*Health Technology Assessment* 1998; Vol. 2: No. 15 (Executive summary)

**Review**

## *Executive summary*

# Ethical issues in the design and conduct of randomised controlled trials

SJL Edwards[1]
RJ Lilford[1]
DA Braunholtz[1]
JC Jackson[2]
J Hewison[3]
J Thornton[4]

[1] Department of Public Health and Medicine, University of Birmingham, UK
[2] Department of Philosophy, University of Leeds, UK
[3] Department of Psychology, University of Leeds, UK
[4] Department of Epidemiology, University of Leeds, UK

**Health Technology Assessment**
**NHS R&D HTA Programme**

# Executive summary

## Objectives

- To review ethical arguments put forward in the literature which bear on randomised controlled trials (RCTs), focusing particularly on uncertainty as an underpinning issue.
- To review empirical data (from comparative, observational and qualitative studies) which may be relevant to the ethics of conducting trials.

## Methods

A review of the literature was conducted. The aims were achieved by completing the following tasks:

- **Ethics:**
  - development of an intellectual framework to structure the ethics literature
  - creation of a database containing references relating to the ethics of conducting clinical trials, including any methodological papers which have implications for medical ethics
  - classification of the articles, according to the type of information contained within (e.g. 'under-powered' trials versus replication of trials)
  - summary of the ethical arguments and commentary on those arguments.
- **Empirical data:**
  - classification of studies according to topic and study design
  - creation of a database containing empirical studies relevant to the ethics of conducting trials
  - abstraction and quality assessment of relevant empirical data
  - summary of the primary data.

## Results

### RCTs

The main reason for using the RCT design is a scientific one: society is likely to suffer as a direct result of avoiding such high quality evidence. The most widely cited assaults on the RCT are claims that patients necessarily sacrifice themselves for the benefit of future patients by participating in trials, and look to Kantian ethics for support. Kantians would object, however, if the investigators use patients merely as the means to societal ends and, given voluntary consent, this is not the case. At any rate, patients are not required to sacrifice themselves (whether voluntarily or not) for the benefit of society if we endorse the uncertainty principle, or, less ambiguously, equipoise, whereby each (or all) comparator treatments are an 'equal bet' in prospect. When equipoise applies, patients do not lose out prospectively, in order to benefit others. Given equipoise, a trial should be acceptable to both utilitarians and Kantians, and hence ethical in its use of patients. If known or potential side-effects of the comparator treatments are unequal, then a trial should be acceptable to both parties provided the expected utilities are equivalent, that is, equipoise is only a 'null' prior belief if there are no trade-offs to be made. Although there are possibly valid objections to the use of RCTs in particular disciplines or cases (e.g. if the offer of trial entry will make the patient very upset), such arguments do not make the RCT necessarily unethical. Further argument concerns the idea of uncertainty as a moral basis for trials as well as the significance of different, less ambiguous, constructs, i.e. collective versus individual equipoise.

The empirical evidence on the whole was seen to support the view that RCTs are justified in clinical practice, contingent, however, on the existence of patient equipoise (informed consent). Indeed, trials themselves may have a beneficial effect on patients' outcome both in terms of physical prognosis (at least, when an effective treatment is already available) and psychological experience, perhaps due to increased levels of care that are unintended. Any such benefit should be incidental to routine care and not used as an incentive to increase recruitment rate, lest the principle laid down in the Helsinki Declaration (that non-participation in a study will not intentionally affect the standard of care) be violated.

### Informed consent

It is evident that patients are unlikely to understand all the information which is given to them by whatever means during consent consultations. Patients have particular problems grasping abstract, as

opposed to concrete, information. Consequently, fully informed consent for all patients at least is an unobtainable ideal. There are three possible responses to this problem: (1) declare all trials unethical, unless the participants are themselves medical experts (or as expert as anyone else in the relevant field), (2) abandon the requirement of informed consent, but rely on other safeguards such as ethics committees to protect individual participants, or (3) retain the spirit of informed consent, taking all practical measures to maximise patient understanding, but still rely on ethics committees as a further level of protection. The authors favour the third option. While difficulties with communication are regrettable and should be reduced as much as possible, some failure would appear inevitable. The need to advance medical understanding is important, but communication difficulties remain ethically critical if a patient decides to participate on the basis that he/she will benefit therapeutically in a way incommensurate with clinical prior belief. It is therefore important that the patient understands that equipoise exists, and so has realistic expectations.

## Conclusions

- The caring professions must articulate clear, ethical justification for trials if public confidence is to be retained.
- Patients should not lose out in prospect by taking part in a trial.
- Given treatments which are generally available, patients do not lose out in prospect when prior estimates of effectiveness and values interact to produce equal expected utilities.
- When treatments are not generally available, patients do not lose out by participating in trials when the expected utility of the new treatment is at least as high as that of standard treatment.
- The term 'uncertainty' prevaricates on prior probabilities and values, making it an inadequate moral basis for trials. It should not be used to disguise such existing data as may affect patient preferences, even when such data are insufficient to engender 'certainty'.
- Patients must be given as much information as they need to bring their values into play.
- Patients are least alarmed and understand the issues most clearly when they have encountered the concept of comparative trials before.
- Practitioners should pay particular attention to explaining abstract ideas (especially that of randomisation).
- Small trials of existing therapies are not necessarily unethical provided that they are in equipoise.
- Clinical trials should start early in the life of a new treatment.
- The idea that patients in trials do better than average, even when the trial produces a negative result, may be true. If the effect is real, it would seem to come from enhanced attention to detail inherent in following the trial protocol for both control and experimental groups. It should not, however, be used as an inducement to accept randomisation since the Helsinki accord requires that the intention should be to provide the 'best' care for all patients.

## Recommendations for research

Areas in the ethics of RCTs which need to be further analysed, include:

- ethical issues in the design and conduct of cluster trials
- ethical issues in interim analysis
- the conduct and constitution of ethics committees.

There are a number of empirical questions which also need to be addressed, and these are detailed in the main report.

## Publication

Edwards SJL, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J. Ethical issues in the design and conduct of randomised controlled trials. *Health Technol Assessment* 1998; **2**(15).

# NHS R&D HTA Programme

The overall aim of the NHS R&D Health Technology Assessment (HTA) programme is to ensure that high-quality research information on the costs, effectiveness and broader impact of health technologies is produced in the most efficient way for those who use, manage and work in the NHS. Research is undertaken in those areas where the evidence will lead to the greatest benefits to patients, either through improved patient outcomes or the most efficient use of NHS resources.

The Standing Group on Health Technology advises on national priorities for health technology assessment. Six advisory panels assist the Standing Group in identifying and prioritising projects. These priorities are then considered by the HTA Commissioning Board supported by the National Coordinating Centre for HTA (NCCHTA).

This report is one of a series covering acute care, diagnostics and imaging, methodology, pharmaceuticals, population screening, and primary and community care. It was identified as a priority by the Methodology Panel and funded as project number 93/41/02.

The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health. The editors wish to emphasise that funding and publication of this research by the NHS should not be taken as implicit support for the recommendations for policy contained herein. In particular, policy options in the area of screening will, in England, be considered by the National Screening Committee. This Committee, chaired by the Chief Medical Officer, will take into account the views expressed here, further available evidence and other relevant considerations.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.



The editors have tried to ensure the accuracy of this report but cannot accept responsibility for any errors or omissions. They would like to thank the referees for their constructive comments on the draft document.

Copies of this report can be obtained from:

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@soton.ac.uk
http://www.hta.nhsweb.nhs.uk

ISSN 1366-5278