume of blood while blood is being taken for a necessary diagnostic process.

(ii) <u>major procedures</u> where to attempt to obtain "informed" consent can be impossible or devastating, eg unconscious patients, acute grave illness, inability to comprehend. In all cases an Ethics Committee will give very close consideration to any proposal to proceed without consent and will satisfy itself that the decision not to seek consent from the individual is ethically acceptable. In circumstances of urgency, eg where a patient is seen with some rare and ill-understood condition, the chairman of the Committee may act, always reporting back at the next meeting of the Committee.

(iii) <u>use of patient records</u> presents real ethical issues. Care should be taken to ensure that such use is in accordance with current codes of

practice and in accordance with any data protection legislation. In the absence of such legislation codes of practice should be established by the responsible medical organisations and voluntarily adhered to. The key issue is that when patients' records are being used for research purposes confidentiality should be preserved.

9. Research involving children. It may well be appropriate to give medical treatment to unwilling children if the parent or guardian consents, but the position would not necessarily be the same for research. In legal terms a person is of full age, and accordingly recognised as an adult, from the 18th birthday. Under that age, the capacity to consent probably depends on the degree of understanding on the part of the individual concerned. The Family Reform Act 1969 states that the consent of a person between 16 and 18 years of age to surgical, medical or dental treatment shall be as effective as it would be if he or she were of full age, and that parental consent is not then necessary. "Treatment" includes diagnostic and ancillary procedures, including the administration of an anaesthetic, and thus probably includes therapeutic research, but it would not be prudent to rely solely on the subject's consent to non-therapeutic research and below the age of 18 parental consent should always be sought. The consent of parent or guardian should be in addition to that of the subject.

The particular problems relating to research involving children have been the subject of several reports. The British Paediatric Association has published guidelines (Ref 4) and has its Standing Ethics Advisory Committee which will respond to requests for advice from individuals or from Ethics Committees. The following general statements are derived from WHO/CIOMS guidelines:

Children should not, except perhaps in some "minimal risk" research, eg a blood sample, be the subject of research that might equally well be carried out on adults*. "However, their participation is indispensable for research on diseases of childhood and conditions to which children are particularly susceptible. The consent of a parent or other legal guardian, after a full explanation of the aims of the experiment and of possible hazards, discomfort or inconvenience, is always necessary".

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* The WHO/CIOMS guidelines say they should "never" be so used.

"To the extent that is feasible, which will vary with age, the willing co-operation agreement of the child should be sought, after [he or she] has been frankly informed of any possible discomfort or inconvenience. Older children may be assumed to be capable of giving informed consent preferably also with the consent of the parent or other legal guardian".
"Children should in no circumstances be the subjects of research holding no potential benefit for them unless with the objective of elucidating physiological or pathological conditions peculiar to infancy and childhood". (Note: Where a child obviously objects to such research, ie he or she withholds assent or agreement, this should be respected. Research should always be planned to ensure that there is negligible distress or harm to the child, eg a venepuncture might be accepted whereas a lumbar puncture would not be in this type of work).

10. Research involving pregnant and nursing women (from WHO/CIOMS Guidelines). "While no special problems of eliciting informed consent exist in the case of pregnant and nursing mothers as such, they should in no circumstances be the subjects of non-therapeutic research that carries any possibility* of risk to the fetus or neonate, unless this is intended to elucidate problems of pregnancy or lactation. Therapeutic research is permissible only with a view to improving the health of the mother without prejudice** to that of the fetus or nursling, to enhancing the viability of the fetus, or to aiding the nursling's healthy development or the ability of the mother to nourish it adequately".

11. Research involving mentally ill and mentally defective persons (from WHO/CIOMS Guidelines). "Substantially similar ethical considerations apply to the mentally ill and the mentally defective as to children. They should never be the subjects of research that might equally well be carried out in adults in full possession of their intellectual faculties, but they are clearly the only subjects available for research into the origins and treatment of mental disease or disability.

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* It may seem impossible to exclude any "possibility" or risk; but any "foreseeable" risk should exclude such work.

** It may be possible to imagine rare compelling reasons where this would not apply.

"The agreement of the immediate family - whether spouse, parent, adult offspring, or sibling - should be sought, but is sometimes of doubtful value, especially as mentally deranged or defective patients are sometimes regarded by their families as an unwelcome burden. Where a subject has been compulsorily committed to an institution by a court order, it may be necessary to seek legal sanction before involving the subject in experimental procedures".

Where patients have no known or accessible relatives, a suitable staff member may be appointed in loco parentis by the Ethics Committee, or the research should not be done. The terms of the Mental Health Act should be complied with.

12. Research involving unconscious or acutely ill persons. The problems are similar to 11 above.

13. Research involving other vulnerable social groups (from WHO/CIOMS Guidelines). "The quality of the consent of candidate subjects who are junior or subordinate members of a hierarchically-structured group requires careful consideration, as willingness to volunteer may be unduly influenced by the expectation, whether justified or not, of adventitious benefits" (see 15).

14. Community-based research (from WHO/CIOMS Guidelines). "Where research is undertaken on a community basis - for example by experimental treatment of water supplies, by health services research or by large-scale trials of new insecticides, of new prophylactic or immunising agents, and of nutritional adjuvants or substitutes - individual consent on a person-to-person basis may not be feasible, and the ultimate decision to undertake the research will rest with the responsible public health authority.

"Nevertheless, all possible means should be used to inform the community concerned of the aims of the research, the advantages expected from it, and any possible hazards or inconveniences. If feasible, dissenting individuals should have the option of withholding their participation. Whatever the circumstances, the ethical considerations and safeguards applied to research on individuals must be translated, in every possible respect, into the community context".

15. Healthy volunteers and patient volunteers. Consent of patients should be sought just as is done with the healthy.

The view has been expressed that patients are not to be considered as volunteers, especially in relation to therapeutic trials, because they are in a special position owing to their illness and degree of understanding, the possibility of personal health gain, and their dependence on the doctor. But these factors are not so fundamental that they remove the voluntary element from participation. Patients who consent to enter a research study from which they may or may not benefit should be regarded as volunteers. Confusion would be avoided if the terms "healthy (non-patient) volunteer" and "patient volunteer" were used. These factors make it particularly important to be scrupulous in obtaining consent. The patient should realise that rather than his seeking help from the doctor, the doctor is now seeking help from him in the pursuit of new knowledge.

If healthy volunteers are to be recruited in another institution, eg students, staff, then a responsible officer (eg Dean, Works Medical Officer, Personnel Director) of that institution should be informed and general approval sought in case participation could adversely affect work performance whether through drug action or absence from work.

In the case of students some institutions (eg University College London) have issued advice, and the Conference of Metropolitan Deans (of Medical Schools) has issued guidelines to recruiting organisations.

> "That any organisation recruiting medical students as volunteers in research should notify the Dean of the names of the students of his school who have volunteered to participate and should also provide the following information: (a) an outline of the research project; (b) evidence of approval of the research protocol by the Ethics Committee of a Teaching District or a formal undertaking not to proceed without such approval; (c) note of the duration and place of study and whether within the normal working week; (d) note of any payment proposed; (e) a statement undertaking that the volunteer would be indemnified for any injury arising from his participation in the study, without regard to legal liability" (see 16).

It will be seen from (e) that the Deans had particularly in mind recruitment of students by commercial organisations undertaking contract research for

pharmaceutical companies. Although the recommendation refers to medical students, it would seem sensible to apply it to all students.

If there is no Committee, eg in a school, factory or office, then alternative appropriate consultation should be made. It will ordinarily be inappropriate for a Committee to agree to a project with the condition that healthy volunteers (eg students) may be recruited from outside but not from within the institution. Advertisements seeking volunteers should be seen and approved by the Ethics Committee or its representative in the institution in which they are to be published.

Subjects other than patients may also be in a potentially dependent relationship with investigators. Recruiting such subjects, eg students, junior medical staff, nurses, employees of pharmaceutical or other industry and members of the armed forces requires special care, including advice from an occupational physician where this is available. Calling for volunteers in institutions may be best done in group situations, or by notices, rather than by direct individual approach. For payments to subjects see 19c.

16. Injuries due to clinical investigations

If an accident occurs, the present legal position is that the individual who is injured is entitled to compensation only if negligence on the part of the research worker or his team or a supplier of drugs or equipment can be shown (legal liability). 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 highest care. In the absence of negligence the only other means by which a participant or his dependent might receive some compensation would be by seeking an ex gratia payment from the sponsor of the research or the authority employing the researcher. This situation is clearly unsatisfactory.

Insurance policies held by institutions covering their employees are invariably, as far as is known, confined to negligent acts or omissions; medical practitioners are covered for negligence through their membership of one of the medical protection organisations. There remains the lacuna of the injury ocurring in the absence of fault.

The major issues of liability will have to await solution on a national basis and there is nothing that individual Ethics Committees can do about them. Responsible research organisations and the DHSS have stated they may offer ex gratia payments to volunteers who are injured as a result of participation in a clinical investigation. It must be remembered that it is often difficult to establish whether there really is a connection between any event and what happened in the investigation and for those and other reasons any payments may be made without admitting liability.

In the special case of pre-marketing trials of new drugs (or trials of marketed drugs for new, unlicensed, indications) on patients which are sponsored by industrial companies the Association of British Pharmaceutical Industry has provided guidelines to member companies which it recommends these companies to accept "without legal commitment". Whilst the position is not ideal, this is a big step forward and, for the present at least, Ethics Committees may consider they have adequately protected patients if the company sponsoring a study puts its acceptance of these guidelines in writing. Where there are extra investigations that carry some risk (eg endoscopies), companies can reasonably be expected to apply the guidelines to these as well as to the medicine itself. (The guidelines, a commentary on them and subsequent relevant correspondence may be found in the British Medical Journal 1983, 287, 675, 676, 1066, 1381). Companies can only be expected to pay compensation if there is reasonable ("balance of probabilities") evidence of causation.

In the case of studies in healthy volunteers sponsored by a pharmaceutical or other company, a contract accepting liability regardless of fault, such as that recommended by the Association of the British Pharmaceutical Industry, should be used. The principal aspects are acceptance by the company of responsibility for injury due to participation in the study (not only due to the drug) without regard to legal liability (ie whether or not there is fault) plus a simple procedure for arbitration of any dispute.

It is not to be expected that pharmaceutical companies will necessarily accept responsibility for any study they have not sponsored or initiated and cover for studies involving marketed drugs for indications already approved, if such cover is desired, will probably have to await changes in the law or introduction of a special voluntary scheme.

17. Medicines (drugs) and official regulations

Medicines fall into four classes:

(i) Medicines for which there is a Product Licence (ie marketed) there has been little difficulty in research with these.

(ii) New drugs for which the producer has either a Clinical Trial Certificate (CTC) from the Licensing Authority (the Ministers of Health, but administered by the Medicines Division DHSS), or has an Exemption (CTX) from the need to hold such a Certificate by having followed approved procedure in lodging its proposals with the Licensing Authority. An investigator should state the exact regulatory status of any drug he intends to use and the Committee should be told whether or no trials of new drugs are in accordance with proposals agreed with the Licensing Authority.

(iii) Medicines not falling into either of the above categories, eg medicines imported from a source that has no organisation within the UK, or from a chemical (not pharmaceutical) manufacturer. It is generally appropriate for the investigator to make an application to the Licensing Authority for a CTX (see above: forms of application are obtainable from the Medicines Division, DHSS, Market Towers, 1 Nine Elms Lane, London SW8 5NQ).

(iv) Studies in healthy volunteers do not at present require any form of official licencing.

The fact that a drug has been accorded a Clinical Trial Certificate or Exemption does not imply that the ethics of the investigation has been subject to significant review and in no way reduces the duties of Ethics Committees. There remains an obligation on investigators to satisfy themselves that they have the information necessary to make a judgement on the safety of the project they propose to undertake, and to satisfy the Ethics Committee of this.

18. Clinical assessment of licensed medicinal products in general practice, ie assessment of marketed medicines used in accordance with the indications in the Product Licence.

In the legitimate pursuit of knowledge of drug use in the community,

pharmaceutical companies organise studies which often involve a number of general practices simultaneously. The Association of the British Pharmaceutical Industry has drawn up a code of practice for these studies in consultation with the British Medical Association, and the Royal College of General Practitioners (British Medical Journal 1983, 286, 1295).

Passages relating to Ethics Committees are as follows:

> "All clinical trials in general practice to which this code relates must have the protocol approved by an independent and properly constituted ethical committee before the study is begun.
>
> "(4.1) Such an ethical committee for clinical research must be constituted according to such guidelines for its establishment as are eventually agreed by the interested parties and which allow for the continuance of those committees which are already in operation and are working well.
>
> "(4.2) Other ethical committees for clinical research with similar membership and selection procedures will be acceptable.
>
> "(4.3) The role of the ethical committee should be to consider the medical ethics only of the proposed trial and, if applicable, grant approval.
>
> "(4.4) The decision of the ethical committee must [sic] be made within 35 consecutive days (excluding bank holidays) of the time that administering staff received the company application. (see end of this section).
>
> "(4.5) The general practitioner who is invited to participate in the study (the investigator) has the ultimate ethical responsibility for his patients and, if in doubt about the ethics of the study, should resubmit the protocol to an appropriate ethical committee for further consideration".

In view of the (apparent) limiting effect of 4.3 above, it should be emphasised that it is open to Ethics Committees to withhold approval until they consider that the scientific aspects of a study have been adequately evaluated.

Both the general practitioner investigator and the Ethics Committee should satisfy themselves that the study has genuine scientific merit and is not merely an exercise in promotion. It will be seen that the code envisages that applications will be by companies rather than by the investigator (4.4 above) who has responsibility for the patients, which latter is the more usual procedure, and that it seems to seek to separate examination of scientific quality from consideration of ethics (4.3 above) (see also 2). It may be thought that an investigator who will take clinical responsibility and who will seek consent from the subjects should always be associated with an application to an Ethics Committee.

19. Miscellaneous topics

(a) The use of a placebo or dummy treatment poses ethical problems (see also 4a) but is often preferable to the continued use of treatments of unproven efficacy or safety. It is not inherently unethical. An investigator who proposes to use a placebo or otherwise withhold effective treatment should specifically justify his intention. Frequently consent can be obtained to the use of a placebo without impairing the scientific validity of the procedure if the patient is invited to agree that an inert preparation will (or may) be used (and why it will be used) at some time during the course of treatment, but without specifying exactly when. The way in which the proposal is put to patients will vary with circumstances; the Ethics Committee should satisfy itself that it will be done in such a way as to create genuine understanding in the patient. Generally, patients easily understand the concept of distinguishing between the imagined effects of treatment and those due to a direct action on the body.

(b) Multicentre projects are increasingly used in the evaluation of treatments. They are organised by a central body which pays attention to ethical issues. They are then submitted to Ethics Committees in each centre. There have been occasions when a project has been approved in some centres and rejected or modified in others. This is no surprise since opinions on ethical issues can legitimately vary and this cannot be escaped. But it is undesirable that this should happen to a multicentre project and multiple submission is cumbersome and probably unnecessary. There is no agreed solution to this at present. Perhaps centres could agree to delegate a decision on a multicentre study to a single Ethics Committee (eg in general practice to the Ethics Committee of the Royal College of General Practitioners), or alternatively to an ad hoc group set up by the organisers;

such procedure seems to be envisaged in the Code of Practice for licensed medicines in general practice (see 18).

Where a member of one institution works in a project in another (but does not conduct the research in his own) the Committee of the home institution need not be involved if the project has been approved in the institution where the study is taking place. If the latter has no Ethics Committee then the investigator should consult his home Committee.

(c) Payments

(i) Payments to subjects. There is a tradition that healthy volunteer subjects should engage in research for purely idealistic or educational motives. Today healthy volunteer subjects cannot always be expected to participate in research without reward.

Many investigations, eg studies of drug absorption and elimination, are tedious and time-consuming and are done routinely, eg in preparation of applications for licensing of drugs. Ethics Committees should be informed of all proposed payments and should be satisfied that they are reasonable and not so large as to induce subjects to take risks primarily for reward. This applies to volunteer patients who may undertake extra activities or attendances which are therapeutically unnecessary as well as to healthy volunteers. It has been suggested that acceptance of payment impairs the rights (ethical or legal) of subjects, but this is not so.

Reimbursement of subjects' expenses, eg journeys, is plainly desirable and should not be overlooked.

(ii) Payments to investigators, departments and institutions

Since personal payments to investigators and their pecuniary relationship with any sponsoring company have ethical implications, these should be reported to Ethics Committees or to representatives designated for that purpose, eg the Chairman and another member. The same applies to payments to departments and to institutions.

The General Medical Council provides the following examples of "inducements which the Council may regard as improper" :

"Clinical trials of drugs.

"It may be improper for a doctor to accept per capita or other payments from a pharmaceutical firm in relation to a research project such as the clinical trial of a new drug, unless the payments have been specified in a protocol for the project which has been approved by the relevant national or local ethical committee. It may be improper for a doctor to accept per capita or other payments under arrangements for recording clinical assessments of a licensed medicinal product, whereby he is asked to report reactions which he has observed in patients for whom he has prescribed the drug, unless the payments have been specified in a protocol for the project which has been approved by a relevant national or local ethical committee. It is improper for a doctor to accept payment in money or kind which could influence his professional assessment of the therapeutic value of a new drug".

"Gifts and loans.

"It may be improper for an individual doctor to accept from a pharmaceutical firm monetary gifts or loans of expensive items of equipment for his personal use. No objection can, however, be taken to grants of money or equipment by firms to institutions such as hospitals, health care centres and university departments, when they are donated specifically for purposes of research".

(d) Research on fetal material. Research on fetal material must be in accordance with the published guidelines: DHSS Advisory Group. The use of fetuses and fetal material for research. London: HMSO, 1972.

Where the fetus is 16 weeks or above parental consent for use of the fetus should be obtained. It is not unusual for parents to ask to see a fetus of this age or above.

(e) Educational activities in institutions may include administration of drugs as well as other procedures. It is desirable that these be put before Ethics Committees.

(f) Publication. It is desirable that authors should indicate that their clinical research has been before an Ethics Committee when they submit it for publication.

(g) The cost of research will not ordinarily be an appropriate concern of Ethics Committees.

(h) Fees. Ethics Committees should not seek a fee from an applicant (eg a pharmaceutical company) for considering an application.

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