Research ethics

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Abstract

Medical professionals have a responsibility to act in an ethical manner in everything they do as part of their professional life. However, in most cases, it is only when they are carrying out research that they have to obtain explicit ethical permission to do their work. This runs the risk that people see research ethics as an exercise in getting regulatory clearance, rather than as performing research to the highest ethical standards. In this paper I outline some of the ethical issues that should be considered when doing research, and also how research proposals are evaluated by a research ethics committee.

Key words

Equipoise; placebo; research ethics committee; research ethics; research governance; scientific design; vulnerable subjects

Key points

- It is vital that all involved in healthcare undertake research and evaluation of clinical practice
- Ethical oversight of research protects patients who participate in research
- Ethical oversight also protects others involved in research, including the researcher
- Ethical approval must be obtained from research ethics committees (RECs)
- Different types of research raise different ethical issues
- When writing a proposal for ethical review, researchers must be aware of the composition of the REC
- It is useful to be aware of the eight factors that the REC will look at when considering a study
- Different approaches are used for ethical decision-making
- When comparing treatments, researchers must be in equipoise, genuinely uncertain of which is most effective
- New treatments should always be compared with current best standard therapy
- Special care must be taken when carrying out research on vulnerable patients
- It is important to conduct the research ethically

- You should published the results, even if they are ‘negative’
- The most important factor in whether research is carried out ethically is the researcher

Importance of carrying out ethical research

Research throughout the entire healthcare system is essential for the prevention and management of disease and the promotion of a healthier society. Research has enabled the advances in medical treatment from which patients currently benefit. We need more research to solve not only present problems, but also emerging challenges: new infectious diseases, antibiotic resistance and issues related to an ageing population. Research (as well as audit and evaluation) should be a duty of all healthcare professionals. Indeed, the Secretary of State for Health in England has a statutory duty to promote research and use the evidence obtained from research, as outlined in the Health and Social Care Act 2012.

Why research needs ethical oversight

An understanding of research ethics, and of the governance system that oversees research in the UK National Health System (NHS), is therefore essential. Systems have developed over the years, often in response to adverse incidents where doctors and scientists have, or have been perceived to have, mistreated patients in the name of science. Sometimes an investigator has become so focused on the science that responsibility for the patient had been forgotten, or there has been unawareness of changing values in society.

Therefore research must take place with appropriate ethical oversight. This protects patients by ensuring an independent evaluation of the research. It also protects the researchers, as they can demonstrate that their research has external approval, and it can improve research. In addition, it protects the various organizations involved in the research (funders, care providers, universities) as they can have assurance that their money, facilities or reputation are being used appropriately. The whole research enterprise is protected as the public are reassured that projects have been scrutinized. it also ensures that the research process has remained aligned to changing public opinion. In addition, for some research, it is a legal requirement that ethical approval is in place. Publishers and funders usually require proof that approval has been obtained. Carrying out research without appropriate approval can have serious repercussions on a career in medicine, including removal from the medical register.

Health Research Authority

I will not describe here the *process* of obtaining ethical approval in detail. The details change and the exact processes depend on the nature of the research and, in some cases, which country in the UK the researcher is based in. Every Trust in England (and the equivalent bodies in the devolved administrations) has a research and development (R&D) office, and similar arrangements are in place for primary care. Talk to someone in R&D office, or its equivalent, at an early stage, and take advice from an experienced researcher in your department. There is detailed information on the Health Research Authority (HRA) website.[1]

Below, I discuss some of the major issues in ethical review, which will provide a framework for understanding what researchers should do when undertaking a research project. One important issue is whether your research really is research (Table 1), and the nature of your research project is also important (Table2).

Table 1 Is your research research?

The first question is whether your proposed project is research, clinical audit or service evaluation. All three activities are vital in improving healthcare, and the divide can at times seem artificial. However, in audit and service evaluation, there are no changes to the treatment or tests that a patient undergoes. This distinction is important because, while ethical approval must be obtained for research on patients, it is not needed for clinical audit or service evaluation. The HRA provides a useful information and decision-making tool for determining whether or not the project is research. Further advice is available from the local R&D office or the HRA..

The research ethics service for England is run by the HRA, which is responsible for the 67 HRA research ethics committees (RECs) in England. The HRA works closely with the devolved administrations in Scotland, Wales and Northern Ireland to allow the provision of a single ethical opinion across the UK. The HRA also runs HRA Approval, a new process for England in which there is an assessment of the governance and legal compliance of research projects. The HRA web pages are a useful source of advice and information on research ethics and governance.

Application to the HRA is made through a single online form (the Integrated Research Application System, known as IRAS) that is also used by other groups who regulate research (e.g. the Medicines and Healthcare products Regulatory Agency, or MHRA, which approves drugs used in studies).[3]

Table 2 Different types of research

Different types of research can raise different ethical issues. For example, research can involve gene therapy or the administration of cells, or can involve testing a new pharmaceutical agent (a Clinical Trial of an Investigational Medicinal Product, or CTIMP); it can be a physiological study of healthy volunteers, a study involving tissue or DNA from individuals, a questionnaire study or an epidemiological study of data. The IRAS application form contains preliminary questions on the sort of research being done, so that the remainder of the form is populated with the appropriate questions.

Some projects, not involving patients or human tissue, can be approved by a university rather than HRA REC. Certain types of research (e.g. gene therapy, CTIMPs, research involving children or participants who may lack capacity) have to go to particular committees with the relevant expertise. These RECs are ‘flagged’ for this type of research. On the other hand, for research on human tissue, the local tissue bank may have permission to release tissue in defined circumstances. Talk to your local R&D office, the HRA or an experienced researcher in your department.

Research ethics committees

Research proposals are reviewed by RECs of up to 18 members. At least one third of these are 'lay' members (i.e. not healthcare professionals or scientists). Their role is to ensure that there is a common-sense approach from someone outside the academic/medical 'bubble', and also to bring their own experience and ability to reason and argue. The rest of the REC are 'experts'. Some are clinicians, scientists or nurses. Others have more specific expertise, such as pharmacy or statistics. When filling in the IRAS form, take into account who will be reading it. There may be no one from your particular medical discipline on the REC, so make it comprehensible to your audience, and do not assume that everyone understands your area of expertise as well as you do.

What RECs consider when assessing a proposal

RECs usually consider eight specific factors (Table 3) when reviewing a study. In general terms, these can be grouped into three main areas: whether the research is valid (is it worth doing, and can it be done successfully?), the welfare of the research participants (the burden and risks of doing the research) and whether the dignity of the research participants is respected (for example, if they are adequately informed and whether their confidentiality is respected?). These cover the main ethical issues for any research project.

For example, the quality of the research is an important ethical issue because if the research has no value, or if it is badly designed, the research participants will be wasting their time and be subject to unnecessary burden and possibly risk for no benefit to society. In making its decision about these issues, the REC may use evidence from other sources, such as independent peer review (e.g. from a funding body) to assure them that the research project is well designed and of value.

Table 3 Eight factors an REC always looks at

(although it naturally considers other ethical issues that are part of the study)

1. The social or scientific value; the scientific design and conduct of the study (including the involvement of patients, service users and the public, in the design, management and undertaking of the research)
2. Recruitment arrangements and access to health information, and fair selection of research participants
3. Whether there is a favourable risk:benefit ratio; anticipated benefits and/or risks for the research participants (present and future)
4. The care and protection of research participants; respect for the welfare and dignity of potential and enrolled research participants
5. The informed consent process and the adequacy and completeness of information for the research participants
6. Suitability of the applicant and supporting staff

7. Independent review

8. Suitability of supporting information

REC members use different approaches to address these eight factors. These include goal-based approaches in which they weigh up the potential benefits and harm of the research and attempt to determine whether the benefits outweigh the harms. Members also use duty-based approaches, in which the researcher has duties to the participants (e.g. duties not to harm, duties not to deceive, etc.). These duties are often similar to those of clinical practice. Finally, many consider the rights of research participants (e.g. right to self-determination, right to confidentiality, etc.), and whether the research would deny participants their rights.

These different approaches to ethical reasoning are discussed more fully in other articles in this chapter, as they relate more widely to ethical behaviour in medicine.

Differences between research and standard clinical practice

While the ethical reasoning can be similar between research and clinical practice, there are differences in how these work out in the different settings. For example, in clinical practice, there is a clear ethical principle that the doctor should act in the best interests of the patient. This often involves evaluating what is the most effective treatment and offering that. However, that is not possible in research – the whole point of research is to find out what the most effective treatment is. What is frequently sought is 'equipoise': at the time the patient is invited onto the trial, it is not known whether the research therapy or conventional standard treatment is better.

Research often involves a comparison between a new therapy (drug or intervention) and the current best standard treatment. This can take the form of a randomized controlled trial in which the patients are allocated at random between groups being given the new therapy and the conventional therapy, usually without knowing which group they are in. It is vital that patients should not be knowingly disadvantaged by taking part in the study, and that equipoise is maintained.

If a treatment is known to be effective for the condition, it is not appropriate to compare the new therapy with a placebo control, in which patients receive an inert or 'dummy' treatment, as the patients in the placebo group would get less good treatment than if they had not been part of the study. However, if there is no current effective treatment, it may be appropriate for one group to be given placebo alone. Placebo treatment is often used to 'mask' from the patients (and indeed the researchers) which group they are in; for example, if an experimental agent is administered more frequently than the current standard therapy, dummy pills can be used to make up the extra doses, so that it is not possible to work out which group the patient is part of.[4]

Special consideration of vulnerable patients

In clinical practice, the doctor's only concern is the well-being of the patient. However, in research the aim is also to add to human knowledge. This therefore gives researchers a particular responsibility for vulnerable patients, who may not directly benefit from the research. These include children and individuals who do not have capacity to consent for research (e.g. those with learning difficulties or dementia). However, there are other groups who are might be under pressure to agree to take part in research, such as prisoners and refugees. It is for these reasons that special arrangements are put in place to ensure that the rights and well-being of these individuals are respected.

And then what?

Once you have received the ethical approval, and the other approvals needed for the research, what happens next? The most important thing is to carry out the research! Follow the approved protocol and, if you need to change it, submit the revision to the REC. If there are any problems, let the relevant people know. You will also have to submit reports on a regular basis.

When the research is over, it should be published. The research is only of any public benefit if it is published – if no one finds out what has been done, the participants' time has been wasted, which is not ethical. Even negative results can be useful. You should also offer to share the findings of your research with those who took part in the study.

The most important safeguard to ensuring that research is ethically carried out is the researcher, so the most important thing is that you conduct your research ethically. This does not just mean following the rules, but also treating research participants appropriately, involving them and keeping them informed about the research. Carry out the research with integrity – in both the conduct of the research and the publication of the results. If there are concerns about the way in which the research is being carried out, raise them with senior personnel in the hospital or university.

KEY REFERENCES

1 Health Research Authority. http://www.hra.nhs.uk/ (accessed 24 Apr 2016).

2 Health Research Authority. Is it research? http://www.hra.nhs.uk/resources/before-you-apply/is-it-research/ (accessed 24 Apr 2016).

3 Integrated Research Application Process. https://www.myresearchproject.org.uk/ (accessed 24 Apr 2016)

4 George AJT, Collett C, Carr A, et al. When should placebo surgery as a control in clinical trials be carried out? *Bull R Coll Surg* 2016; **98:** 75–9.

FURTHER READING

There are a large number of guidelines and other information on the conduct of ethical research that address particular areas of importance. The most comprehensive and overarching is that issued by the Royal College of Physicians, which provides a good overview of the whole area.

1 Royal College of Physicians. Guidelines on the practice of ethics committees in medical research with human participants. https://shop.rcplondon.ac.uk/products/guidelines-on-the-practice-of-ethics-committees-in-medical-research-with-human-participants?variant=6364998469 (accessed 24 Apr 2016).

Test yourself
To test your knowledge based on the article you have just read, please complete the questions below.

Question 1 A researcher proposed a research project in which one group of five patients would be given current best therapy that was effective in some patients, and another group of five patients would be given a new form of treatment that had been tested in animals but not previously used in patients (although it had been given to healthy volunteers to test for safety). An independent statistician indicated that the study was underpowered. This study was rejected by the research ethics committee.

What is the most likely reason for this?

A There is already an effective treatment

B The study involves too many participants, exposing more patients than needed to the experimental therapy

C The study involves too few participants, thus limiting its ability to produce an answer

D The drug has been tested in animals

E It would be unethical to deny some patients the new form of treatment

Answer: C

Feedback: It is reasonable to undertake research where there is equipoise between the two treatments and the current best therapy is not effective for all patients (or has other drawbacks). Given that it is not known which treatment is best, it is ethical for the two groups of patients to be given different forms of treatment. However, the study must be properly designed and not include too many research participants (avoiding exposing more people than needed to the research) or too few (which is likely to result in the study failing to produce an outcome). A statistician found that the study was underpowered, with too few patients recruited, and this is likely to be the reason for the research ethics committee's rejection. It is usual for new treatments to be tested in animals, as they give indications of both safety and efficacy.

Question 2

A research project was proposed in which women in the final stages of labour would be asked to consent to which of two drugs they would be given for pain relief. Both drugs were in routine use. The women would be given a comprehensive 22-page document outlining the nature of the research project, what would happen to them if they agreed to take part and the risks of the study. It would also explain that the research was being paid for by a pharmaceutical company, and that the hospital would receive money for every patient recruited. The women would be asked to read the document and sign the consent form. This study was not approved by the research ethics committee.

What is the most likely reason for this?

A The study is being paid for by a pharmaceutical company

B The hospital is to receive funding for the study

C Pregnant women would be being presented with information at the wrong time

D The drug being given to the women might affect the fetus

E Research must not be carried out on women in labour as this is an important period for them and their families

Answer: C

Feedback: If treatments during childbirth are to be improved, it is essential that research is carried out on women who are pregnant and in childbirth, so this is not likely to be the reason. The research ethics committee (REC) would want assurance that safety aspects of doing research on these participants have been fully considered. They would also want to know that the study would not interfere with the mother's experience of birth. In addition, it is normal for pharmaceutical companies to pay for studies and to reimburse hospitals for their patients' participation; the REC would want to know that this would be done properly. In this case, the REC is likely to consider that a woman in the final stages of childbirth would not be in a position to take in 22 pages of information and make an informed choice on whether or not she wanted to participate in the research. The REC is likely to ask the researchers to think of alternative ways of giving the women the necessary information at a time and in a way that allows them to make a decision.

3 A researcher completed their study of a new drug and showed that it was no better (and indeed was slightly worse) than the current standard treatment. The researcher decided not to publish any papers as this was a negative result that no one would be interested in.

Which of the following is a reason why even negative results should be published?

A The researcher may in future need a publication for promotion purposes

B Publication of these data will alert future researchers to the results

C The researcher can send the publication to the patients who took part in the study to alert them to the results

D It is the law that you should publish the results of all research studies

E If the researcher does not publish the study, the funder will not reimburse the study costs

Answer:

Feedback: BAlthough publishing papers can help a researcher's career, and the funder may (or indeed may not) wish the results of the study to be published, it is not a legal requirement for all results to be published. However, the Health Research Authority does have expectations for the publication and dissemination of research findings. It is also good practice to offer information about the study to those who took part in it, although giving all patients a primary research paper may not be the best way to do this. The main reason for publishing even negative results is to alert future researchers to the results. This has several benefits. One is that others can learn from the results and not waste time and resources on work that will not yield benefit. A second is that this reduces the risk of publication bias. If only positive studies are published, and negative results ignored, the publication record will be biased to the positive results. This can lead to some new forms of therapy looking effective when they are not.