A question of ethics

Robert Higgins looks in detail at research regulations and ethical issues in medical research.

Introduction

Ethics is described as the discipline and process of describing behaviour, practices, thinking and moral values commonly agreed to be acceptable to society. In this context, ethical issues are those that determine whether a proposal for research conforms to the accepted guidelines and rules on ethics[1].

Research regulation focuses on safeguarding those individuals who take part in medical research either from harm or failure to respect autonomy. The principal concern is to ensure that the enthusiasm of the researcher or interests of society do not override the interests of the individual. Much of the tension that can arise between a medical researcher and a research ethics committee can be attributed to the history of the regulation of research and clinical practice[2].

All proposals for research that involve human participants must be submitted to an independent, prospective ethical and scientific review. An underpinning principle of the Declaration of Helsinki (1964) equires a review of a proposal to ensure scientific validity and ethical considerations – this applies irrespective of the source of the proposal and is inviolable and acts as a safeguard for both participants and researcher[3].

Clinical audit vs research

Clinical audit was first introduced into the National Heath Service (NHS) in 1993. This was then reinforced in 1997 with the White Paper, *The New NHS*, which stated that clinical audit was an essential element of professional practice in the Health Service.

An accepted definition of clinical audit is: *a quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change*[4]. However, research concerns the acquisition of new knowledge about what works and what doesn't.

Although research and audit projects may look similar, what differentiates them is purpose (see Table 1). For example, a research project may examine outcomes of particular forms of surgery in order to conclude what represents best practice. A clinical audit project looking at the same topic would examine if the recommended surgical method was producing the expected outcomes[4]. Nonetheless, there are some similarities, including:

- Both aim to answer 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 data[4].

Research	Audit
Creates new knowledge	Tests care given against knowledge gained from research
Is based on a hypothesis	Measures against standards
May involve experiments on patients and/or volunteers and will usually require submission to a Research Ethics Committee (REC) for ethical approval	Should never involve anything beyond normal clinical management. Abides by an ethical framework but doesn't usually require ethical approval
May involve random allocation to different treatment groups, including placebo	Never involves random allocation or placebo treatment
Usually carried out on a large scale over a prolonged period	*Usually* carried out on a relatively small population over a short time span
Rigorous methodology – power calculations for sample sizes, statistical tests, etc	Different methodology from research – less need for large sample sizes and statistical significance of results
Results are generalisable and therefore publishable, influencing the activities of clinical practice as a whole	Results are only relevant locally, influencing activities of local clinicians and teams (although the audit process may be of interest to a wider audience and therefore publishable)

Table 1: Differences between clinical audit and research (courtesy of [4]).

History of research ethics

What follows is a brief description of how and why research regulations and ethical considerations came about.

◆ **The Nuremberg Code:** this was established in 1948, following the criminal proceedings against 23 leading German physicians and administrators for their willing participation in war crimes and crimes against humanity. This included charges of German physicians conducting medical experiments on thousands of concentration camp prisoners without their consent. Although it did not carry the force of law, it was the first international document to advocate the voluntary participation and informed consent of research participants[5].

◆ **The use of Thalidomide:** this drug was sold to pregnant women in the late 1950s and 60s to help them sleep and to combat morning sickness and other symptoms during pregnancy. It was made available in almost 50 countries, but it wasn't until 1961 that it was found to be teratogenic in foetal development (a cause of congenital malformations), affecting around 15,000 children.

Although Thalidomide was approved as a sedative in Europe, it had not received approval for use by the Food and Drug Administration (FDA) of the United States of America (USA). Following the revelations of the teratogenic effects of Thalidomide and the fact that many patients did not know they were taking a drug not FDA approved, the United States (US) Senate in 1962 passed a law to ensure greater drug efficacy and drug safety. This resulted in drug manufacturers having to prove to the FDA the effectiveness of their products before marketing them[6].

◆ **Tuskegee syphilis study:** during 1932-1972, a research project conducted by the US Public Health Service monitored 600 low income black American males (400 of whom were infected with syphilis) for 40 years. Free medical examinations were given, but the subjects were not told about their disease, despite a proven cure (pencillin) being available. Many of the subjects died of syphilis during the study. It was finally stopped in 1973 by the US Department of Health, Education and Welfare only after its existence became public knowledge and a political embarrassment[5].

◆ **The Declaration of Helsinki:** in 1964, the World Medical Association (WMA) established recommendations guiding medical doctors in biomedical research which involved human subjects. The Declaration of Helsinki governs international research ethics and defines rules for 'research combined with clinical care' and 'non-therapeutic research'. It has been revised five times since then (the last in 2000) and forms the basis for good clinical practice (GCP)[2,5]. Issues addressed by the Declaration include:

- Research with humans should be based on the results from laboratory and animal experimentation
- Research protocols should be reviewed by an independent committee prior to initiation
- Informed consent from research participants is necessary
- Research should be conducted by medically/scientific qualified individuals
- Risks should not exceed benefits[5].

Principle 13 of the Declaration of Helsinki (WMA 2000) states that: *The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance and, where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence*[2].

The Declaration of Helsinki is a multicultural, multilingual declaration made by physicians that confirms the role of the physician above that of the investigator. It is not intended to be a guideline or set of rules, but rather is considered to be a set of principles which define the standards that should apply to biomedical research worldwide[1].

The Declaration of Helsinki is divided into three sections: introduction; basic principles for all medical research; and additional principles for medical research combined with medical care. Despite a number of criticisms levelled against it, such as not being a historical document (and therefore it cannot be changed) and the fact that the revisions made to the original in 1964 may not have improved it and may have made it worse, it still remains a fundamental guiding principle in research ethics[1].

Research ethics committees

◆ **In the UK:** these are only concerned with research and not clinical practice. In 1968, the Department of Health (DoH) recommended that hospitals should operate ethics committees. However, it wasn't until 1984 that guidelines for ethics committees were produced by the Royal College of Physicians (RCP). These were further clarified to identify the aims of such committees and to name them as local research ethics committees (LRECs), with their task to '*maintain ethical standards of practice in research, to protect subjects of research from harm, to preserve subject's rights and to provide reassurance to the public that this is being done*[7]'.

A centralised system of research ethics committees (REC) was introduced in 1991, with at least one independent LREC in each district in order to advise NHS bodies on the ethical acceptability of research proposals involving human participants[8]. LREC membership consists of a range of experience and expertise, reflecting a mix of gender, age and ethnic backgrounds and includes hospital medical staff, nursing staff, NHS professional staff and lay persons[7,8].

The ethical conduct of a research project involves achieving a balance between the rights and needs of the potential research participants, society and the researcher/s. LRECs have responsibility in maintaining this balance, but LREC members, researchers and the public can have different views about the LRECs role and function. Kent[9] looked at this by using a questionnaire distributed to general practice (GP) patients (as proxies for potential research participants) and found that while GP patients believed that the main function of LRECs was to ensure that research participants did not come to harm, LREC members were more concerned with the protection of participant's rights. There was also some disagreement between

LREC members and researchers with regard to the consideration of proposals on the grounds of scientific merit. From this comparison, Kent[9] concluded that LREC members need to be aware of the potential differences in views and should make their priorities clear, and that membership of LRECs ought to reflect the views of both researchers and potential research participants.

Multi-centre research ethics committees (MRECs) were set up in 1997 as an advisory body to provide independent advice on the science and ethics of multi-centre research (in five or more LREC's geographical boundaries). Membership is similar to that LRECs with the exception that MRECs have paid administrative staff[7]. Other issues related to UK ethics include:

- **Caldicott report (1997):** this concerns the flow of patient-identifiable information (each needs to be justified and also covers data protection issues and confidentially/anonymisation).
- **Alder Hey report (1999):** after it had emerged that organs had been removed at necropsy from children without consent and improperly stored, the Royal College of Pathologists (RCPath) issued guidelines on the storage and use of human tissues.
- **Informed consent:** the right of a research participant to know what exactly is being done[3,10].The ethics process was further changed in March 2004, so that all ethics submissions had to use the Central Office for Research Ethics Committees (COREC) online electronic form[11].

◆ **In other European countries:** the basis for the Swedish ethics committee is only the Declaration of Helsinki, whilst in Turkey there are no ethics committees concerned with patient's rights but they are concerned with controlling research and can stop any if malpractice is identified. The German Federal Medical Council has a central ethics committee which comprises 16 members from medical specialities, philosophy, theology, natural sciences, the law and politics. However, it has no patient representative[7].

The Danish Council of Ethics produces a report each year outlining its activities (mainly making policies), but also considers one subject in depth such as genetics or human rights for publication. A similar situation exists in Portugal, but it is administratively and financially supported by the Prime Minister's office[7].

Whilst there are national differences in the organisation of ethics committees within Europe, there are also directives from the European Union on Good Clinical Practice (GCP) to which member states have to adhere[7].

Informed consent

Informed consent is defined in section 1.28 of the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) (GCPICH) guidelines as *'a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate'*.

Regardless of country, the primary role of ethics committees is to protect research participants (especially vulnerable ones) from coming to harm. Therefore, one of the most important documents reviewed by the ethics committee is the informed consent form. This is usually presented in two parts: a written information sheet describing the project and a form which the participant signs to document that he/she has given consent to take part in the project (see Appendix I and II at ***www.sor.org/members/pubarchive/pub_search.htm***)[1].

The first section of the information sheet should provide the potential participant with brief and clear information on the essential elements of the project, ie, what the research is about, the voluntary nature of involvement, any potential risks or inconvenience and their responsibilities. This should allow the participant to make an initial choice of whether or not they are willing to participate[12].

The second section should contain additional information on factors such as confidentiality and data protection, indemnity and compensation. This should be read and understood before the participant decides whether they want to take part in the project and give informed consent[12].

Information sheets should be written in simple, non-technical terms and be easily understood by a lay person – a suggested guide is that the level of language used should be no more difficult than that used in information sheets for medicines for the general public and bullet pointed lists should be used where appropriate. The tone should be invitational and not coercive or overly persuasive. The first page should use headed paper of the hospital where the research is being carried out

Huge fundraising aids ultrasound purchase

Thanks to the tireless support of members of the Abergavenny branch of the Thrombosis and General Research Fund, Nevill Hall Hospital in Abergavenny, South Wales, has recently taken delivery of an Acuson X300 ultrasound system from Siemens.

The new system is being used as an adjunct within the hospital's arthritis clinic for the early diagnosis and treatment of rheumatology patients.

Improving the quality of service to rheumatology patients, Dr Stuart Linton, consultant rheumatologist, confirmed: "We chose this system because it clearly fulfilled all our requirements, particularly excellent image resolution in power and colour Doppler, and it will be used to significantly enhance the service we provide to our patients suffering with early inflammatory arthritis".

From left: Jo Wiles, clinical nurse, specialist rheumatology; Dr Stuart Linton, consultant rheumatologist; Peter Bishop, chair of awarding committee and Brian Lane, vice chair of the Thrombosis and General Research Fund, Abergavenny branch.

Michelson Diagnostics and UCH announce successful imaging of oral cancer

University College Hospital's testing of oral cancer tissue using Michelson Diagnostics' (MDL's) OCT imaging technology has demonstrated break-through imaging quality. OCT is anticipated to revolutionise the surveillance of oral pre-cancers, eliminating waiting time for biopsy results and minimising surgery through improved disease mapping.

MDL has an exclusive, worldwide license to a powerful biophotonic approach patented by the University Health Network (UHN), Toronto, Canada. This extends the depth of focus, improving imaging performance by the use of multiple optical beams. The collaboration will demonstrate the technology using invivo flexible probes, working towards its use in gastrointestinal endoscopy.

Colin Hopper, senior maxillofacial surgeon, University College Hospital, London, using the Michelson Diagnostics' EX1301 OCT microscope.

How to use this article for CPD

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Ethics is sometimes seen as a rather dry subject that is the province of erudite academics but the reality is, of course, that we are all frequently faced with decisions involving ethical considerations. Increasing levels of professional autonomy and accountability and public awareness of serious instances of breaches of patient trust mean that the healthcare practitioner must tread ever more cautiously – and reference to an appropriate code of ethics is potentially good defence (if your decision is challenged) as well as professionally appropriate.

Robert Higgins' article is a highly readable and thought-provoking account of the development of modern ethical thinking with regard to medical research. The following scenarios will enable you to explore some research-related ethical issues within the context of your general practice, through personal reflection, discussion with a colleague, mentor or supervisor, or group discussion.

SCENARIO 1

You receive a referral from a local chiropractor for a pelvic x-ray of a 45-year-old female. The clinical indication given is 'as per discussed research project'. You know nothing of any such project and when you check with a senior colleague she says: "Oh yes, I think that has been discussed with one of the consultant radiologists". ***What action do you take?***

SCENARIO 2

A 70-year-old male, apparently in poor health and considerable pain, presents for a CT scan as part of an approved and appropriately documented research project in which your department is involved. It is clear to you as you prepare for the examination that the patient will undergo a significant degree of pain and distress if the examination is to be completed properly. You raise the matter with a colleague who says: "Yes, but he would have to put up with the discomfort if we were scanning him for diagnostic reasons and he has agreed to take part in the research project". ***What are your thoughts and what actions would you take?***

SCENARIO 3

You are interested in developing your research skills and your manager suggests that you could take part in clinical audit. You are keen to add this work to your CPD portfolio and you see that **CPD Now** outcome 20 is 'knowledge and skills in audit and research'. ***Does this mean that audit and research are the same thing? What skills are common to both processes? How do the processes differ?***

CPD Now outcomes likely to be covered by these activities include:
02 Knowledge base
04 Legal and ethical
05 Communication skills
08 Patient centred care and choice
09 Inter-professional or inter-agency working
20 Knowledge and skills in audit and research
22 Further the profession

Sean Kelly, CPD Officer

and must include a relevant local contact name/s and telephone number. Pages should be numbered and all consent forms and information sheets should be version dated to ensure that the most recent is used[12].

Obtaining approval

◆ **Why is ethical approval required?** All research projects are monitored to ensure that they are ethical in order to protect both the research participants and the institution carrying out the research. It is also a mandatory requirement, as discussed earlier. All research proposals are reviewed by a multi-disciplinary LREC consisting of medical, other academics and lay members and will end in one of four possible outcomes: approval; approval according to stipulated amendments; request for further clarification; rejection[13].

◆ **Procedure for gaining ethical procedure:** the first priority is to identify whether the project needs the approval of an NHS ethics committee, which will be dependent on whether it is considered to be a clinical audit or research. If 'research', then approval will be required if the proposed research involves any of the following:

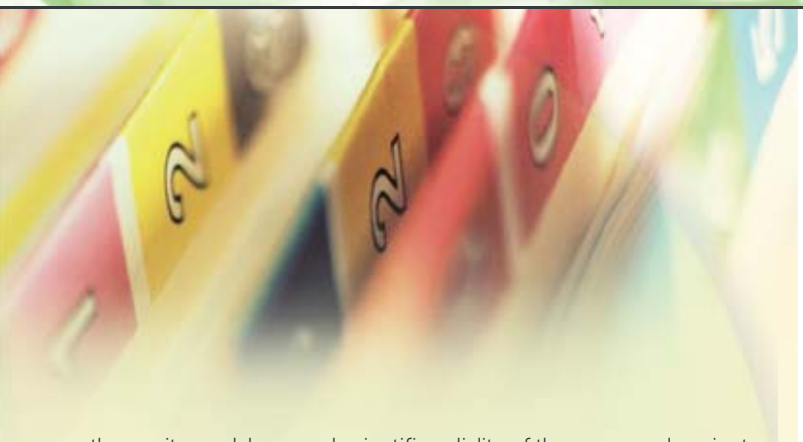
- Patients and users of the NHS. This includes all potential participants recruited by virtue of the patient's or user's past or present treatment by, or use of, the NHS. It also includes NHS patients treated under contracts with private sector institutions
- Individuals identified as potential research participants because of their status as relatives or carers of patients and users of the NHS
- The use of, or potential access to, NHS premises or facilities
- NHS staff recruited as research participants by virtue of their professional role[13].

If approval is required, an approval application form needs to be submitted to the LREC that covers the Trust where the research will be undertaken and where participants will be recruited. A standard NHS ethical approval application form needs to be completed electronically using a form filling programme accessed on the Central Office for Research Ethics Committees (COREC) website[12], covering the following sections:

- Proposed project aims
- Background to the study
- A justification for carrying out the project and expected gains
- The proposed sample size, measures, design and procedures
- An information sheet for participants
- A consent form for participants
- Copies of questionnaires or interview schedules if they are to be used[13].

Guidance notes and procedure for ethical approval for the Royal Liverpool University NHS Trust can be seen in Appendix III and the completed COREC form submitted for ethics approval can be seen in Appendix IV (both can be seen at ***www.sor.org/members/pubarchive/pub_search.htm***).

◆ **Peer review:** increasingly, ethics committees are now asking for all submissions to be peer reviewed. This allows project proposals to be examined by uninvolved professionals who can comment on



the merits, problems and scientific validity of the proposed project. Committees vary in their procedure for doing this; some accept internal peer review while others ask for comments from another appropriately qualified professional[13].

◆ **Indemnity for research:** the COREC ethics form asks how the research will be indemnified. Because the research for this project is on NHS patients then indemnification is through the NHS Trust where the project is being undertaken[13].

◆ **Radiation and research:** the use of diagnostic and therapeutic techniques that involve exposing patients to ionising radiation is subject to the Ionising Radiation (Medical Exposure) Regulations (IRMER) 2000. IRMER requires that procedures are in place to ensure that the use of potentially harmful radiation is justified on a case-by-case basis and that the techniques are optimised so as to minimise radiation exposure consistent with the clinical objective[12].

IRMER not only just applies to routine clinical practice, but also to research. The COREC form is designed to identify and quantify radiation risk. There is also a section concerned with the administration of radioactive substances. These are subject to additional regulations that require a nuclear medicine practitioner to have a relevant certificate from the Administration of Radioactive Substances Advisory Committee (ARSAC) of the DoH[12]. In order for this section to be completed, a medical physicist expert (MPE) needs to provide an estimate of radiation dose and an assessment of risk and sign it. The chief investigator also needs to provide the name of the IRMER and ARSAC practitioner[12].

◆ **How long does ethics approval take?** One constant problem with the workload of LRECs is that it can take up to nine months to clear protocols, while in Denmark, for example, researchers wait approximately two weeks[7]. Depending on the number of applications being processed, ethics committees may meet anything from every two weeks to two months so the time taken from submission to approval varies as well[12].

Addendum

It should also be added that since this article was written, COREC has now become the National Research Ethics Service (NRES) (as of 1 April 2007), which also comprises all NHS RECs in England (http://www.nresform.org.uk/). The current online application form is also being replaced by a new online application form IRAS (Integrated Research Application System (www.myresearchproject.org.uk) which will be mandatory from summer 2008.

About the Author

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References and appendices for this article are at:
www.sor.org/members/pubarchive/pub_search.htm