The ethics of clinical trials

Bernard A Foëx

Abstract
Beneficence, non-maleficence, autonomy and justice: these are the four pillars of modern medical ethics. To ensure beneficence, and non-maleficence, in our treatment of patients, we need the evidence of clinical trials. The Declaration of Helsinki of 1964, and its numerous amendments, provides the ethical ground rules for the conduct of clinical trials. Key elements include the concept that the well-being of the individual takes precedence over the interests of society, informed consent, voluntary participation and the right to opt out. Randomization of patients is ethical only if there is equipoise between the different interventions. Patients should be entered into only those trials which are adequately powered. There is also the need to monitor the safety of trials and to stop the trial if there is loss of equipoise. Trial participants should also expect the same standard of confidentiality as other patients. For all the regulation of clinical trials there remain areas of controversy. Is it reasonable to compare a new treatment with placebo? That will depend on whether placebo is the current standard of care. Is it ethical to stop a trial early for commercial reasons? Does commercial funding of trials influence their results? There is certainly evidence to suggest publication bias. The issue of informed consent remains problematic for trials involving children, incompetent adults, emergency situations and the critically ill. However, all these groups have the right to benefit from medical advances, which can be made only through clinical trials.

Keywords clinical trial; confidentiality; Declaration of Helsinki; equipoise; ethics; placebo; randomization

What are the ethical principles that govern clinical trials?

Medical ethics
Codes of conduct for physicians are probably as old as medicine itself, and Western medical ethics still owes some of its basic principles to the Hippocratic writings of the fourth century BC. Much of the rest has been superseded by Beauchamp and Childress’s four principles: beneficence, non-maleficence, autonomy and justice. So it remains true that doctors should do their best, or what is best for their patients, and should do no harm.

Bernard A Foëx, BM, BCH, PhD, FRCSE, FCSEM, is a Consultant in Emergency Medicine and Critical Care at Manchester Royal Infirmary. He qualified from Oxford University and trained in Manchester and Paris. His research interests include the cardiovascular and biochemical responses to haemorrhage and trauma and the ethics of biomedical research. Conflicts of interests: none declared.

How do we know what is the best treatment for a given condition? How do we know that a particular new treatment causes no harm? We could just guess, try it and see what happens ... Or we could design a clinical trial with defined end-points, statistical analysis and monitoring of adverse events. Clinical trials provide us with some of the knowledge to practise medicine in an ethical manner.

Principles of biomedical research ethics
Although there were codes of conduct covering clinical practice, there were very few rules to regulate medical research until after the Second World War. The Nuremberg Code (1947), drawn up as a result of the Nuremberg Trials, formalized rules to govern the use of human subjects in biomedical research. Its primary clause stated that ‘The voluntary consent of the human subject is absolutely essential’. The Code also stipulated that subjects should be legally competent, should be able to exercise free choice and should be fully informed. Other clauses addressed the responsibility of the investigator to end the study if ‘the experiment is likely to result in injury, disability, or death to the experimental subject’, and the right of the subject to end the experiment.

For all its good intentions the Nuremberg Code was largely ignored. The medical profession did, eventually, take some ownership of ethical principles governing research with the publication of the Declaration of Helsinki in 1964. This has been much revised. The key elements in relation to this article are shown in Table 1.

• See http://www.wma.net/e/policy/b3.htm for the Declaration of Helsinki.

Randomization and equipoise
Randomization is predicated on the premise that there is equipoise between the two arms of the study. This means that there

Summary points on the Declaration of Helsinki

• Well-being of subjects should take precedence over the interests of science/society
• Subjects should be volunteers
• Subjects should give informed consent
• Experimental protocols should be approved by an independent ethical review committee, in conformity with the laws and regulations of the country in which the study is performed
• Research should be preceded by an assessment of the predictable risks and burdens to the subject
• Research should stop if the risks outweigh the benefits or if there is conclusive proof of benefit
• Subjects have a right to confidentiality
• Subjects have a right to withdraw from the research
• Research is justified only if the research population is likely to benefit from the results
• Safeguards for incompetent adults and children
• Obligation to publish results – negative as well as positive
• New methods should be tested against best current practice

Table 1
must be genuine uncertainty as to which treatment or intervention is best: it would be unethical to treat a patient with an inferior treatment.

**Adequacy of the trial and power calculations**

Any trial involves an element of risk, even though it is predicated on equipoise: one group of patients may miss out on an effective treatment; one group may be exposed to an unexpected adverse event. This risk must be balanced by a potential benefit; namely, an answer to the clinical question addressed by the trial. The question will be answered only if the trial has an adequate ‘power’. It is now recognized that many trials in the past were far too small to answer the original question: they found no difference between two treatments because not enough patients were recruited into the trial. They could be regarded as unethical because patients were exposed to a risk with no chance of any benefit. It could also be argued that they were unethical in that they were a waste of the investigator’s time and other resources. This problem is now minimized by the need to calculate a sample size as part of the design process for the trial.

**Safety and monitoring**

Patients will agree to take part in clinical trials on the understanding that they are not exposing themselves to unreasonable risks. In any trial there is an element of uncertainty. For this reason, safety monitoring is now specified in the EU Clinical Trials Directive (see [http://www.wctn.org.uk/downloads/EU_Directive/Directive.pdf](http://www.wctn.org.uk/downloads/EU_Directive/Directive.pdf)), which will include the reporting of adverse events (AEs), adverse drug reactions (ADRs), serious adverse events (SAEs), serious adverse drug reactions (SADRs) and suspected unexpected serious adverse reactions (SUSARs).

At the same time a trial can continue only if there is equipoise between the different treatments. The advent of the large multicentre, multinational trials running for several years has resulted in the need for planned interim analyses. This allows the trial to be evaluated to see whether there is already clear evidence of a difference between the interventions, in which case the trial may need to be stopped. It allows the safety of the trial to be reviewed and also allows compliance with protocols to be checked. Centres not complying with the correct conduct of the trial may need to be removed from the trial and their data censored.


**Data management (confidentiality)**

Maintaining patient confidentiality is one of the oldest of the principles of medical ethics. It applies as much to research as it does to clinical practice (and is covered by the Data Protection Act 1998).

- See [http://www.ico.gov.uk/Home/what_we_cover/data_protection.aspx](http://www.ico.gov.uk/Home/what_we_cover/data_protection.aspx)

**Current controversies in the ethics of clinical trials**

**Problem of placebo:** randomized placebo-controlled trials are often thought of as the ‘gold standard’ in evidence-based medicine. However, the use of placebo arms in clinical trials continues to arouse controversy. A trial of dronedarone versus placebo to prevent recurrence of atrial fibrillation should really have been dronedarone versus amiodarone. But as amiodarone is not licensed for this indication, the trial might not have been approved by the US Food and Drug Administration (FDA): a conflict between clinical/ethical standards and the standards of regulatory authorities. Indeed, the placebo-controlled trials to reduce maternal–fetal human immunodeficiency virus (HIV) transmission in developing countries, when triple therapy was the standard treatment in the West, resulted in specific amendments to the Declaration of Helsinki in 1996, stipulating that trials should, generally, be against best current practice.

**Stopping early:** a clinical trial may be stopped early for a variety of legitimate reasons. Serious adverse events may be reported to the Safety Monitoring Committee or an interim analysis may show that one treatment is superior to the other, which results in the loss of equipoise. It then becomes unethical to continue to randomize patients and the trial is stopped. Paradoxically, it may then take years for the results to be published and implemented.

However, there are other reasons why trials are stopped early. Many trials have been stopped early because of a failure of recruitment or because they reach the end of their funding without reaching their recruitment target (e.g. the CORTICUS trial of steroids in sepsis). The trial failed to show a survival benefit from steroids, but was underpowered because of the failure to recruit. Should further funding have been sought to finish the trial? Or would that have been an inappropriate use of resources? Many trials now have built into their interim analysis stopping rules, which will determine whether it is futile to continue recruiting because it is unlikely that a significant result will be obtained.

Much more controversial is the halting of trials for commercial reasons. As Boyd has argued, such early termination violates the principles of the Declaration of Helsinki.

**Drug money and sponsorship of clinical trials:** conducting clinical trials is becoming an increasingly expensive business. The result is that many trials of new drugs can happen only if funded by the pharmaceutical industry, which may result in a conflict of interest. The potential problems arising from this situation have been reviewed. Sponsored studies are more likely to report favourable results and tend to have better results than independent studies. This may simply be a reflection of the fact that studies with greater resources are better designed and carried out. There is now an acceptance that trials with major public health implications should be funded by the ‘State’ rather than by the pharmaceutical industry. This was the rationale for the Medical Research Council-sponsored CRASH trial (steroids in head injury) and is the rationale for the Health Technology Assessment-funded OSCAR trial (high-frequency oscillation in acute respiratory distress syndrome).

**Publication ethics:** in general, trials showing the benefit of a new treatment are more likely to be published than those which do not. This publication bias may have important consequences: it will tend to overstate the efficacy of a treatment and it may mask adverse events. This has been well demonstrated in the
case of trials of antidepressants.\textsuperscript{7} The authors concluded, ‘We cannot determine whether the bias observed resulted from a failure to submit manuscripts on the part of authors and sponsors, from decisions by journal editors and reviewers not to publish, or both.’ Before the publication of the ENHANCE trial\textsuperscript{8} on the treatment of atherosclerosis in patients with heterozygous familial hypercholesterolaemia there was controversy about whether the delay was because the results suggested that the new drug was ineffective.\textsuperscript{9}

Whatever the reasons for publication bias in general, it is now recognized that the results of trials need to be made available even if they are not published in peer-reviewed journals. In the USA this has now been made a legal requirement under the FDA Amendments Act, passed in 2007.\textsuperscript{10} From September 2008 not only must trials regulated by the FDA be registered at clinicaltrials.gov, but the results will also have to be posted on the site.

• See http://clinicaltrials.gov/ct2/home

**Surrogate outcomes:** surrogate outcomes tend to be measurable outcomes used in a trial to infer a potential clinical benefit from a drug or intervention. If renal failure is one of the features of severe sepsis then in a trial serum creatinine measurements may be used as a surrogate for renal failure or even mortality. This is a major assumption. In the case of sepsis many of the early, smaller trials of innovative therapies relied on surrogate markers or outcomes to show a potential benefit. When the trials were repeated to test for survival benefit they failed. In relation to the ENHANCE trial (above) Colin Baigent, Professor of Epidemiology, commented that ‘surrogate outcomes are simply useless for determining whether a drug will be clinically useful’.\textsuperscript{9} However, they continue to be used because it is usually much easier to power a trial to show an improvement in a surrogate outcome than one such as mortality or morbidity.

**Trials involving children:** participation in trials should be voluntary and participants should give informed consent. In the majority of cases children will not fulfil these criteria. It should follow that they should not participate in clinical trials. At the same time it would be unethical to treat children using untested drugs or techniques. Therefore, it becomes imperative to involve children in clinical trials, with certain safeguards. A number of revisions of the Declaration of Helsinki have addressed this problem. Provisions for the use of children in research have been made in the Medicines for Human Use (Clinical Trials) Regulations 2004, and there is also guidance from the BMA and the Royal College of Paediatrics and Child Health (Table 2).

• See http://www.rcpch.ac.uk/Research/Research-Activity

**Clinical trials in emergency situations and the critically ill:** the ethical issues are much the same. In most emergency situations, or when patients are critically ill, they are unable to give informed consent and so should not be recruited into trials. Should we then stop all research into new treatments for these patients, or not test new treatments before introducing them? It would be equally unethical to deprive future generations of better treatments and to deprive critically ill patients of the opportunity to take part in trials. This has been recognized by an amendment (2006) to the Medicines for Human Use (Clinical Trials) Regulations 2004.

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<th>Summary points on research involving children</th>
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<tr>
<td>• Research involving children is important for the benefit of children</td>
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<td>• Research should be carried out only if the answer could not be obtained from research on adults</td>
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<td>• Children are not small adults</td>
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<td>• Research should be approved by a research ethics committee</td>
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<td>• Informed consent should be obtained from the child, parent or guardian, as appropriate</td>
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<td>• When consent is given by a parent or guardian the agreement of the child should also be obtained, if the child is old/mature enough</td>
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**Research in incompetent adults:** adults with certain forms of mental illness may also be incompetent to give informed consent to take part in research. As with the critically ill and children, research will still be necessary. The same ethical arguments can be deployed and the problem has been addressed by the Mental Capacity Act 2005 (Table 3).

**Inclusion and exclusion criteria:** trials aim to answer a specific question about the treatment of a certain condition or group of patients. It follows that the trial should only include patients fulfilling certain inclusion criteria. It also follows that certain

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<td>• Research must be approved (research ethics committee)</td>
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<td>• Research is connected to the ‘impairing condition’ or its treatment</td>
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<td>• The research could not be carried out on those with capacity to consent</td>
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<td>• Research must either:</td>
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<tr>
<td>1. be of potential benefit and not impose a disproportionate burden on the patient, or</td>
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<td>2. be related to the treatment of those with a similar condition and pose negligible risk to the patient</td>
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<td>• Attempts should be made to identify a carer or person with the patient’s welfare at heart. That person should be informed and asked to give an opinion on whether the patient would want to take part (substituted judgement)</td>
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<td>• An advance decision or statement against participation in research should be respected</td>
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<tr>
<td>• Nothing should be done to which the patient appears to object</td>
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<td>• Attempts should be made to maximize the patient’s understanding of the research and to enable him/her to take part in the decision to participate</td>
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<td>• Usual research requirements must also be met</td>
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**Table 2**

**Table 3**
patients will not be eligible for the trial: either because they do not fulfil the inclusion criteria or because they specifically should not be exposed to the trial (such groups often include children, pregnant patients, patients expected to die from a terminal disease not covered by the trial, patients thought to have a positive indication for one or other of the treatments and patients thought to have a contraindication for the same).

Multicultural involvement in research

Britain is a multicultural society, and increasingly so. All in a multicultural society should benefit from advances in medicine. By the same token all should be able to participate in the trials that fuel these advances. No one group should bear a disproportionate amount of the ‘risk’ of participating in trials. However, the practicalities of obtaining informed consent do not favour multicultural involvement. The difficulty of preparing patient information in different languages and using interpreters to obtain informed consent effectively means that in many trials non-English speakers are excluded. Does this really matter, or is this just ethical nit-picking? Yes, it does matter: trial participants must represent the population which will later use the treatment. Certain ethnic groups may bear a disproportionate burden of a disease. Not only should these groups be encouraged to participate in trials, but trials should be aimed at them.11

The ‘eliminating disparities in clinical trials’ (EDICT) initiative in Houston is one example of an attempt to improve the diversity of participation in clinical trials. Increasing diversity will come at a cost: if trials need to be bigger to allow meaningful subgroup analyses (e.g. according to gender, race or age), then this will increase the cost of the trial, the time needed to recruit and the time to completion.

• See http://www.bcm.edu/edict/PDF/EDICT_Barriers_to_Clinical_Trial_Participation.pdf for the report
• See http://www.bcm.edu/edict/PDF/EDICT_Project_White_Paper.pdf for the report
• See http://www.bcm.edu/edict/PDF/EDICT_Project_Policy_Recommendations.pdf for the recommendations.

REFERENCES


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