

Ethical issues in the design and conduct of randomised controlled trials

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



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Ethical issues in the design and conduct of randomised controlled trials

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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).

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Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context but a glossary is provided for the non-specialist reader. In some cases usage differs in the literature but the term has a constant meaning throughout this review.

Glossary

Altruism Benevolent concern for the interests and welfare of other persons, and is typically contrasted with egoism. The possibility of genuine altruism has been debated – apparently altruistic individuals may themselves benefit.

Autonomy A person's capacity for self-determination. Respect for autonomy is often contrasted with Paternalism.

Bayesian statistics Based on the concept of probability as subjective degree of belief and is named after Reverend Thomas Bayes (1702–1761), whose theorem is interpreted as the probability of A given the data are proportional to the probability of A, multiplied by the probability of the data, given A.

Beneficence The moral principle of doing good. One of the four principles in medical ethics proposed by Beauchamp and Childress.

Blinding The term is used in trials to refer to keeping individuals ignorant of the treatment allocation. Individuals include any combination of physicians, patients, observers and statisticians. A double-blind trial is one where both the physician and the patient are blind.

Case-control study A type of observational analytic epidemiological investigation in which subjects are selected on the basis of whether they do (cases) or do not (controls) have a particular disease under study. The groups are then compared with respect to the proportion having a history of an exposure or characteristic of interest.

Categorical imperative An ought-statement that is independent of any condition that a certain end is desired by the agent. According to Kant, an action has genuine moral worth only if the ought-statement that motivates the agent is categorical.

Clinical trial A prospective controlled study involving patients, i.e. one in which an intervention is allocated and patients are followed up.

Cluster trial An interventional design which attempts to make inferences about individuals but where the intervention is allocated to clusters of individuals.

Crossover designs An interventional study in which more than one treatment is allocated sequentially to at least some patients, often with a 'wash-out' period between active treatments.

Data monitoring committee A group of people, typically independent from the trial, which decides if and when to stop the trial early.

Decision analysis A formal mathematical approach, based on (typically Bayesian) probability theory, to making decisions under uncertainty.

Deontology Strictly, the study of 'duty' or 'obligation' from the Greek 'deon' meaning 'must'. This may include theories according to which the rightness of an action is not exclusively determined by the value of the consequences.

Duty Having a duty to do something implies that one ought to do it. The converse statement is not valid – there are things one ought to do without having a duty to do them. Kant distinguished between 'perfect' and 'imperfect' duties. The former can be expressed by the **Categorical imperative**. A perfect duty is absolute, and an imperfect duty is desirable but not necessary.

Epistemology Strictly, the study of knowledge. Philosophers have focused was on what is it to know something and knowledge has been defined as justified true belief.

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Equipose Various forms of equipose have been proposed. Equipose refers to a state of regarding two treatments as an equal bet in prospect. Collective equipose is where the profession at large is equally balanced, while individual equipose refers to the individual.

Equivocation Semantic ambiguity of meaning where a word(s) sometimes means one thing and, at others, something different.

Ethics The reflective inquiry into how people should think or behave with a view to formulating norms of conduct and evaluation of character. Contrast with **Morality**. Applied ethics is the study of what standards are applied to actual situations.

Expected utility The expected utility of an action is the probability of an outcome times its value (utility), summed over all possible outcomes.

Feedback trial This is a trial in which any preliminary findings are publicly available. See also **Open trial**.

Frequentist statistics Based on a concept of probability that is objective (typically relative) frequency. Many of the methods employed are based on hypothesis tests.

Hazard ratio A ratio of two hazards. A hazard is an instantaneous risk.

Helsinki Declaration World Medical Association Declaration of Helsinki – recommendations guiding doctors in biomedical research involving human subjects. These were adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, and revised by the World Medical Assembly in Tokyo, Japan, 1975, in Venice, Italy, in, 1983 and in Hong Kong in, 1989.

Hippocratic Oath An oath sworn by Hippocrates of Cos who was an influential Greek physician of the fifth century BC. This oath has formed the ethical basis of medical practice ever since.

Hypothetical imperative An ought-statement which describes an action necessary to achieve a certain end that is desired by the agent. Such an imperative is thus conditional to the particular end in question and is to be distinguished from the **Categorical imperative**.

Individual Anything regarded as a single unit, especially a person. One view of individualism

is that the ideal individual should be self-determining, making decisions independently.

Induction Inference from a finite number of particular cases to a further case or generalisation.

Interim analysis Statistical analysis, performed before the trial has ended, the results of which are typically made available to a **Data monitoring committee** alone.

Justice A property of a political system. Often called an ‘imperfect duty’. Justice can be retributive or distributive. The latter aims at allocating resources or tasks fairly amongst a given population.

Liberalism A set of ideas in social and political thought which underlines the importance of individual rights. The role of the state is primarily to protect these rights.

Medical research Systematic investigation to establish facts and reach conclusions. Contrast with **Medical practice**.

Meta-analysis The statistical analysis of data from more than one study of the same intervention (or association) in an attempt to summarise the current state of knowledge.

Morality Beliefs about what is good or bad, right or wrong. See also **Ethics**.

n of 1 trial A **crossover** trial involving only one person where one or more treatments are evaluated for their effectiveness for the individual in question. The order of exposure might be random.

Non-maleficence The moral principle of not doing harm. One of the four principles in medical ethics proposed by Beauchamp and Childress.

Null hypothesis The proposition to be tested statistically, that the experimental intervention has ‘no effect’.

Nuremberg Code In 1947 an International tribunal declared the Nuremberg Code the standard by which a group of doctors in Nazi Germany should be judged.

Obligation Having an obligation to do something implies that one ought to do it. Often used synonymously with **Duty**.

Odds ratio A ratio of two odds. Odds are the ratio of a probability and its complement.

Open trial We use this to mean that the treatment assignment is known by the physician and patient. Contrast with a blinded trial (see **Blinding**).

Paternalism Any situation in which decisions are taken on behalf of a competent person. Contrast with an autonomous choice (see **Autonomy**).

Placebo A chemically inert substance which has a psychologically suggestive effect and is used in place of an active drug. Also used as a control in a clinical trial to determine whether improvement and/or side-effects can be attributed to the active substance.

Pluralism A philosophical point of view that an inquiry into morality should draw on more than one theory, as no single theory can fully explain it.

Posterior probability distribution What a rational Bayesian observer should believe, given his/her prior beliefs, the data and the model.

Prior probability distribution What an observer believes prior to seeing additional data.

Probabilistic dominance This situation arises in decision analysis where there are only two outcomes, e.g. life or death.

Probability The meta-physics of chance or the state of being probable. There are two main theories of probability: frequentist and Bayesian.

Protocol A formal and explicit treatment regimen for care. A clinical trial will have two or more such protocols along with a description of the research design or method, eligibility requirements and the proposed method of analysis. It can also be used to describe the comprehensive written document detailing all procedures to be followed in a trial, though we do not use it in this sense.

Randomised controlled trial An intervention study in which treatments are allocated to patients on a random basis, thereby avoiding any uneven distribution of patients with known, or unknown, risk factors between treatment arms

Right A moral or legal power belonging to an individual or group. Although it may be permissible for a person to exercise a right, it may not be the morally 'right' thing to do.

A right can be to be free from interference or allied to an external duty.

Relative risk Ratio of risks. The risk of (poor outcome) given exposure over the risk of (poor outcome) given non-exposure.

Sequential trial A trial design in which the results are continuously monitored and the trial terminated according to a predefined 'stopping rule'.

Social contract theory A moral theory which emphasises the need for social cohesion and preservation. Individuals 'agree' to relinquish some of their natural liberty in a civil society for the sake of collective advantage.

Society An organised collection of people with shared values.

Trust Confidence in the reliability of another. The primary quality of the doctor-patient relationship.

Uncertainty In common parlance, uncertainty is simply the opposite of certainty. Compare with **Equipose**.

Utilitarianism A theory of morality which assigns moral significance only to the consequences of action. An action is right if it produces good consequences (typically this is happiness for the greatest number). Some utilitarians include rules-of-thumb to get round problems the problem of being able to say with certainty what the right course of action is in advance.

Virtue ethics The moral theory that emphasises a person's character, rather than actions or guiding principles. A virtue is often seen as the 'golden mean' between the vices of excess and deficiency.

Zelen's design A randomised controlled trial design in which a novel treatment is compared with standard treatment. Randomisation occurs, and then consent is elicited from participants. Typically, consent is only sought from the study, not control, group in order to bolster recruitment or avoid distress at not receiving a preferred therapy.

The glossary was compiled with reference to the Penguin Dictionary of Philosophy (Mautner, 1997) and Penguin Dictionary of Psychology (Reber, 1985), and Epidemiology in Medicine by Hennekens and Buring (1987).

continued

List of abbreviations

ACAS	Asymptomatic Carotid Atherosclerosis Study*	HRT	hormone replacement therapy
ALL	acute lymphoblastic leukaemia	IDU	injection drug user*
AMIS	Aspirin Myocardial Infarction Study*	IRB	Institutional Review Board
ARC	AIDS-related complex*	ISIS-2	Second International Study of Infarct Survival
BDI	Beck Depression Inventory*	LATE	Late Assessment of Thrombolytic Efficacy*
BHAT	Beta-blocker Heart Attack Trial*	MRC	Medical Research Council
BIDS	Bath Information Data Services	NHMRC	National Health and Medical Research Council, Canberra*
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk for Ischemic Events*	OR	odds ratio
CCSG	Children's Cancer Study Group*	PEFR	peak expiratory flow rate*
CCT	controlled clinical trial*	RCT	randomised controlled trial
CI	credible interval	RR	risk ratio
COMS	Canadian collaborative Ocular Melanoma Study*	SCI	Science Citation Indices
CSS	Cancer Surveillance System*	SOLVD	Studies of Left Ventricular Dysfunction*
DFS	disease-free survival*	SSCI	Social Science Citation Indices
DMC	data monitoring committee	STAI	State-Trait Anxiety Inventory
ECMO	extra-corporeal membrane oxygenation	TPN	total parenteral nutrition*
FDA	(US) Food and Drugs Administration	UKALL	UK Acute Lymphoblastic Leukaemia*
GUSTO	Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries*		
HMRI	Hospital Medical Records Institute*		
HR	hazard ratio		

* Used only in tables



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.

Chapter I

Introduction

During this century, the medical profession has acquired a growing capacity to distinguish between what they know and what they do not, thereby changing the professional emphasis from demanding public trust without sound epistemological basis to an ‘evidence-based’ approach. This is typically contrasted with practice based on intuition, though the two approaches may lead to the same ‘answer’ of course; it is just that scientific knowledge provides explicit justification for belief. Clinicians can therefore talk more frankly about their uncertainty and the randomised controlled trial (RCT) has played an enormous role in producing valid data upon which practice can rely. The clinical trial is an experiment which most closely resembles that in the natural sciences, since it is based on the idea of an intervention, rather than simple observation. Carefully designed, conducted and analysed trials typically provide the strongest epistemological clues to the existence and nature of a cause–effect relationship. Observational studies may produce false clues due to various forms of bias (mostly confounders), and/or chance. The RCT has the unique advantage of using randomisation as a method of determining patient allocation to treatment, which eliminates selection bias if correctly executed. Any imbalance between trial arms with respect to other variables (that might confound the analysis) can only then arise by chance. Bias in the observation of outcomes or execution of therapy can be minimised by the use of blind or double-blind procedures. Having eliminated bias, only chance (random error) remains a source of false clues to the ‘true’ effect of a given intervention; this risk can be reduced by increasing sample size. Drawing general conclusions from trial populations to ones with different characteristics inevitably involves extrapolating beyond the data. To provide reassurance that the data are externally valid, the trial investigator should describe the patients entered, so that practitioners can make a judgement about the applicability of results to particular patients (or groups of people).

The main reason for using the RCT design is therefore a scientific one: properly conducted RCTs produce valid data from which society can benefit. Research enables advances in medical practice, and hence the alleviation of suffering. However, not all scientifically sound

(well-designed) research is justified, and this report is concerned with the need to advance medical knowledge while protecting patients in research from harm at the same time (and protecting a patient’s rights). Many ideas have been articulated and rehearsed, but there is still considerable diversity of opinion over what constitutes justification for trials. If the necessary and sufficient moral conditions for conducting RCTs are clearly set out, then patient and public confidence would be reinforced, and clinicians would be encouraged to offer participation in trials as an option in health care. To address this debate, we have conducted a review of the topic, and, in so doing, we have identified a key underpinning issue: whether uncertainty over relative treatment effectiveness is sufficient justification for randomisation. A theoretical framework based around this issue was superimposed on the literature in order to make sense of the various arguments and assertions contained within. The arguments that we lift from the literature, and our discussion of these, relate to utilitarian and Kantian traditions in moral philosophy predominately. There are variations of both utilitarian and Kantian theories. For present purposes, let us understand the utilitarians to hold that one’s ultimate duty is to maximise utility by producing happiness of the greatest number of people – all other duties being derived from this. Let us understand Kantians to hold that one should always treat people with respect – **never** treating them merely as the means to other people’s ends. The putative tension between the individual and society is brought to the fore because both utilitarians and Kantians see the need to balance duties to, and rights of, the individual and society.

There are other traditions in philosophy besides utilitarian and Kantian. Recently, there has been a revival of interest in the virtues. But the focus on virtues concerns most directly character rather than principles or rules. Although character is broadly supportive of apt choices, rules and principles are still needed to determine aptness, as one cannot simply read the relevant rules from the virtues. Social contract theories provide another alternative to utilitarian and Kantian accounts of duty. Contractarians explain general obligations in terms of our shared needs – our need to live in peace and the rules we need to

live by if we are to live in peace. However, both utilitarians and Kantians may incorporate social contract theory into their own. In any case, whichever theory one draws on, the basic issue that concerns us here is how to handle competing claims of the participants involved in trials on the one hand and of society at large on the other: what trade-offs are ethically defensible and why?

Clinical research and RCTs in particular have often been accused of resting exclusively on utilitarian grounds and of using people as ‘guinea-pigs’ by sacrificing the individual patient for the good of future patients: this represents a ‘lose/win’ situation for participants and future patients, respectively. However, since the formulation of the Hippocratic Oath, the medical profession has embraced the notion of physician–patient trust as the primary moral requirement for medical practice and has sought to do its ‘best’ for each individual patient. The importance of trust in the doctor–patient relationship can be derived from either Kantian or utilitarian philosophies, and is widely discussed in the context of rationing of scarce resources or situations where a doctor may have a conflict of interests (e.g. clinical research). Under the Hippocratic Oath, every patient is entitled to receive the ‘best’ quality treatment available, and should not stand to lose so that others might gain, that is, patients may not be used merely as the means to an end, however admirable that end might seem. In some circumstances, a doctor may have to put society or other patients before the current patient – for example, a doctor may be called away from a patient to attend an emergency (to focus on the case which is most in need of immediate medical attention) or may deliberately avoid using an antibiotic which the profession wishes to reserve for the sickest cases, so as not to build up resistant strains. However, these are cases where a scarce resource is involved so treatments given to different patients are not independent. It is a matter of more serious debate whether a doctor can morally withhold access to an otherwise freely available treatment in order to encourage compliance in a trial thereby improving future care. If this is held to be unacceptable, it may still be morally possible to conduct a clinical trial if the physician does not ‘know’ which treatment is ‘best’ – this (possibly) represents a no-lose/win situation for participants and future patients, respectively. However, many authors point out that there are problems here are with the words ‘know’ and ‘best’.

Dealing first with ‘knowing’. Consider first two treatments (A and B) with **equivalent** (or no) side-effects. ‘Knowing’ can have two meanings:

(1) there is no preference between treatments since they have identical side-effects and A is as likely to be better than B and vice versa, or (2) there is some preference in the sense that one of the treatments is more likely to be superior, but this is uncertain; treatment A has not been ‘proven’ to be more effective than B. Indeed, Gifford (1986) observes that most arguments which use uncertainty as justification for RCTs equivocate on the term ‘know’, sometimes meaning one thing and sometimes something else. This is not simply for want of definition as uncertainty has a precise, yet ambiguous, meaning in common parlance, that is, the opposite of certainty. If there is ‘absolute’ uncertainty, the decision-makers are ‘agnostic’ or in ‘equipose’, that is, the mean benefits in prospect from both treatments are equal, then the prospects for the patient are the same, whether or not a trial is conducted (here there is a separate argument about whether doctors can be absolutely uncertain). For those familiar with Bayesian thinking, this situation would arise where the median of a symmetrical prior distribution was a null result given no side-effects.

We also need to clarify the meaning of ‘best’. Two situations apply: firstly, suppose treatments A and B (two treatments are discussed here for convenience) have equal side-effects in prospect, and the major outcomes are binary (e.g. live or die). In this situation, A is preferred to B, provided it is more effective (a situation we refer to as ‘probabilistic dominance’ because values do not enter into the equation). Equipose exists if the expected effectiveness of A and B are equal.

However, we must acknowledge that treatments might have unequal side-effects *a priori*. A, for example, might be mutilating surgery, while B is a smaller operation. In order for the treatments to be equally desirable for the patient (i.e. for equipose to exist), A must be better than B in prospect to the extent that the difference in effectiveness will be traded-off against its greater side-effects. In decision analytic language, the expected utilities of A and B should be the same. This could be called the point of effective equipose to indicate that equipose occurs when something other than a null result (on the main outcome measure) is perceived as the most likely result in prospect. If the expected difference in outcome equals, but does not exceed, the trade-off that an individual patient would require, then the patient is in individual effective equipose. Potential participants are not disadvantaged if equipose applies (unless a trial has intrinsic negative side-effects as a result of psychological

distress associated with the offer of randomisation). Since values are personal, equipoise is primarily a property of the patient. It is therefore not surprising that many authors argue for non-paternalistic consultations that allow patients to bring their values into play. This can only take place through detailed discussion with the patients themselves. In this way, doctors can respect a patient's autonomy in the spirit of Kantian ethics, do their best for a patient, and still recruit those patients who are equipoised into the study. All this assumes that the patient is competent and there is an individual decision to be had. We discuss later special situations where this is not the case, such as trials involving young children.

Much has been written of collective equipoise which is said to occur when the scientific community as a whole is split over treatment preference. This is an interesting point to which we return in the discussion section.

We also consider the situation that might arise when a new and unusual treatment that is not widely available is compared with an existing treatment. We discuss the argument that equipoise between such treatments is not required, since a patient's best interests are not sacrificed by trial entry, provided the new treatment is perceived *a priori* as being at least as good as the standard. However, there is an interesting issue of whether it is necessary to inform control patients that they are involved in an experiment – we present arguments on both sides of this debate.

We approach the ethics of conducting RCTs from the perspectives of ethics committees, of the clinicians who must decide whether or not to offer trial entry to their patients (where individual prior and patient equipoise must be considered), and of data monitoring committees (DMCs) who must decide whether to stop a trial earlier than planned. Since further work needs to be done on combining statistical and ethical concepts in the context of interim analysis, we introduce the last of these perspectives, those of DMCs, with a view to pursuing it in more detail later.

Although we have homed in on the ethics of conducting RCTs, it must be made clear that this is not a self-contained topic within ethics, and we must not lose sight of the broader context. Methodological issues have a bearing on ethics, and not only are there different designs from which researchers might choose but there are also different phases of evaluation which culminate in the Phase 3 RCT. Commonly, Phases 1 and 2 of the evaluation of a new technology are designed to determine toxicity and dosage, and are not randomised. However, some have argued for randomising from the 'first' patient, perhaps most fervently Thomas Chalmers, so that the process of randomisation gets off the ground while equipoise is still common, subsuming Phases 1 and 2 as a result. Additionally, there are alternative study designs in analytic medicine or, more specifically, health technology assessment (designs that seek to establish a cause-effect relationship between exposure to a technology and outcome), but detailed discussion of these falls outside our current remit, except for deciding when such alternatives are morally desirable. Furthermore, even though formal medical experimentation sits alongside a tradition of routine practice, the two processes are interrelated and sometimes even converge, as in the case of $n = 1$ trials. Even more broadly, ethical issues in routine practice are relevant to those in RCTs and medical experimentation generally, for example the doctor-patient relationship in routine practice impacts on the ethics of conducting trials.

The bibliography resulting from our literature search provides a resource for researchers and philosophers working in the field of RCTs, and the review itself provides a concise overview of issues and arguments. We review the philosophical material in the style of the late medieval academic philosophers who used what was called the *quaestio* format for discussing and debating issues. This format requires an author to review or document a sometimes long series of arguments on both sides of a question before providing his/her own opinion in reply. We have provided a glossary of terms at the start of this review.

Chapter 2

Research questions

Degrees of uncertainty and the ethics of conducting RCTs

The subject of the review was the ethics of conducting RCTs and, as the review unfolded, the primary focus became the issue of uncertainty; we sought to understand how the concept of uncertainty, and degrees of uncertainty in particular, affect the ethics of conducting RCTs. In so doing, we reviewed arguments for and against RCTs in general, and in particular disciplines or cases, adding authorial comment where appropriate.

What are the physical effects of participating in trials?

We sought primary data on how participating in trials might affect a patient's physical outcome. In particular, we sought to identify whether patients could benefit from participating in trials, even in the absence of notable treatment effects.

What are the psychological effects of participating in trials?

Again, we sought primary data on how trials *per se* might affect outcome, but this time we were interested in psychological effects. If patients are distressed by the experience of being offered trial entry and subsequent participation, then we need to understand what it is about RCTs which is frightening, and consider options to remedy this. On the other hand, if patients are happy to participate and thrive on the level of care offered by involvement in trials, then we can be more comfortable within current practice.

What is the 'best' method for obtaining informed consent?

It would be nice to think that comprehension, emotional well-being, and recruitment rates are positively correlated in relation to informed consent. However, a liberal patient-centred perspective would put the need to maximise patients' understanding ahead of maximising recruitment, should better informed patients exhibit a higher refusal rate. In order to answer the empirical question, we sought primary data from comparative studies of different procedures for offering entry into trials on understanding, anxiety, attitudes and recruitment rates.

What is the quality of informed consent in practice?

In order to answer this question, we sought primary data on how much patients, who were offered entry into real trials, understood of the various aspects of the trial process. In effect, this could be seen as an audit of communication with patients. Differences in levels of understanding, according to trial and type of information overlap with the previous question.

How do patients, the public and healthcare professionals view RCTs?

It is important to identify how the RCT is perceived by patients who participate in them, the public in general, and healthcare professionals who might enrol their patients into such studies. If clinicians are reluctant to recruit patients, then a trial cannot get off the ground, however good its design. If clinicians are keen to become involved in research, then we need to know whether the patients themselves view trials as important and for what reasons. In particular, we sought data on what motivates patients to participate in clinical trials.

Chapter 3

Review methods

Literature search strategy and retrieval

We carried out a search of the literature relating to the ethics of conducting clinical trials, including empirical studies which might inform such discussion. We used five different methods to ascertain the relevant articles: an electronic literature survey (conducted on the three databases, MEDLINE, PsycLIT and Bath Information Data Services (BIDS) Science and Social Science Citation Indices), hand searches, personal contacts, an original collection of the second author, and 'explosion' of articles obtained by the above methods. The electronic surveys were performed with in-house algorithms, and were limited to the English language (see appendix 1). In this way, a total yield of 812 references was achieved.

The electronic survey provided a yield of 183 such articles (see appendix 1). The MEDLINE search was repeated seven months into the project as the database is reindexed on an annual basis. We identified another 20 relevant articles in this way. It became the habit of the investigator to make searches of journals (volumes ascertained as above) when working in the library, and a further 32 articles of interest were found. Also, 88 additional articles (seven were published in a foreign language) were ascertained through a search of the database at Edinburgh (HTA project No. 93/43/02), and 59 through other contacts in the field. This was a useful source of unpublished material ($n = 8$). One hundred and twenty-nine articles had been accumulated by the second author over the years, and a further 328 articles were ascertained by 'exploding' the articles, that is, by examining the references used by the authors of articles ascertained by one or more of the above methods.

Our next task was to create a database of articles which contained references, classified according to type of information, that is, ethics versus empirical data. There were 176 articles which contained data, and 636 which dealt with the ethics of conducting clinical trials directly. Four articles contained both, and were recorded under both headings on the database (Alderson, 1996; Blum *et al.*, 1987; Johnson *et al.*, 1991; Lilford, 1994). Many of the empirical articles, which were concerned with the quality of informed consent in practice and/or how

best to approach patients, simply made reference to ethics and so were not recorded twice.

The empirical articles were then classified according to the research question posed and study design, while the ethics literature was managed with the help of a well-structured framework (see below). Some topics were abandoned due to overlap with other projects commissioned by the HTA methodology programme, for example the ethical issue of informed consent was discussed in detail by the Liverpool project (93/41/04), and empirical data on recruitment rates to trials were sought by the Edinburgh project (93/43/02).

Some studies covered more than one empirical topic, for example Aaronson *et al.* (1996) not only evaluated consent formats used in trials but examined participants' understanding of their trial (audit of communication). Likewise, some ethics articles dealt with more than one issue, for example Collins *et al.* (1992) addressed both uncertainty as justification for an RCT and under-powered studies. Such articles were recorded under all the relevant topic headings on the database of articles.

A collaborative group was set up to discuss the methods and progress of the review at regular intervals throughout the project (a list of group members is given in appendix 2). The quality of the articles was assessed independently by two authors as indicated below. Any disparity in our findings was resolved by group discussion.

Ethics literature

A total of 636 articles contained ethical issues relating to RCTs directly. Our next task was to narrow down, further subdivide, and record articles on our database, according to our intellectual framework. Four hundred and forty-nine articles addressed degrees of uncertainty and the ethics of conducting RCTs. The arguments in these articles related to how degrees of uncertainty affect the obligations of healthcare professionals to society as a whole and to the individual patients under the ambit of their care. The former discussion brings in considerations such as statistical power, replication of results and the need for research to inform practice. The latter

includes detailed analysis of the obligations of doctors to patients, degrees of knowing (including Bayesian conceptions of probability), notions of values (and hence decision analysis), and related issues, such as use of placebos. It was necessary to commission translation of one of the studies (Gracia, 1993) from the original Spanish. We were able to get a translation of a German article from the authors (Ernst and Resch, 1995).

We identify issues of current ethical concern and offer a summary of arguments. Although we report all references, it is not necessarily possible to derive a consensus view, nor should readers imbue the number of references behind a particular argument as a mark of its validity. Most of the arguments do not take the form of syllogisms; some simply make bold assertions while others are based on analogy, such that it would be difficult to perform a check for internal consistency (which is a key feature of argumentative quality). Besides, internal consistency of itself does not guarantee that the conclusion is true, since it may be built on false premises. As a result, a critique of the arguments is limited as far as possible so as to give a concise description of what is out there, thanks to our intellectual framework, the derivation of which is discussed in the Introduction. More in-depth philosophical analyses of papers are being prepared for specific topics in light of our own appreciation of the subject (see the discussion of review results, page 11). Indeed, the first of these deals with the ethics of conducting 'under-powered' studies and is included since it is complete and is

published in *The Lancet* (Edwards *et al.*, 1997). Work on the ethics of conducting cluster trials and issues surrounding early stopping is in progress.

Articles published between 1994 and 1996 were reviewed independently by SE and JJ so that the degree of agreement over the articles' content and quality could be documented. Articles preceding this date were reviewed by the first author only.

What are the physical effects of participating in trials?

There were 17 articles which examined the effects of participating in clinical trials on the patient's physical condition. One of the articles was a review in its own right which looked at the more general issue of the use of treatment protocols (both within and outside clinical trials) and treatment centres on the outcome of care (Stiller, 1994). Another article was primarily methodological and did not report sufficient data for analysis of a possible trial effect (Olschewski *et al.*, 1992). Thus, we are left with 15 articles containing analysable primary data concerning the effects of being in a trial on mortality and/or physical morbidity (*Tables 1 and 2*)*. Eight of the 15 studies are included in Stiller's review.

Included studies compared randomised patients in trials with at least one non-trial control group (*Figure 1*). The control groups were either patients who were offered entry in a trial but declined or

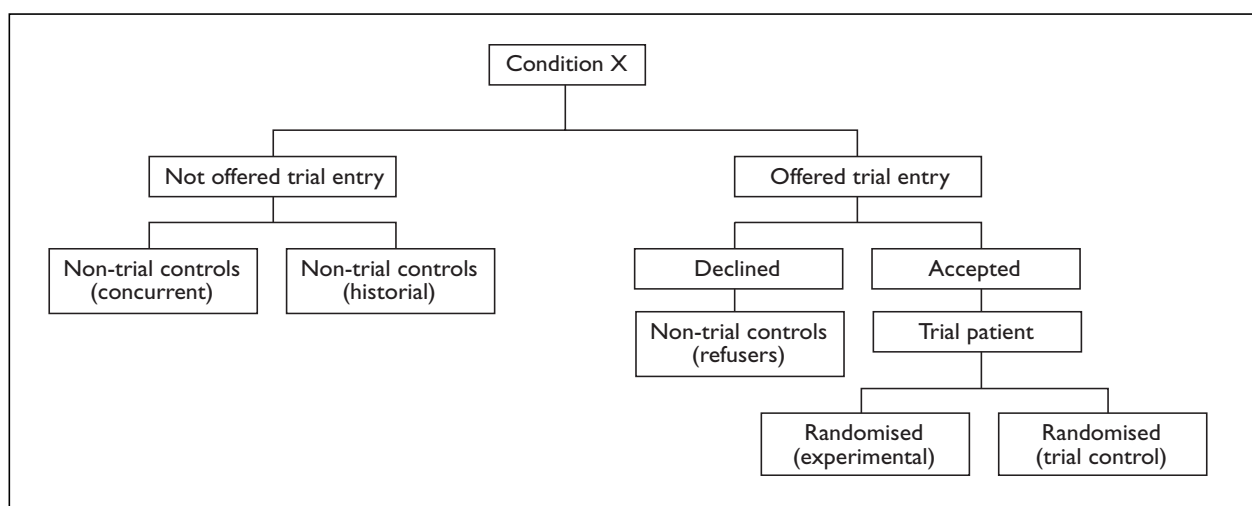


FIGURE 1 Generation of controls. The figure illustrates how the control groups for studying a possible trial effect were generated by different authors. The non-trial controls were either patients who were offered entry in a trial but declined or patients who had the same medical condition as the trial patients, but who had not been offered trial entry. The latter patients were either treated concurrently with the trial patients or they constituted historical controls. Of those who accepted trial entry, patients were assigned to the trial control or experimental arm on a random basis and, in some cases, the trial and non-trial controls were compared

* For clarity, the tables are collected together at the end of this report (see page 77)

patients who had the same medical condition as the trial patients, but who had not been offered trial entry. The latter were either treated concurrently with the trial patients or they were historical controls. In each case, we noted whether the author had compared the trial and non-trial control groups for disparity in the incidence of prognostic variables and, if so, noted whether a statistical adjustment was made to allow for any difference found. We also noted the results of any comparison of outcome across groups within the RCT. In the case of an experimental and control treatment, this allowed us to compare outcomes across trial and non-trial controls; if trials *per se* have a therapeutic effect, then an improvement in outcome among trial patients (compared to non-trial controls) should not be confined to those in the 'experimental' arm (Figure 2).

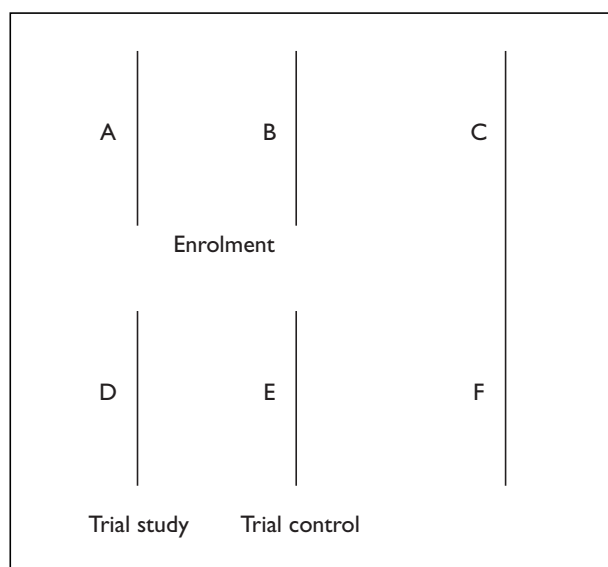


FIGURE 2 Example study design to determine the physical and psychological effects of trial participation. Tests should be taken at time points A–F. The baseline result can be represented by A + B versus C, and a positive effect of participation could be represented by D + E versus F or E versus F

Quality assessment of all the studies was carried out by SE and independently by JT using an agreed quality of data checklist (Table 3). Data sets from these studies were then categorised (Table 4a) and listed (Table 4b) by DB with a view to plotting the hazard ratios (HRs) for individual trials and strata within studies.

What are the psychological effects of participating in trials?

We review studies which examine the psychological effect of participating in clinical trials. Only three

studies were found which provided comparative data on the effect of trial participation (Table 5).

Studies were included if they sought an effect of a trial on patients' psychological state using concurrent controls and repeated measures (see Figure 2).

Quality assessment was carried out by SE according to an agreed checklist (Table 6).

What is the 'best' method for obtaining informed consent?

We reviewed comparative studies of different methods for obtaining informed consent (Tables 7a and 7b). There were 14 such studies, and all except three (Dal-re, 1991; Levene *et al.*, 1996; McLean, 1980) were RCTs; that is, they were RCTs of the effects of different methods of offering entry to trials. It was necessary to commission translation of one of the studies (Dal-re, 1991) from the original Spanish.

The outcome measures varied from study to study, but included any one or number of the following: recruitment rates, attitudes to trials, anxiety and understanding. Our search also uncovered three reviews of empirical literature (not included in the above figures) which included RCTs of different consent methods to clinical research in general (but including clinical trials), namely King (1986), Meisel and Roth (1983), and Silva and Sorrell (1988). However, the search strategies of these articles were not given, and the yield was much lower than that which we obtained (the most recent review by Silva and Sorrell (1988) reviewed only one relevant study, and King (1986) reviewed only two); we reviewed the cited studies ourselves.

Quality assessment was carried out by SE, and a random sample (one in two) was reassessed independently by JT. Studies were assessed according to a quality of data checklist (Table 8). Any disparity in our findings was resolved by group discussion.

What is the quality of informed consent in practice?

Twenty-four studies examined participants' knowledge and understanding of their trial (audit of communication), of which one used qualitative study methods (Snowdon *et al.*, 1997). Our search also uncovered three reviews of empirical literature (not included in the above figures) which included

knowledge and understanding of clinical trials, namely King (1986), Meisel and Roth (1983), and Silva and Sorrell (1988). However, the search strategies of these articles were not given and the yield was much lower than that which we obtained (the most recent review by Silva and Sorrell (1988) reviewed only one relevant study, and King (1986) reviewed only one). We reviewed the cited studies ourselves. It was necessary to commission translation of two studies from the original Dutch (Oddens *et al.*, 1992) and French (Gallet *et al.*, 1994).

Studies were included in the review if their design consisted of questionnaires/interviews to assess patient comprehension of real trials, or transcriptions of consent discussions.

Quality assessment was carried out by SE, and a random sample of papers (one in four) was assessed independently by JH. Studies were assessed according to a quality of data checklist (*Table 9*). Any disparity in our findings was resolved by discussion with RJL.

How do patients, the public and healthcare professionals view RCTs?

There were 58 studies of views of patients, the public and healthcare professionals on clinical trials. Eight of these were qualitative studies, which are not included in the results tables although we do summarise their main findings (Elbourne, 1987; Garcia, 1987; Madden, 1994; Marsden, *et al.*, unpublished; Roberson, 1994; Snowdon *et al.*, 1997; Twomey, 1994; Wynne, 1989). There were 51 quantitative studies (which provided data on the frequency with which particular views were expressed) which were grouped into studies of patients and the public (in both real and hypothetical clinical trial scenarios, $n = 34$), and those of investigators and physicians ($n = 21$). One study performed both qualitative (focus groups) and quantitative (structured questionnaires) methods to ascertain their data (Marsden *et al.*, unpublished), while another used both real and hypothetical scenarios (Bevan *et al.*, 1993). Our search also identified three reviews which included

views on clinical trials (King, 1986; Meisel and Roth, 1983; Schain, 1994), but only one was a systematic review which gave only limited information about the quality of evidence of the composite studies (Meisel and Roth, 1983). In all three cases, the yield was much lower than we obtained, even in the systematic review (only three studies reviewed by Meisel and Roth (1983) were relevant), and the most recent review (only six studies reviewed by Schain (1994) were relevant). It was necessary to commission the translation of one study (Dal-re, 1993) from the original Spanish.

In summary, studies were included if they used questionnaires and/or interviews to elicit the views of the public, potential participants, participants and physicians on 'clinical trials'. Sometimes the terms 'clinical trial' or 'randomised controlled trial' were explicitly included in supplied questionnaires and sometimes not, in which case we had to rely on what the investigators themselves reported. For example, misunderstanding of 'clinical trials' during a pilot study led to the investigators interchanging this with the more general term 'research' in the main study (Gerard *et al.*, 1995). Since 'research' and 'clinical trial' are not synonymous, this may lead to difficulties comparing the results with other studies which did use the words 'clinical trial'. However, it is difficult to know how serious this is, methodologically speaking, as, in many cases, what respondents understood by 'clinical trial' was not documented anyway (*Table 10*).

Abstraction of results and quality assessment for all studies were carried out independently by SE and JH. Quality assessment was difficult, in many cases, because insufficient information was given by the authors. The dimensions of methodological rigor used are listed in *Table 11*; we had originally planned a more comprehensive review of methodological issues, but found that some items had to be dropped as they were seldom mentioned by authors, while others failed to gain acceptance from the collaborative group set up to discuss the methods and progress of the review at two intervals during the project, (a list of group members is given in appendix 2). Any disparity in the findings of SE and JH was recorded and resolved by group discussion.

Chapter 4

Review results

Degrees of uncertainty and the ethics of RCTs

Obligations to society of physicians and ethics committees

Societal benefits

The epistemological argument for RCTs. Forty-one articles sought to defend the RCT by using an epistemological argument: a well-designed and conducted RCT is the most reliable method of obtaining epidemiological data and, because valid evidence is needed to inform widespread practice, the RCT can be justified on utilitarian grounds (Baum, 1983; Byar, 1979; Byar, *et al.*, 1976; Cavan, 1981; Chalmers and Chalmers, 1994; Chalmers *et al.*, 1972; Cowan, 1981; Editorial, 1992; Eichler, 1995; Engelhardt, 1988; Ernst and Resch, 1996; Gilbert *et al.*, 1977; Gillon, 1994; Fox, 1960; Haines, 1979; Harrison, 1986; Hill, 1958, 1963; Kardinal, 1994; Lasagna, 1970; Marquis, 1983; Mike, 1988, 1989a, 1993; Miller, 1985, 1993; MRC, 1991; Passamani, 1991; Raju, 1992; Roy, 1986a; Russell, 1989; Schafer, 1982; Shaw and Chalmers, 1970; Silverman, 1985; Smith *et al.*, 1993; Stephenson, 1996; Sutton-Tyrrell *et al.*, 1991; Tukey, 1977; Uberla, 1981; Visscher, 1970; Zelen, 1979). One of the references placed the professional duty not to harm above that to benefit, and so distinguished between the need for scientific evidence to benefit society (collective beneficence) and to prevent possible harm from unproven therapies (collective non-maleficence), claiming that an epistemological argument for RCTs supports the latter, not the former goal (Mike, 1989a). Three of the 41 references stated simply that utilitarian justification is not sufficient; that is, societal benefit is necessary but insufficient to justify the RCT (Fox, 1960; Roy, 1986b; Marquis, 1983). However, they did not take the argument further.

Two additional articles attempted to show that the RCT was not the most scientifically reliable method after all, and argued that the randomisation process does not eliminate systematic error as is commonly assumed (Taves, 1974; Urbach, 1993).

Taves (1974) proposed a refinement, called 'minimisation', to the randomisation process, which matches study and control groups for

known confounding variables, thereby reducing bias more effectively. The smaller the study, the more likely a confounding variable is to distribute itself unequally, and the greater the argument for 'minimisation' (see 'under-powered' studies, on page 12). However, 'minimisation' does not tackle the problem of unknown confounders linked to different clinicians or patient variables which are not or cannot be enumerated but which nevertheless impact on the clinician's psyche and skew allocation. Burkhardt and Kienle (1983) further pointed out that the RCT is inevitably flawed in that the sample is inevitably unrepresentative of the population. However, this could be said of any alternative research method and, while randomisation is not a perfect solution, it is perhaps the least bad scientific option for evaluations (Uberla, 1981).

When second best is best. Ninety-nine articles recognised that a well-designed and conducted RCT is good science, but observed that good science is not necessarily good ethics and/or pointed out problems with RCTs in particular disciplines or situations (Abraham, 1941; Altman, 1980, 1983; Ambroz, 1978; Anderson, 1980; Angell, 1984; Anonymous, 1979; Baum, 1995; Beauchamp and Childress, 1989; Berkowitz, 1995; Bleich, 1995; Block and Elahoff, 1979; Bonchek, 1979; Burkhardt and Kienle, 1978, 1983; Buyse, 1991; Byer, 1983; Canner, 1970; Caplan, 1984; Cassel, 1985; Challah and Mays, 1986; Cornfield, 1966; Cutler *et al.*, 1966; Day, 1969; De Deyn, 1995; Donner, 1977; Dudley, 1983, 1986; Elander and Hermon, 1995; Ernst and Resch, 1996; Feinstein, 1973; Feenberg, 1992; Fleming, 1982; Fried, 1974; Freireich and Gehan, 1979; Freund, 1970; Ganz, 1989, 1990; Gehan and Freireich, 1974; Giertz, 1980; Gifford, 1986, 1995; Gilbert, 1995; Glasziou, 1995; Gross, 1993; Grunkemeier and Starr, 1992; Hellman, 1979; Hellman and Hellman, 1991; Henry and Hill, 1995; Hilden *et al.*, 1987; Hilden and Habbema, 1990; Kadane, 1986; Kassirer, 1983; Kardinal, 1994; Katz, 1993; Kaufman, 1993; Kleijnen *et al.*, in press; RJ Levine, 1991; Levine and Lebacqz, 1979; Lockwood and Anscombe, 1983; Love, 1975; Lurie, 1994; Mackillop, 1986; McPherson, 1994; Marquis, 1983; Minogue *et al.*, 1995; Morris and Brown, 1995; Neubauer *et al.*, 1991; Nicholson, 1986; Palmer, 1995; Passamani, 1991; Pollock, 1989; Pringle and

Churchill, 1995; Raju, 1992; Rudicel and Esdaile, 1985; Ruse, 1988; Rutstein, 1970; Schafer, 1982, 1985; Schwartz *et al.*, 1980; Shuster *et al.*, 1985; Simon, 1977, 1994; Spiegelhalter *et al.*, 1994; Spodick, 1973, 1982; Steinberg, 1991; Stirrat *et al.*, 1992; Takaro *et al.*, 1976; Tauer, 1994; Toynbee, 1996; Trochim and Cappelleri, 1992; Van der Linden, 1980; Vere, 1981; Visscher, 1970; Wallenstein *et al.*, 1980; Weinstein, 1974; Zelen, 1969).

Thirty-one of the 99 articles argued that, in specific cases, second best could be best, that is, where alternative non-randomised designs such as retrospective studies are morally or practicably preferable:

- (1) When equipoise does not apply (Fleming, 1982; Kadane, 1986; Levine *et al.*, 1991; Ruse, 1988; Shuster *et al.*, 1985). We might infer that those arguing that RCTs should be undertaken only when equipoise applies would also find alternative designs preferable when equipoise does not apply, at least when the treatments are widely available. (See also page 22 for a definition of equipoise and a discussion of situations where equipoise does not apply.)
- (2) When the primary purpose of study is the **estimation** of toxicity and effectiveness, as in Phase 1 and 2 trials (Gehan and Freireich, 1974).
- (3) When large differences between treatments are expected (Ernst and Resch, 1996; Gehan and Freireich, 1974; McPherson, 1994; Palmer, 1995; Passamani, 1991; Raju, 1992).
- (4) When proposed treatment can be compared to standard treatment from a recent previous trial (Gehan and Freireich, 1974); this could be seen as part of the first stipulation above, since the earlier trial might dispel equipoise. (See also page 13, on the scientific need for replication.)
- (5) When a disease, if left untreated, is lethal and for which there is no known effective treatment (Byar, 1990; Cutler *et al.*, 1966; Ernst and Resch, 1996; Minogue *et al.*, 1995; Palmer, 1995; Rutstein, 1970).
- (6) When a current treatment can produce a virtually assured cure, that is, when the goal is to reduce toxicity at the possible expense of effectiveness (Shuster *et al.*, 1985).
- (7) When there are repetitive emergencies associated with a condition (Spodick, 1982).
- (8) When the patient could act as his/her own control, for example typical diseases in paired organs (Spodick, 1982).
- (9) Research in general practice, given the importance of the physician–patient relationship (Pringle and Churchill, 1995).
- (10) Research using placebos, where crossover designs may be preferable, so that all patients have access to active therapy (Elander and Hermon, 1995).
- (11) Research involving surgery due to various technical difficulties (Anderson, 1980; Berkowitz, 1995; Byer, 1983; Bonchek, 1979; Grunkemeier and Starr, 1992; Love, 1975; Van der Linden, 1980; Wallenstein *et al.*, 1980); this could also be seen as part of the first stipulation above as surgical skill must be taken into account.
- (12) When the disease is rare, and recruitment slow, case–control studies may be preferable (Baum, 1994; Byar, 1979; Gehan and Freireich, 1974; Spodick, 1982). (See also ‘under-powered’ studies, below.)

Three articles pointed out that, historically, some medical breakthroughs did not require an RCT to produce valid evidence, such as the effectiveness of penicillin (Abraham, 1941; Kaufman, 1993; Nicholson, 1986), but this leaves open the question of what to do about potential moderate, but worthwhile, effects (see stipulation (3) above).

Five further articles suggested that there is a continuous scale of reliability and that too much emphasis is put on the RCT (Botros, 1990; Dudley, 1983, 1986; Reemtsma, 1986), while another author suggested pooling both historical and prospective data wherever possible (Pocock, 1975).

Cappelleri and Trochim (1995) and Trochim and Cappelleri (1992) proposed a compromise position and suggested that, when it is unethical or impractical to randomise all patients, a cut-off-based design is ethically acceptable, according to which the new treatment is given to the most sick, control treatment(s) is given to the least sick, and patients who are moderately sick are randomised. However, it could be argued that the most sick are the most vulnerable and, since their competence may be brought into question due to possible desperation, they should be ‘protected’ from investigative procedures, though this might then depend on how novel the treatments are. (See also page 15, on the risk associated with new therapies.)

‘Under-powered’ studies. Six references stated categorically that conducting ‘under-powered’ studies is **necessarily** unethical on the grounds that, since they are unlikely to produce clear-cut answers, society might be misled with potentially devastating

consequences (Altman, 1980, 1983; Anonymous, 1979; Freund, 1970; Gracia, 1993; Mike, 1989b; Newell, 1978; Shuster *et al.*, 1985). This argument is supported by a further 15 articles, stipulating that it is statistically necessary for random errors in measured effects of treatments to be small in comparison with the size of therapeutic effect sought (Ambroz *et al.*, 1978; Brown, 1980, 1987; Chalmers and Sinclair, 1985; Clayton, 1982; Collins *et al.*, 1992; Fetter, 1989; Freiman *et al.*, 1978; Hall, 1982; Kaufman, 1993; McPherson, 1982; Sutherland, 1994; Van der Linden, 1980; Yusuf *et al.*, 1984; Zelen, 1983). Indeed, Feinstein (1973) saw limited value in randomisation in small trials since the results would be potentially misleading anyway – avoiding error through selection bias is of little value if error results through imprecision.

The use of meta-analysis to increase the statistical power of small trials was proposed, in an ethical context, by ten authors (Anello and Fleiss, 1995; Barnard, 1990; Chalmers and Lau, 1993, 1996; Collins *et al.*, 1987; Dagan, 1992; Horwitz, 1995; L'abbe *et al.*, 1987; Light, 1987; Report to the Health Services and Public Review Board, 1993). This argument (see the discussion section, on page XX) is predicated on the reliability of meta-analysis as a method (Antman *et al.*, 1992; Cappelleri *et al.*, 1996; Detsky *et al.*, 1992; Fortin *et al.*, 1995; Gilbaldi, 1993; Hasselbald *et al.*, 1995; Lau and Chalmers, 1995; Lau *et al.*, 1995; Peto, 1987; Stewart and Parmer, 1993).

Eight references recommended that, given the choice between a small trial and no trial, the small trial is preferable and/or that Bayesian designs are most appropriate in such cases (Pocock and Hughes, 1990; Fayers and Machin, 1995; Goodman and Berlin, 1994; Powell-Tuck *et al.*, 1986; Rahimtoola, 1985;), especially in rare diseases (Freedman, 1989; Lilford *et al.*, 1995). However, there are situations where worthwhile gains are small in relation to the precision achievable by all envisaged trials such that power remains ethically critical (Barnard, 1990; Buyse, 1991; Collins *et al.*, 1987; Lilford, 1990; Lilford and Thornton, 1992; Lilford and Johnson, 1990; Mathews, 1988; Pocock and Hughes, 1990). Even then, a trial is not necessarily unethical since, given equipoise, the patient does not lose out in prospect and a more precise estimate (though not a 'definitive' answer) is obtained by going ahead with a trial than by eschewing randomisation altogether. (Lilford, 1990; Lilford and Thornton, 1992; Lilford and Johnson, 1990).

A valid statistical association from an RCT can be attributed to a causal relationship between

exposure to a technology and outcome or chance, since bias has been eliminated in theory. Other factors can be taken into account when evaluating the role of chance, including biological credibility and consistency with other studies; in the case of rare diseases, results from 'under-powered' trials (which may be more prone to errors than adequately powered trials) might be interpreted alongside case-control studies, for example. See also the scientific need for replication, below.

The scientific need for replication. Thirty-five references looked at confirmatory trials, and all except Morris and Brown (1995) saw a need for repeating trials given certain conditions. The exception described an anecdotal case where enough evidence was acquired through Phase 1 and 2 trials of Tarcolimus to make the start of a multicentre RCT unethical (Morris and Brown, 1995).

Thirteen references put forward an epistemological argument and were concerned that trial results should be 'confirmed' by replication, even if a previous result was 'statistically significant' (Banta and Thacker, 1990; Buyse, 1991; Byar *et al.*, 1976; Fleming, 1982; Gehan, 1982; Henry and Hill, 1995; Nicholson, 1986; Senn, 1991a; Simon, 1982, 1994; Spiegelhalter *et al.*, 1994; Stamer and Lee, 1982; Zelen, 1982). In this way, generalisations might derive inferential support from the process of induction which proceeds from particular cases to generalisations. Inductive support which takes the form of multiplicity of the same observation is called 'enumerative' induction. A different type of induction, called 'eliminative' induction, is based on variety, not multiplicity, of instances. Seven references were concerned to enhance generalisability of results by repeating trials on different samples, for example HIV vaccine trials in developing countries where there is considerable strain variation (Burkhardt and Kienle, 1978, 1983; Ellenberg *et al.*, 1990; Glasziou, 1995; Lantos, 1994a; Lurie *et al.*, 1994; Pringle and Churchill, 1995). However, Senn (1991a) points out that repeating a trial on a different sample will not necessarily improve generalisability (if the same factors lead people to participate, for instance). (See also page 16, on the risk that research will not inform practice). We point out that a variety of study designs might be used to 'confirm' results by way of eliminative induction (see also page 12, on under-powered studies). A third type of inductive inference is concerned with subjective degree of belief (or Bayesianism) and is able to avoid taking sides on the multiplicity versus variety debate

above. Some theorists reject inductive inference altogether on the basis that its logic is invalid. Senn (1991a) examined Karl Popper's philosophy of science which rejects induction as a process of logical inference, but, at the same time, recognises its psychological necessity. According to Popper, a scientific theory can only be falsified by deduction from observations that refute the hypothesis. Theories can never be confirmed, only 'corroborated' as attempts to refute them fail – a probabilistic solution to the problem of induction is to take a subjectivist position in respect of probability and use Bayesian methods (see appendix 3).

Nine references were concerned to balance the need for equipoise with the putative scientific requirement to replicate results, given the possible tension between the alleged need to repeat a trial, once evidence has been made available, and the requirement of upholding the moral principles of beneficence and non-maleficence implicit in accepting the need for equipoise (Byar, 1990; Royall, 1991) – see uncertainty as justification for RCTs (page 19). Thus, it could be argued that it is unethical to embark on a new trial without first preparing a systematic review (or meta-analysis) of the relevant existing trials (Chalmers and Lau, 1993, 1996). If the necessary review of previous studies yields an overall odds ratio (OR) close to 1, then (any) pre-existing equipoise is likely to be maintained, especially if confidence limits are wide, and a repeated trial would not violate the moral principle to do the best for patients, in prospect. Three of the nine articles suggested that recruitment is acceptable when it is carried out by individual physicians who are equipoised despite existing evidence sufficient to convince all but the most sceptical (Collins *et al.*, 1992; ISIS-2 Collaborative Group, 1988; Simes, 1991). There was no reference to the possibility that physicians may still be equipoised because they are unaware of a previous result, or that they might previously have believed a treatment to be inferior, moving into equipoise only after seeing results favouring it. (See also page 16, on risks that research will not inform practice.) The British clot-buster trial, the Second International Study of Infarct Survival (ISIS-2), was conducted in precisely such circumstances (ISIS-2 Collaborative Group, 1988). An interesting situation arises when the cognoscenti believe A is better than B, but most practitioners do not. Assuming that the practitioners had different (more sceptical) starting beliefs, repetition would be entirely justified. If, however, the data are so strong as to shift almost any reasonable prior belief, or if 'slow adapters' are slow because they are unaware of results, or, for other reasons, then

what is needed is education and not just more trials (see page 16, on the risks that research will not inform practice.) If it is expected that replication will be necessary, it might be more appropriate to conduct independent trials concurrently (wherever possible), thereby circumventing the problem (Levine, 1988, 1991).

Seven references showed how repeating a trial might be justified when (1) the previous evidence was in some way flawed (Hellman, 1979), (2) previous evidence was from an 'explanatory' trial which is inadequate to demonstrate effectiveness such that a subsequent 'management' trial might be justified (Willan, 1994), (3) evidence from previous work was based on surrogate markers as opposed to hard end-points which patients would recognise and value (Nowak, 1994), or (4) if previous trials had been stopped early with imprecise results (Ashby and Machin, 1993; Fleming, 1982; George *et al.*, 1994, Tannock and Boyer, 1992). In all cases, equipoise might or might not have been dispelled by the previous evidence. (See also page 16, on the risks that research will not inform practice.)

One article suggested that RCTs are justified, even when there is evidence from previous research, and highlighted the problems of using old treatments in new situations, arguing that effects cannot simply be inferred from data obtained in similar, but different, settings (Tukey, 1977). On the other hand, Gehan and Frieireich (1974) would object to randomised designs when new 'bits' are simply bolted onto old treatments. This may, however, be a case for equivalence trials, especially if the costs are unequal, although others have pointed out that, given equipoise, all trials are 'equivalence', and the issues at stake are (1) size of effect which would change practice, and hence which the trial should measure, and (2) whether a null result, or some other result, is most likely in prospect. (See also page 23, when equipoise does not apply.) More data might be needed to show that a treatment justifies its financial cost, even in the face of a positive result, e.g. the Extra-corporeal Membrane Oxygenation (ECMO) trial. In that case, the new treatment may be made available only in the trial on the basis of collective equipoise (see also page 22, on when equipoise does not apply).

Early stopping to make beneficial treatments widely available. Seventy articles discussed the ethics of stopping trials early when there is some evidence of efficacy (Anscombe, 1963; Armitage, 1963, 1975; Ashby and Machin, 1993; Baum *et al.*, 1994; Bellisant *et al.*, 1994; Berry and Ho, 1988; Berry

et al., 1992; Bulpitt, 1983; Chalmers, 1979; Chalmers and Lau, 1996; Canner, 1979; Crowley *et al.*, 1994; de Groot and Kennedy, 1995; Fleming, 1993; Fleming and DeMets, 1993; Fleming and Waterlet, 1989; Freedman and Spiegelhalter, 1989; Freedman *et al.*, 1994; Geller, 1987; Geller and Pocock, 1987; George *et al.*, 1994; Goldman, 1987; Goodyear and Levine, 1987; Green *et al.*, 1987; Greenhouse, 1992; Hamilton, 1983; Hetjan *et al.*, 1992; Hilden and Habbema, 1990; Hill, 1962; Hill and Sancho-Garnier, 1979; Hughes, 1993a, b; Hughes *et al.*, 1992; Klimt and Canner, 1979; Laupacis *et al.*, 1991; Lewis, 1993; Liberati, 1994; Lockwood and Anscombe, 1983; Lurie, 1994; Machin, 1992; McPherson, 1982; Meier, 1979; Meinert, 1979; Parmar and Machin, 1993; Peto *et al.*, 1976; Pfeffer, 1993; Pignon and Arrigada, 1994; Pocock, 1977, 1979, 1993; Pocock and Hughes, 1989; Pollock, 1989, 1993; Prescott, 1979; Propert *et al.*, 1991; Raju, 1992; Rubinstein, 1982; Ruse, 1988; Seibert *et al.*, 1993; Simberkoff *et al.*, 1993; Simon, 1994; Smith *et al.*, 1993; Spiegelhalter *et al.*, 1993, 1994; Stamler, 1979; Sutton-Tyrrell *et al.*, 1991; Whitehead, 1994; Working Group on Arrhythmias of the European Society of Cardiology, 1994). All authors except Ashby and Machin (1993), Berry (1988), Freedman and Spiegelhalter (1989), George *et al.* (1994), Hilden and Habbema (1990), Hill (1962), Hughes *et al.* (1992), Laupacis (1991) Lewis (1993), Liberati (1994), Machin (1992), Peto *et al.* (1976), Pignon and Arrigada (1994), Pocock and Hughes (1989), Pocock (1993), Pollock (1989), Prescott (1979), Raju (1992), Rockhold (1993) and Working Group on Arrhythmias of the European Society of Cardiology (1994) believed that it is always unethical to continue a trial once efficacy has been established and/or that fixed-sample trials with no mechanism for early stopping are unethical.

Chalmers and Lau (1996) argued for early stopping when a trend conforms with the results of a previous meta-analysis.

Problems associated with early stopping are:

- (1) Failure to establish long-term safety (Berry, 1988; Rockhold, 1993), but Stamler (1979) observes that no trial can ever answer every question about potential toxicity.
- (2) Reduced statistical precision (Ashby and Machin, 1993; George *et al.*, 1994; Hill, 1962; Lewis, 1993; Machin, 1992; Peto *et al.*, 1976; Pignon and Arrigada, 1994; Pocock and Hughes, 1989), though Pocock and Hughes (1989) suggest that statistical adjustment, for example Bayesian 'shrinkage', could be made for this.

- (3) Artificial heterogeneity of results may appear in subsequent overviews (Hughes *et al.*, 1992).
- (4) Practitioners may not be persuaded (Freedman and Spiegelhalter, 1989; Liberati, 1994; Prescott, 1979); this overlaps with point (2) above, but is not identical as more precision may be needed to drive change in some contexts than others.
- (5) The secondary aims of a trial may be compromised (Crowley *et al.*, 1994; Fleming, 1982; Green *et al.*, 1987; Greenhouse, 1992; Hilden and Habbema, 1990; Hughes *et al.*, 1992; Laupacis *et al.*, 1991; Lewis, 1993).
- (6) Some outcome measures are not obtained quickly (Raju, 1992). We point out that longer-term follow-up may compensate for adverse effects on short-term outcomes.
- (7) Some people may be denied restricted treatments (i.e. when treatments are not expected to be available outside a trial) – randomisation might be the only route to a preferred therapy (Lockwood and Anscombe, 1983).

Given the moral advantages of early stopping in certain circumstances, five articles argued that a predefined stopping rule should be followed and that recruitment should be halted when the pre-specified boundary had been crossed (Bellisant, 1994; de Groot and Kennedy, 1995; Lurie *et al.*, 1994; Whitehead, 1994; Working Group on Arrhythmias of the European Society of Cardiology, 1994). Fourteen articles, however, argued against the sole use of stopping rules, and suggested that they are merely guidelines and not strict rules (Ashby and Machin, 1993; Fleming, 1982; Fleming and DeMets, 1993; Freedman and Spiegelhalter, 1989; Goldman, 1987; Goodyear and Levine, 1987; Lewis, 1993; Liberati, 1994; Ruse, 1988; Simon, 1994), and/or that data outside the trial should be taken into account (Ashby and Machin, 1993; Baum *et al.*, 1994; Parmar and Machin, 1993; Spiegelhalter *et al.*, 1994). We also point out that, by incorporating a frequentist stopping rule, early termination may introduce bias as well as imprecision. (See also early stopping when there is some evidence of toxicity, on page 24.)

However, one reference asserted that a researcher has the right (if not the obligation) to finish a trial to statistical significance, without being forced to make premature conclusions (Ruse, 1988). (See also page 24, on the censure of interim results.)

Risks to society

Risks associated with new therapies. Nine references were in favour of restricting new

treatments to trials in order to establish definitive results before equipoise is lost (Dupont, 1991; Freedman, 1992; Freedman *et al.*, 1989; Freston, 1986; Pfeiffer, 1993; Reidenberg, 1987; Silverman, 1985), or to hedge in respect of new therapies (Chalmers and Chalmers, 1994; Lantos, 1995) – we would argue, however, that, if equipoise applies, expected benefit is sufficient to offset any risk such that randomisation does not reduce the risk associated with such technologies, though restricting them to trials might serve to reduce the risk to society as a whole. One reference, however, distinguished between general and desperate sufferers, and asserted that such restriction was only justified in the former population (Ruse, 1988). Six further references were concerned to make new treatments widely available early (especially when patients are desperate), claiming that patients have an overriding ‘consumer’ right (Ellenberg *et al.*, 1992; Fennberg, 1992; Illich, 1976; Institute of Medical Ethics, 1992; Levine, 1991; Young, 1993).

The desire to contain risk of harm from society at large and to protect the ‘window of opportunity’ (equipoise) can be distinguished from restrictions due to scarce resources such that equipoise is not a necessary condition for trial entry (Challah and Mays, 1986; Freund, 1970; Hill, 1963; Markman, 1992).

In both cases, but particularly in the latter, concerns about distributive justice should prevail (see also page 23, on when equipoise does not apply.)

Risks associated with non-participation in trials.

Twenty-three articles addressed the ‘double standards’ issue where there are different, more stringent, standards which apply to RCTs than to innovative practice. This implies that there is greater ‘care’ associated with trial entry than with routine practice such that non-trial patients incur an implicit risk by being treated routinely. Eight articles expressed a need to resolve this double standard by embracing one universally applicable standard: Kleijnen *et al.* (unpublished) stated that there should be a single standard across the board and that this should be determined by the society in question (Collins *et al.*, 1992). An editorial (1995) regarded the regulations in normal practice as adequate for RCTs also; whereas Lantos (1994b) and Chalmers and Silverman (1987) expressed a need to tighten the non-trial procedures in practice so that they are on a par with RCT regulations. Segelov *et al.* (1992) proposed that the decision not to participate in an approved trial should be subject to the same ethical requirements as trial

entry. Buyse (1991), Challah and Mays (1986), Chalmers (1975a, 1990), De Deyn (1995), Goodare and Smith (1995) and Tauer (1994) simply complained of the existence of the double standard, while Hutton (1996) made explicit the uncertainty over treatments used in routine practice apparently given in the patient’s best interests. The literature did not address the possibility that different standards may be ethically justified such that they are not ‘double’. It could be argued that a defence for different standards can be made in that RCTs carry a potential, if not actual, conflict between the two roles of physician (as scientist and as therapist). That said, a doctor may harbour any number of interests which may conflict with the interests of his/her patient. Allied to this, the default assumption for patients may be that they are not in a trial, and patients’ perceptions of the detail which is warranted may hinge on whether or not they are in the default situation.

Three references observed that double standards exist within trials: (1) there is no regulation of n of 1 trials (Levine, 1991), and (2) there is less stringent regulation of pharmacological than surgical trials, and, while there are intrinsic differences, there remains the potential for a conflict of interests in both cases (Cornfield, 1966; Spodick, 1973).

Risks that research will not inform practice. Three articles presented evidence to suggest that RCTs do have a measurable influence on general medical practice patterns: on treatment of myocardial infarction (Friedman *et al.*, 1983; Lamas *et al.*, 1992), and the practice of radiotherapists and medical oncologists (Stephens and Gibbons, 1993). The authors, however, do recognise that there is sometimes a time lag between production of compelling research evidence and change in practice.

Seven references provide examples of medical practice which has followed research only after considerable delay; this is arguably a case for repeating trials when such replication is likely to convince others. Ernst and Resch (1996) described the famous case of scurvy: it took the British Navy 50 years before the regimen of citrus fruit was adopted after the publication of trial evidence of its benefit in 1743 by Lind, itself not the first evidence of therapeutic or prophylactic benefit. Since then, the quality of evidence has increased, but not the speed with which it filters down to practice. Avorn *et al.* (1982) reviewed comparative studies of propoxyphene analgesics versus aspirin versus placebo, and found no treatment effect,

yet 20% of a sample of physicians working in the field were under the misconception that aspirin was the superior therapy. Chalmers (1974) and Chalmers and Sinclair (1985) noted that despite evidence from six controlled studies to suggest that stilboestrol had no effect on preventing spontaneous abortion, a large number of pregnant women continued to receive the drug after 15 years or more. Elliott (1992) and Fisher and Fisher (1996) described the continued use of antidepressants in children despite evidence to suggest that the treatment has no advantage over placebo, while Lamas *et al.* (1992) showed that, although ISIS-2 and other randomised trial results supporting the use of aspirin for myocardial infarction were 'clear-cut', as many as 29% of patients studied were not taking aspirin long after the results had been published. Clinicians would be behaving ethically if they recruited while equipoise remained, but they would not appear to be justified in continuing to randomise their patients without disclosing a loss of equipoise, simply in order to persuade others. This really would be merely using patients as means to societal ends and would thus violate the injunction of Kant, though it would be acceptable to utilitarians if the greatest happiness for the greatest number were, in fact, served thereby.

Pelligrino and Thomasma (1981) state that individual physicians have the right to bypass research results and that they are justified in relying on their own individual judgement as opposed to scientific consensus. It is important, given the premise that autonomy is crucial, that they are familiar with research findings, whether or not they act accordingly, and education and dissemination should be as pervasive as possible.

The importance of disseminating results is widely recognised (Antman *et al.*, 1992; Boissel, 1989). Indeed, having looked at the empirical evidence, Boissel (1989) concludes that, at present, doctors do not even know RCT findings and, consequently, do not use RCTs as a basis for determining patient care, but instead use technologies which have not been adequately tested with RCTs. What is more, important results are sometimes not even published in standard textbooks and review recommendations (Antman *et al.*, 1992). One article pointed out that clinical trials are carried out for a variety of audiences and, while a result may be persuasive for one audience, it may not be for another (Brown, 1980). Possible audiences are trial investigators, investigator peers, practising specialists, general physicians, licensing agency (e.g. the US Food and Drugs Administration (FDA), or the consumer, that is, patients and those who

formulate health insurance and reimbursement policy. Indeed, evidence will impact differently according to what prior beliefs are held. Of course, as evidence accumulates, so everyone's beliefs should, at least in theory, converge on the truth.

In order to change practice in light of RCT findings, it has been hypothesised that a meta-analysis of trials might be more persuasive than a single large trial (Stewart, 1992). However, conducting an audit of practice, while known to raise medical standards, may also improve awareness of research findings. As a result, Liberati (1994) sees the relationship between trials and practice as very complex, and Avorn and Soumerai (1983) suggest that that commercial tools for disseminating scientific information are most effective, i.e. using the principles of behavioural science, market research and communications theory. Boissel (1989) concludes that research into evaluating the effectiveness of dissemination is urgently needed and that an appropriate method for evaluating the impact of RCTs is yet to be designed.

Dual obligations of physicians to society and to the individual patient

The legacy of Hippocrates: the therapeutic obligation

Sixty-four articles addressed the ancient debate over whether or not the interests of the individual should take precedence over those of society. Four of the 64 articles suggested that tension between society and the individual could be reduced by the use of adaptive designs or a mixture of frequentist and Bayesian statistics (Clayton, 1982; Palmer, 1993; Palmer and Rosenberger, 1998; Roy, 1986a). Adaptive designs, in this context, alter the randomisation ratio to favour the treatment which appears 'ahead' at any one time as the trial progresses. However, adaptive designs are not a perfect solution to the problem since they do not maximise individual expected utility which would be achieved by opting for the therapy currently showing the most promise (Kadane, 1996; Royall, 1991; Simon, 1977). This must be so, since the expected utilities (which, given equipoise, were equivalent at the start) are sensitive to any alterations in probability. (See also page 23, on when equipoise does not apply.)

Thirty-four of the 64 articles expressed unwavering support for the absolute primacy of the 'therapeutic obligation'; that is, a physician always has a duty to do his/her 'best' (see the introduction, page 1) for each individual patient (Anonymous, 1979; Barry and Molyneux, 1992; Beecher, 1966; Blumgart, 1970; Byer, 1983; Engelhardt, 1988; Fried, 1974; Giertz,

1980; Gillon, 1994; Goodare and Smith, 1995; Hellman, 1979; Hill, 1963; Kairys, 1996; Kardinal, 1994; Katz, 1993; Lantos, 1994b; Levine, 1992; Marquis, 1983; Miller, 1993; Moore and Papp, 1996; Nyapadi, 1995; Pfeffer, 1993; Pringle and Churchill, 1995; Schafer, 1982; Schwartz *et al.*, 1980; Scoles and Silagy, 1993; Shaw and Chalmers, 1970; Smith, 1992; Thornton, 1992; Toynbee, 1996; Veatch, 1981; Vere, 1981; Visscher, 1970, 1990). In addition, one reference suggested that society does not have a right to pursue the Melioristic goal of medical progress (the attempt to make the world a better place by human effort) and that medical experimentation objectifies the patient (Jonas, 1969).

Three of the 64 articles had a more utilitarian outlook and so viewed valid RCTs as ethical, at least where society is likely to benefit (Baum, 1995; Dworkin, 1987; Kennedy, 1988). However, two references made the distinction between rule- and act-utilitarianism, claiming that the former permits the use of rules/rights in order to maintain trust for the greater 'good' (Dworkin, 1987; Kennedy, 1988). This means that respecting patient autonomy might promote the greatest good for the greatest number in the long run. However, one article argued that the rule-utilitarian doctrine allows too many exceptions, that is, an act contrary to the rule is permissible if the consequences on that particular occasion are good, but this then destroys the distinction between acts and rules (Nicholson, 1986). However, it could still be argued that the consequences of a general infraction of the rules would be disastrous to patients and the public view of trials and of the behaviour of clinical professionals. Better still, the rules themselves could be amended so that the exception becomes part of the rule (Lyons, 1965) and the inclusion of deontic notions of respect for autonomy may serve to increase social utility without need for rules-of-thumb. Two references raised the interesting situation of an epidemic during which such individualism might be an unaffordable luxury (Fethe, 1993; Jonas, 1969), despite flying in the face of Kant's injunction. Four references thought that strict individualism (i.e. individual rights should **always** trump social needs) should be relaxed in the context of trials (Editorial, 1983; Elander and Hermon, 1995; Gifford, 1986, 1995), while 11 articles addressed the idea of a 'social contract' which might impose a duty on the individual to contribute to medical research due to their having benefited from previous research (Ackerman, 1994; Caplan, 1984; Gilbert, 1995; Gilbert *et al.*, 1977; Hilden and Habbema, 1990; Lesser, 1989; Levine, 1981; Mackillop, 1986; Marquis, 1983; Meier, 1979; National Commission

for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978). None of these were explicit about accepting some loss of expected utility in order to honour the said contract. All references examining the 'social contract' except Hilden (1990) acknowledged that not all individuals will have benefited and so would not carry such an obligation and/or that the 'social contract' should be an optional transaction and should not be rule governed. Alternative ideas of the 'social contract' appeal to the following four different ideas:

- (1) Justice, but then any debt should be discharged to past not future patients (Gilbert, 1995; Marquis, 1983).
- (2) A duty to rescue according to which the therapeutic obligation should be overridden if research may prevent or remove important harms to others while imposing no more than a minor compromise to the individual. The therapeutic obligation is still regarded as the primary obligation which must be satisfied, but not always fully satisfied (as with the Rawlsian 'lexical priority' dictate), before a secondary obligation can be discharged (Ackerman, 1994; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1978).
- (3) If an individual acts only on that maxim he/she could at the same time will that it should become a universal law (the Kantian requirement that one's maxims be universalisable), and if he/she does not will that everyone should deny consent to RCTs, then he/she should consent to trial entry (Marquis, 1983). However, while we may not wish to make universal a policy of never helping others, we may not wish to commit everyone to helping others in just the same way (an imperfect duty – see the glossary). It is not clear why there should be a duty to participate in an RCT even if we do not wish everyone to be selfish. A maxim in refusing consent might be: let people participate in trials, but only if they informedly consent to. This is universalisable and does not commit everyone to take part just in case they do not want to.
- (4) The Lockean idea that we are better off with an institution that conducts RCTs than without. Cases (3) and (4) do not, however, imply that patients could be conscripted without (or against) consent (Marquis, 1983), and, since consent should unmask any lack of equipoise, only altruistic patients would consent given a preference and freely available trial treatments.

Three references argued against the idea of patients or healthy volunteers having a social obligation to participate in research on the basis that any such obligation would invalidate informed consent (Fethe, 1993; Jonas, 1969; Lesser, 1989).

It could be argued that, rather than a patient having or not having an obligation to some external entity, that is, society, he/she may see participation as a process of self-realisation (following the Hegelian tradition), but recruitment to conventional trials still rests on the valid consent of the individual in question, such that any lack of equipoise is transparent.

In light of the above constellation of arguments, we would say that there are no compelling arguments to support a clinician entering patients in trials for societal gain against the individual's best interests. Arguments that patients have a duty to do so are only a little stronger – acts of altruism can only be anticipated when a patient has little to lose and should not be expected in life or death decisions. This is, however, predicated on the informed consent of the individual in question.

Is the RCT at odds with the therapeutic obligation?

Seventeen of the 34 articles which expressed unwavering support for the therapeutic obligation further stated that RCTs could be seen as an adjunct to good individual patient care, rather than as a threat to it (Anonymous, 1979; Blumgart, 1970; Engelhardt, 1988; Fennberg, 1992; Gillon, 1994; Goodare and Smith, 1995; Hill, 1963; Kardinal, 1994; Lantos, 1994a; Levine, 1992; Marquis, 1983; Nyapadi, 1995; Pfeffer, 1993; Schafer, 1985; Scoles and Silagy, 1993; Smith, 1992; Visscher, 1970). However, none of these articles considered cases when equipoise does not apply.

Conversely, ten of the 34 articles thought that RCTs necessarily violate patient rights to the best treatment available and see the individual as 'sacrificing' him/herself for the benefit of future patients (Beauchamp and Childress, 1989; Giertz, 1980; Hellman, 1979; Pringle and Churchill, 1995; Schafer, 1982; Schwartz *et al.*, 1980; Thornton, 1985; Toynbee, 1996; Vere, 1981), particularly in surgical trials, according to Byer (1983).

Uncertainty as justification for RCTs

Uncertainty and substantial uncertainty. In an attempt to resolve the putative tension between societal and individual interests, 129 articles addressed the notion that, if there exists uncertainty over treatment effects, then the individual

patient has nothing to lose, in prospect, by trial participation (Alderson, 1996; Angell, 1984; Anonymous, 1979; Bartlett and Cornell, 1991; Baum, 1994; Baum *et al.*, 1994; Beecher, 1966; Berkowitz, 1995; Block and Elahoff, 1979; Boissel, 1989; Botros, 1990; Bracken, 1987; Bradley, 1993; Brewin and Bradley, 1989; Burkhardt and Kienle, 1978; Buyse, 1991; Byer, 1983; Capron, 1978; Chard and Lilford, 1998; Challah and Mays, 1986; Chalmers, 1968, 1975b, 1982; Chalmers *et al.*, 1972; Chipman, 1993; Clayton, 1982; Collins *et al.*, 1992; Coulehan *et al.*, 1985; Cowan, 1981; Curran, 1979; Cutler *et al.*, 1966; de Groot and Kennedy, 1995; Dudley, 1983; Eichler, 1995; Emrich and Sedrank, 1996; Fetter *et al.*, 1989; Freedman, 1987, 1992; Freedman and Spiegelhalter, 1992; Freedman *et al.*, 1984, 1994; Feinstein, 1973; Ferner and Neumann, 1992; Fried, 1974; Freireich and Gehan, 1979; Ganz, 1989, 1990; Gehan and Freireich, 1974; Gifford, 1986, 1995; Gilbert *et al.*, 1977; Gillett, 1994; Gillon, 1994; Goodyear and Levine, 1987; Gore, 1995; Grady, 1991; Gross, 1993; Harrington *et al.*, 1994; Hellman, 1979; Hellman and Hellman, 1991; Hilden and Habbema, 1990; Hill, 1963; Hollenberg *et al.*, 1980; Hutchins and Eckes, 1996; Hutton, 1995; Ingelfinger, 1972; Institute of Medical Ethics Working Party, 1992; Johnson *et al.*, 1991; Kadane and Seidenfeld, 1986, 1996; Kassirer, 1983; Katz, 1981; Kaufman, 1993; Kennedy, 1988; Korn and Baumind, 1991; Lantos, 1994; Lebacqz, 1977; Levine, 1988, 1991; Levine and Lebacqz, 1979; Lilford, 1987, 1988, 1994; Lilford and Jackson, 1995; Lilford *et al.*, 1991; Lockwood and Anscombe, 1983; Machin, 1994; Marquis, 1983; Mike, 1989a; Miller and Appelgate, 1993; Moore and Papp, 1996; Neugebauer *et al.*, 1991; Nicholson, 1986; Oakley, 1990; Oettinger and Berger, 1989; Passamani, 1991; Pfeffer, 1993; Peto *et al.*, 1976; Pollock, 1989, 1993; Raju *et al.*, 1992; Report to the Health Services and Public Health Review Board, 1993; Royall, 1991; Rudicel and Esdaile, 1985; Sacks *et al.*, 1982; Schafer, 1982, 1985; Schaffner, 1996; Sedrank, 1996; Senn, 1993; Shaw and Chalmers, 1970; Shimm and Spece, 1983; Shinebourne, 1984; Spodick, 1982; Steinberg, 1991; Stephenson, 1996; Stirrat *et al.*, 1992; Tannsjö, 1994; Taves, 1974; Thornton, 1992; Thornton and Baum, 1995; Toynbee, 1996; Van der Linden, 1980; Veatch, 1981; Weinstein, 1974; Wennberg, 1990; Weymuller, 1996).

All references except 24 expressed the idea of clinical uncertainty in terms of the concept of equipoise. Equipoise only arises when treatments are an equal bet in prospect. Equipoise is more than indifference between treatments as it captures the uncertainty over which treatment is best, as opposed

to confidence that they are the same. The exceptions failed to recognise that, since medicine is an inexact science, further constraints are necessary otherwise any RCT would be justified, irrespective of current evidence (Anonymous, 1979; Barry and Molyneux, 1992; Bracken, 1987; Burkhardt and Kienle, 1983; Buyse, 1991; Capron, 1978; Challah and Mays, 1986; Chalmers, 1968; Clayton, 1982; Collins *et al.*, 1992; Curran, 1979; Dudley, 1983; Gillon, 1994; Hutchins, 1996; Lantos, 1995; Mike, 1989a, 1993; Miller, 1993; Moore and Papp, 1996; Oakley, 1990; Peto *et al.*, 1976; Pringle and Churchill, 1995; Raju, 1992; Schafer, 1982). The remainder discussed different forms of 'equipoise' which put varying constraints on the idea of clinical uncertainty. One reference discussed what the rationale might be for mounting a trial when equipoise exists, i.e. there must be some 'reason' for running a particular trial rather than to do nothing in such circumstances. However, equipoise is not necessarily the same as thinking that a null result is most likely, because, although improved outcome as the main comparison may be likely in prospect, its likely extent may be in doubt, so that it is unclear whether the 'costs' are warranted. In this case, equipoise may apply and a trial may then release a 'locked' decision (Chalmers, 1968; Gifford, 1995). There is also some evidence to suggest that trial patients fare better than those treated in routine practice (Stiller, 1989; Thornton and Baum, 1996), but this should not be offered as an inducement to patients, since it conflicts with the Helsinki requirement to do the 'best' for all patients, whether in a trial or not. Interestingly, another article produced evidence to suggest that innovations which were brought to the stage of RCTs were 'successful' only half of the time and they were 'highly preferred' only one-eighth of the time (Gilbert *et al.*, 1977). This result gives substance to the claim that there is, as a general rule, little basis for choosing between a standard and a new therapy prior to a trial, and would provide the rationale for clinicians to remain in equipoise in the face of theoretical equivocal evidence. However, this relates to the basis for prior beliefs, not the ethics of what to do given the physicians' or patients' prior beliefs.

Eight of the 129 articles stated explicitly that RCTs are necessarily unethical, even when equipoise applies, because allocating treatment by lot is contrary to a patient's need for the advice of his/her physician by diluting the salutary effect of the physician him/herself appearing to know what to do, even in the face of uncertainty (Mike, 1989; Schafer, 1982) or equipoise (Gilbert, 1995; Harrington, 1994; Hellman, 1979; Kassirer, 1983; Thornton, 1994; Toynbee, 1996).

Eight of the 129 articles specifically attacked the polarisation of knowledge (know or not know) and hence directly or indirectly invoked the concept of degrees of knowledge and hence of equipoise (Botros, 1990; Gifford, 1986, 1995; Hellman, 1979; Hellman and Hellman, 1991; Lilford and Jackson, 1995; Lockwood and Anscombe, 1983; Royall, 1991). Seventeen articles argued that the concept of equipoise was seldom achievable in practice and/or was merely an ethical construct and so was inevitably elusive in practice (Byer, 1983; Challah and Mays, 1986; Cutler *et al.*, 1966; Dudley, 1983, 1986; Lockwood and Anscombe, 1983; Nicholson, 1986; Schafer, 1982; Stephenson, 1996; Weinstein, 1974), especially in surgery (Berkowitz, 1995; Buyse, 1991; Gross, 1993; Oettinger and Berger, 1989; Pollock, 1989, 1993; Schafer, 1982). While six articles proposed that RCTs are necessary despite this objection (Buyse, 1991; Challah and Mays, 1986; Cutler *et al.*, 1966; Gross, 1993; Schafer, 1982), and perhaps putting more emphasis on informed consent in order to compensate (Stephenson, 1996), others thought that the RCT was unethical on this basis (Berkowitz, 1995; Pollock, 1989), or sometimes simply unnecessary (Dudley, 1983, 1986; Oettinger and Berger, 1989). The remainder simply mooted this point (Buyse, 1991; Byer, 1983; Nicholson, 1986; Pollock, 1993; Weinstein, 1974).

Collective and individual equipoise. Nineteen articles regarded the existence of collective equipoise as sufficient justification for a trial, that is, a trial is ethical if experts in general, rather than the particular clinician (or clinician-patient pair) are equipoised (Alderson, 1996; Baum *et al.*, 1994; Chipman, 1993; Collins *et al.*, 1992; de Groot and Kennedy, 1995; Eichler, 1995; Emrich and Sedrank, 1996; Freedman, 1987; Gillett, 1994; Johnson and Lilford, 1991; Kadane, 1986, 1996; Passamani, 1991; Pfeffer, 1993; Schaffner, 1996; Sedrank, 1996; Shimm and Spece, 1983; Tannsjö, 1994; Weymuller, 1996). This willingness to discredit individual 'hunches' in favour of the collective equipoise is buttressed by evidence which indicates that innovative therapies that are brought to the stage of an RCT are 'successful' only half of the time (Gilbert *et al.*, 1977) and that people who hazard, even educated, 'guesses' are frequently much further off the mark than they expect to be (Albert and Raiffa, 1969). Johnson *et al.* (1991) argue that, while collective equipoise must apply within certain limits (preference ratio 80:20), a physician has a duty, if holding a personal preference, to disclose (or, at least, offer to disclose) this preference. However, four of the 19 articles found the idea of collective equipoise difficult to conceptualise in

Bayesian terms, given degrees of expertise among the medical community and the difficulty in aggregating individual 'priors' to form a collective 'prior' (Gifford, 1986, 1995; Hilden and Habbema, 1990; Machin, 1994). Kadane (1986, 1996), Schaffner (1996) and Sedrank (1996) invoke a concept of collective equipoise to determine the appropriate allocation of trial subjects to treatments – a treatment is acceptable to ethics committees if at least one expert prefers it to the alternative(s). (See also patient equipoise, on page 22.)

Thirty-three articles discussed what size of risk is morally acceptable for trial participants from the perspective of an ethics committee. All except Elks (1993) were concerned to establish the appropriate level of risk, regardless of the risks patients themselves are willing to take, while the exception suggested that individuals should always be able to decide for themselves without any paternal protection (Elks, 1993) – see also patient equipoise, on page 22. Tannsjö (1994) distinguishes two different philosophical views: the rational decision analysis, which simply combines utilities and probabilities, and an 'insurance' analysis, which encapsulates the view that some risks are simply not worth taking, whatever the expected benefits. The latter, known formally as the minimax method, attempts to minimise maximum expected loss. We would argue that the rational (or Bayesian) analysis can incorporate an 'insurance' policy and that there is a small probability of severe outcome associated with everyday action, so that, by minimising it, most action would be ruled out anyway. Furthermore, the values assigned to outcome are an integral part of the concept of equipoise (Levine and Lebacqz, 1979) – see above.

Berglund (1995), Byar *et al.* (1990), Cassel (1985), Feenberg (1992), Gillet (1994), Goldberg and McGough (1991), Hutchins and Eccles (1996), Kauffman (1994), Lebacqz (1983), and Levine and Lebacqz (1979) state that probable benefits must outweigh the risks and that the greater the expected benefits, the greater the acceptable risk of harm, thereby advocating a decision analytic approach to determining collective equipoise when there are trade-offs. However, they do not provide any definitive standards, and Nicholson (1986) worries that participants in trials where they can expect considerable benefit may be less protected than in other trials which offer only small (or no) expected benefit, such as Phase 1 trials. (See also page 16 on the risks associated with non-participation in trials.)

Ten articles examined the implications of research on children. Six references believed it unethical to confer greater than 'minimal risk' of harm on children irrespective of possible benefits (Berglund, 1995; Kopelman, 1981, 1989; Munir, 1992; Nicholson, 1986; Tauer, 1994), whereas Dworkin (1987), Freedman *et al.* (1993), Kauffman (1994) and the MRC (1991) believed that greater than minimum risk was acceptable when it is offset by the expected benefits. However, there is a variety of standards, namely the National Health and Medical Research Council, Canberra (NHMRC), Medical Research Council (MRC), British Paediatric Association, Royal College of Physicians, and the US Department of Health, Education and Welfare (Berglund, 1995). The most often cited interpretation of 'minimal risk' was that risk of harm should not be greater than that ordinarily encountered in daily life or during routine medical practice (MRC, 1991). However, in an attempt to identify what exactly is meant by 'everyday' risks, Freedman (1993) and Kopelman (1989) point out that the risks incurred by everyday life vary across societies (or, indeed, classes within societies) such that some trials might be acceptable in one place (e.g. the developing world), which would not be acceptable elsewhere (e.g. the industrialised West). However, both references argue for 'trans-cultural' ethics which take into account the norms of different societies (or groups). In addition, some references sought to quantify 'minimal' risk. Nicholson (1986) observed that, by US standards, minimum risk of death is < 1 per million, a minimum risk of major complication is < 10 per million, and minimum risk of minor complication is < 1 per 1000, and, by UK standards, minimum risk of death is 1–100 per million, minimum risk of major complication is 10–1000 per million, and minimum risk of minor complication is 1–100 per 1000. However, Freedman (1993) stated that such decisions should not be derived quantitatively but rather on a categorical basis, since risks associated with new experiences (rather than with what actually happens in everyday life) are, by definition, not fully known. We do not think that this analysis is applicable to therapeutic research where equipoise implies that the risks and benefits balance out in prospect.

More than minimum risk was also considered to be inappropriate for 'incompetent' patients in general (Ackermann, 1994; MRC, 1991; Prentice *et al.*, 1993).

Gillet (1994), Mariner (1990) and Tauer (1994) also discussed the level of risk acceptable for healthy volunteers where any trade-off between

medical benefits and risk is questionable, even when fully informed consent is obtained. Here, we are talking about non-therapeutic research in the sense that no clinical benefit is anticipated. However, it could be argued that altruism could be factored into the decision analysis, so that participation is not *ipso facto* irrational.

Bruera (1994) examined the ethical basis of research in palliative care where expected benefits are limited. Here, the maximum possible loss might be small whereas benefit could be long-lasting and hence large, but, despite this, he did not believe it ethical to impose greater than a 'minimum risk' because of the greater vulnerability of such patients. The reverse argument seems more plausible to us; that is, if there is so little to lose and so much to gain, a new intervention, even if risky and/or relatively untested, might seem attractive to a rational, but desperate, person.

Hammett and Dubler (1990) suggested that 'minimum' risk should be applied to research in prisons given the potential coercion implicit in the environment from the institution, while Lasagna (1970) supported research in general, given that participation may of itself be beneficial in breaking the monotony of prison life.

One article suggested that individual physicians have a duty to exclude individual patients if they are at risk from research and not rely **solely** on the eligibility criteria of the trial (Weijer and Fuks, 1994).

It seems to us that this discussion of acceptable level of risk is germane only to non-controlled studies (typically Phase 1 and 2 trials), but not to prospective comparative studies (typically Phase 3 trials), for example RCTs which are designed to compare two (or more) treatments or treatment with a placebo. Here, it is the balance of cost/benefit that is important. Considerable risks from a treatment are justified if considerable gains are equally likely in prospect – hence the need for decision analytic approach, at least to provide a theoretical underpinning to the debate. We believe this approach is applicable to both competent adults who can give consent and to more vulnerable groups whose proxies may give consent. At any rate, by the time a Phase 3 trial is approved, then the level of risk will have been set by preceding Phase 1 and 2 trials. (See also randomisation from the 'first' patient, on page 25.)

Patient equipoise. Once a trial has been sanctioned by an ethics committee on the basis of collective

equipoise, ten articles argued that the individual physician must also be in equipoise for an RCT to be ethical (Angell, 1984; Fried, 1974; Gehan and Freireich, 1974; Gore, 1994; Hellman and Hellman, 1991; Hill, 1963; Korn and Baumind, 1991; Lilford and Jackson, 1995; Peto *et al.*, 1976; Van der Linden, 1980).

Three references argued for a 'range of equivalence' from a statistical standpoint or 'equiphase' from a psychological perspective such that small preferences (within set limits) do not impact on the decision to offer trial entry (Freedman and Spiegelhalter, 1992; Freedman *et al.*, 1994; Chard and Lilford, 1998).

Four references raised the objection that equipoise could not account for individual patient preferences or utilities (Angell, 1984; Fried, 1974; Kennedy, 1988; Weinstein, 1974). However, 34 references explicitly included patient preferences within their concept of equipoise. Twenty-eight articles thought that this should take the form of utilities (as exemplified in decision analysis) resulting in 'effective equipoise' or the use of preference trials – where people choose treatment A, treatment B, or a trial of A versus B, but where outcomes are collected from all eligible patients (Baum, 1994; Botros, 1990; Bradley, 1993; Brewin and Bradley, 1989; Chard and Lilford, 1998; Dudley, 1986; Emrich and Sedrank, 1996; Ganz, 1989, 1990; Hilden and Habbema, 1990; Institute of Medical Ethics Working Party, 1992; Kadane, 1996; Kassirer, 1983; Katz, 1981; Lebacqz, 1983; Lebacqz and Levine, 1977; Lilford and Jackson, 1995; Lilford and Thornton, 1992; Oettinger and Berger, 1989; Schaffner, 1996; Silverman and Altman, 1996; Stirrat *et al.*, 1992; Sutherland *et al.*, 1994; Veatch, 1981; Weinstein, 1974; Wennberg, 1990; Williamson, 1996). However, one additional reference suggested that data from preference trials are uninterpretable (Kadane, 1996), because the people who accept randomisation may be systematically different from those to whom the result may be applied. Presumably this problem increases as the plausibility of a link between preference and outcome rises. We offer the observation that where this is plausible, 'feedback' trials or many trials (where preferences can change according to accumulating prior evidence), offer advantages because it is then possible to test the hypothesis that effect size is stable across the factors that may lead to expressed preference (or lack of preference).

Four references regarded informed consent as sufficient evidence of patient involvement in the decision-making process (Alderson, 1996;

Coulehan *et al.*, 1985; Curran, 1979; Miller and Appelgate, 1985).

When equipoise does not apply. Twenty-six articles were concerned with the ethics of conducting an RCT when the individual physician is not equipoised. Bartlett and Cornell (1991), Beecher (1966), Challah and Mays (1986), Freund (1970), Hill (1963), Lilford and Jackson (1995) and Markman (1992) thought that individual equipoise is not always a necessary condition for the ethicality of the RCT or, more specifically, in circumstances where a preferred experimental drug is restricted, i.e. available only within a trial. As Lilford and Jackson (1995) point out, this has intuitive appeal when resources are scarce. It may be inappropriate to ask individuals to be the principal gate-keepers of medical developments, thereby making it acceptable to restrict resources in this way – randomisation may thus act as a justifiable form of distributive justice. For example, there may be doubt as to whether or not putative benefits are sufficient to outweigh the societal costs of a new treatment, as in the ECMO trial. In such cases, an RCT may still be ethical, in spite of patient equipoise, if the central authority proscribes the new treatment outside a trial. Put another way, the RCT in these circumstances provides the best hope of getting the preferred therapy. (See also the risks associated with new therapies, on page 15.)

What should an individual clinician do when a preferred treatment is not restricted but when individual equipoise is seldom present? Gore (1995), Peto *et al.* (1976), Sposto and Krailo (1987) suggested that randomisation in unequal ratios might be ethically acceptable. The ratio is set at the start of the trial, in accordance with individual preferences, and remains constant throughout (even though preferences may not). Another method is the adaptive design which might start with the ratio 50:50 (on the basis of widespread equipoise), and then change according to any evolving treatment difference with accumulating data. This is said to minimise the tension between individual and collective ethics during the course of the trial. (See also page 17, on the legacy of Hippocrates, and group randomisation, below.) However, Lilford and Jackson (1995) argue that altering the randomisation ratio does not avoid reduced expected utilities for individual trial patients (see above).

Another idea to cope with different prior beliefs is the use of physician-centred randomisation (Korn and Baumind, 1991), especially in surgery (Rudicel and Esdaile, 1985; Van der Linden, 1980).

This technique involves assigning a treatment to the clinician, according to the clinician's preference. The patient's treating clinician is thus out of equipoise, though a third-party clinician who is in equipoise randomises and subsequently refers patients to the treating clinicians. However, this implies that allocation to treatment group takes place before the patient has seen a responsible surgeon/physician and this is rarely the case except in a healthcare system in which patients have no choice of where and by whom they are treated (Gross, 1993). Also, such a study may not answer the relevant scientific question, especially if surgeons using a new experimental technique are few and highly (self-) selected. (See also randomising the first patient, on page 25.)

Four articles examined the ethics of randomisation to units other than the individual patient or physician, i.e. cluster randomisation, and acknowledged that this may entail larger patient sample sizes (Fetter *et al.*, 1989; Kramer and Shapiro, 1984; Pocock, 1985; Pringle and Churchill, 1995). Randomisation of clusters is scientifically desirable when there is a risk of 'contamination' between arms of the trial. Pocock (1985) further discussed randomisation in unequal ratios to groups when standard treatment effects are well known or ethical concerns warrant more subjects receiving a new treatment (see above). Discussion in the literature surrounding the rationale for, and the ethical implications of, conducting cluster randomised trials is very thin on the ground and this has prompted further discussion elsewhere (Edwards *et al.*, in preparation), though we pursue it here in the discussion section.

n of 1 trials

There were 11 articles which examined *n of 1* trials, of which ten saw them as intrinsically ethical when there is doubt over the generalisability of results from large trials or when there are no data available (Eick and Kofoed, 1994; Guyatt and Jaeschke, 1990; Guyatt *et al.*, 1986, 1990; Jaeschke *et al.*, 1990, 1991; Johannessen, 1991; Johannessen *et al.*, 1991; Larson *et al.*, 1993; Spiegelhalter, 1988). The exception stated that the widespread use of *n of 1* trials could not be advocated as they are largely uncontrolled by ethics committees (Mahon *et al.*, 1995).

Placebo-controlled trials and alternative treatments

Eighteen references stipulated that there must be no better alternative outside a trial for equipoise to be valid, that is, so that the patient does not lose out, in prospect (Anderson and Baden, 1971; Block

and Elahoff, 1979; Brown, 1980; Byar, 1990; Cavan, 1981; Clarke, 1993; Cleophas, 1995; Coulehan *et al.*, 1985; Fetter *et al.*, 1989; Levine, 1985, 1991; Marquis, 1983; Mike, 1989b; Moore and Papp, 1996; Rothman, 1996; Rothman and Michels, 1994; Shaw and Chalmers, 1970; Spiro, 1986). This implies that placebos should be used only when there is no 'standard' effective treatment already available, notwithstanding arguments that 'absolute' efficacy from placebo-controlled trials is scientifically more valuable than 'relative' efficacy. Four references maintained that the placebo-controlled trial is ethical even in the face of existing therapies since it yields the most reliable data (Collier, 1995; Glasser *et al.*, 1991; Katz, 1981; Wilhelmsen, 1979), while another asserted that placebo-controlled trials are scientifically most valuable but argued that the problem of withholding (possible) effective treatment can be circumvented by the use of dose-response studies wherein the control patients are given a very low dose of the experimental treatment which is claimed to be tantamount to placebo in terms of effectiveness and side-effects (Freston, 1986). However, this argument is fallacious because, if a very low dose of a potentially effective treatment is, indeed, tantamount to receiving a placebo in terms of therapeutic benefit, then we are still guilty of withholding effective treatment (standard or otherwise), only this time we are withholding a dose sufficient to produce any benefit. We would argue that placebo-controlled trials are only more valuable scientifically (in that they would ask the relevant clinical question) if it subsequently transpired that the standard treatment is *de facto* worse than nothing at all. There is no intrinsic scientific reason why placebo-controlled trials should be more 'reliable', than trials of new versus standard.

Early stopping in relation to trial participants

Data accumulates during a trial and, if it favours one of the comparator treatments, then, at a certain point, it may be deemed inappropriate to continue randomising patients. There is a balance here between obligations to trial participants and society at large (see page 17, on the legacy of Hippocrates – the therapeutic obligation). When a trial is stopped 'early', the beneficial treatment may be made widely available, so that patients who would otherwise have been allocated to the trial control treatment would be provided with the superior therapy (Ruse, 1988). However, the result may be less persuasive than it would otherwise be since it is of a lower statistical precision. Other possible reasons for stopping early are: the existence of a harmful side-effect (Ashby and Machin, 1993; Berry, 1988; Bulpitt, 1983; Fleming and

Waterlet, 1989; Geller and Pocock, 1987; Goldman, 1987; Hughes, 1993b; Klimt and Canner, 1979; Ruse, 1988; Seibert and Clark, 1993; Sutton-Tyrrell *et al.*, 1991; Working Group on Arrhythmias of the European Society of Cardiology, 1994), or an improbability of achieving a conclusive outcome (Ashby and Machin, 1993; Klimt and Canner, 1979; Meier, 1979; Working Group on Arrhythmias of the European Society of Cardiology, 1994). While Fleming and Waterlet (1989) proposed that the same criteria for early stopping should be used for both positive and negative trials, Berry (1988) thought that asymmetrical stopping boundaries which pick up toxicity earlier than efficacy were more appropriate.

Censure of interim analysis

Twenty-nine articles acknowledged that equipoise might be dispelled during the course of the trial, should the results be made available, thereby losing the ethical basis for further recruitment. We point out that an individual physician, having lost his/her equipoise cannot then justify recruiting a fixed sample by claiming that he/she is still 'uncertain', where 'uncertainty' is defined as anything short of statistical significance from the RCT in question – this would make the definition of uncertainty a circular one. Such justification is only valid if, and only if, we endorse the premise that knowledge is dichotomised into certain or uncertain and that the only route to certain knowledge is via the RCT in which a clinician is engaged.

As a result, it is widely accepted that interim data should be censured. Indeed, 17 of the above articles urged for censure of preliminary results such that physicians would remain ignorant of the findings until the trial had stopped (Burkhardt and Kienle, 1978; Byar, 1990; Chalmers, 1991; Chalmers *et al.*, 1972; Clayton, 1982; Editorial, 1983; Geller and Pocock, 1987; Hellman, 1979; Marquis, 1983; Peto *et al.*, 1976; Pocock, 1977, 1989; Pollock, 1993; Prestifilippo, 1993; Royall, 1991; Shaw and Chalmers, 1970; Shimm and Spece, 1983). Eleven articles perceived a duty, on the part of the physician, to discover any information which might make a difference to his/her decision to recruit patients (Clayton, 1982; Freedman *et al.*, 1984; Freedman, 1987; Gifford, 1986, 1995; Hutton, 1995; Kadane, 1996; Kennedy, 1988; Lantos, 1994a; Mike *et al.*, 1993; Schaffner, 1996), but we point out that this implies that the physician is free to seek out such information as may be available – it would exclude results revealed only to a DMC. Schafer (1985) suggested that patients could consent to having preliminary evidence withheld from them. However, we point out that 'voluntary ignorance'

draws on Gerald Dworkin's work where 'consent' would become an autonomous expression of a second-order preference and this overrides a less important first-order preference (to obtain all details about the intervention before making a decision). However, in this context, the patient could only be said to 'assent', not consent, to ignorance of preliminary data, for open disclosure (in Dworkin's language, the first-order preference) is not an option (unless the trial design is a 'feedback' one). The only choice to be had for the patient is to enter a trial on the understanding that preliminary information will be withheld or to refuse entry altogether.

Another option is to conduct a 'feedback' trial where preliminary data (though not treatment assignment) is disclosed (or a series of small fixed-size trials) and hope that, while some individual clinician-patient pairs are moving out of equipoise (as a consequence of seeing the results to date), others will move into equipoise (Lilford and Jackson, 1995). That said, feedback trials may be problematic if recruitment is thwarted by their use.

Randomisation from the 'first' patient

Seven articles insisted that the 'first patient' should be randomised in order to exploit the 'window of opportunity' where equipoise applies (Chalmers, 1968, 1975a, 1976, 1982; Chalmers *et al.*, 1972; Boissel, 1989; Ingelfinger, 1972). On the other hand, nine articles saw some preliminary evidence as necessary to test the feasibility of, and provide the rationale for, a large trial (Cowan, 1981; Freireich and Gehan, 1979; Hollenberg *et al.*, 1980; Levine, 1991; Schafer, 1985; Spicker *et al.*, 1988; Steinberg, 1991) or thought that randomising the first patient was not feasible due to the number of experimental treatments being offered (Feinstein, 1973) or because the first patient is difficult to define (Schafer, 1985). Twelve articles were concerned that the evolutionary nature of a new operation was incompatible with randomising the first patient because self-perception of skill is an important factor in determining equipoise (Anderson, 1980; Bonchek, 1979; Brown, 1980; Byar, 1983; Gross, 1993; Leading article, 1985; Neugebauer *et al.*, 1991; Pollock, 1993; Rudicel and Esdaile, 1985; Shinebourne, 1984; Stirrat *et al.*, 1992; Takaro *et al.*, 1976), while two references thought that the 'learning curve' could be incorporated into the RCT (Report to the Health Services and Public Health Review Board, 1993; Spodick, 1982) or that higher quality informed consent is appropriate during the early days of such trials. (See also page 23, when equipoise does not apply.)

Discussion

This review of the literature on the ethics of conducting RCTs has provided a summary of the various arguments and assertions surrounding the issue of uncertainty as justification for trials. We can see that, once put into context, some arguments are unsustainable while others generate healthy controversy. We have tried to provide a concise account of the topic, but have elucidated points where appropriate.

Moral theory and RCTs

The RCT is not always scientifically necessary or even desirable, but is most useful when expected treatment effects are small, yet worthwhile, due to its unique capacity to minimise potential bias. A common criticism, however, is that any RCT rests exclusively on utilitarian justification and is blind to the interests of current patients who participate in them as a result. However, utilitarianism is not the only theory from which RCTs can be defended. Kantians recognise that individuals have duties to society. Inviting individuals to make sacrifices from good motives need not be exploitative. The usual reaction against patients being 'used' is that they are **invited** to participate and enrolled only with **informed consent**. Hence Kantians should have no difficulty with the ethics of RCTs as such. But RCTs using proxies to consent are another matter, unless the proxy has been chosen by the patient.

Uncertainty as justification

In this context, 'equipoise' is more meaningful than uncertainty (Lilford and Jackson, 1995). 'Uncertainty' is ambiguous in two respects: firstly, knowledge comes in degrees and therefore uncertainty, used as the opposite of certainty in common parlance, includes many possibilities (a concept represented mathematically by a probability distribution); secondly, in circumstances where a known side-effect of treatment must be traded-off against possible benefits, uncertainty may relate, not only to the prior probabilities of the benefits, but also to how they are valued. Uncertainty therefore means different things depending on context and its use amounts to, what philosophers call, equivocation. Equipoise, on the other hand, implies that expected size and probability of improvement balance the size and probability of side-effects (perceived risks) of comparator treatments; in decision analytic language, the expected utilities of the comparator treatments are equal and the participant does not lose out in prospect. It has been argued that, while equipoise has a precise and unambiguous logical meaning, the concept is elusive in practice since its measurement is inevitably imprecise. However, it is our

opinion that it provides a clear goal to aim at in contrast to the ambiguous term ‘uncertainty’. Indeed, it has been proposed that, psychologically, though not mathematically speaking, we function on the basis of categories rather than points such that it would be ethical to recruit a patient on the basis of ‘equiphase’ (Chard and Lilford, 1998); that is, where the decision is robust to small changes in expected utilities. We would argue that a doctor would be happy to be randomised him/herself.

Further argument concerns the moral significance of different types of equipoise – collective and individual. Freedman (1987) has argued that equipoise among relevant clinicians (collective equipoise) is sufficient to make a trial ethical, even if the individual clinician has a preference. Others point out that patients may wish to know what their care-giver thinks or to make up their own mind on the basis of such evidence as may be available. In the usual situation where trade-offs are concerned (see above), equipoise turns on values as much as prior probabilities, and so it cannot be determined outside the consulting room. Equipoise is primarily a property of the (competent) patient, rather than of the doctor. As individual (patient) equipoise is the ethical basis of most trials, the invitation to participate (informed consent procedure) is therefore critical – see below.

One can speak meaningfully of collective equipoise only in a situation of probabilistic dominance (i.e. a treatment has no side-effects), because the only valued outcome of relevance is that which is being measured in the trial, for example if more lives are saved with treatment A, it is to B and vice versa. In the perhaps more usual situation where more than one outcome is at stake and where some knowledge about the effect of treatment (i.e. where side-effects are involved), we argue that it is not meaningful to speak of collective equipoise, unless the patients are not ‘competent’ and an ‘average’ value set must be assumed. As soon as more values come into the frame (and the patients are **competent**), it is reasonable to think in terms of collective prior belief about probability, but not collective **equipoise** for the latter would assume that we know the patient’s values even before she has been asked. The notions of collective equipoise/prior belief throw up two interesting issues which we discuss with reference to the literature: (1) what to do if the ‘vote’ is not split 50:50, but 80:20, say. We discuss the single paper which has sought public opinion on how much ‘expert’ consensus is needed to make a trial ethical from the point of view of an ethics committee, and (2)

whether a clinician should be bound by individual or collective equipoise. Once the premises are accepted that (a) equipoise is morally important, and (b) equipoise turns not just on probabilities, but individual values as well, and (c) values are likely to vary from patient to patient, the issue becomes one of whose prior probabilistic belief should be disclosed. This question can be deconstructed into whether a clinician should give a personal prior probability estimate, a corporate prior probability one, or both, though we recognise that corporate beliefs are seldom measured and might fluctuate in any case.

Under-powered trials

Recognition of the central role of equipoise has some radical implications. Firstly, if equipoise is accepted as the moral basis for trials, then ‘under-powered’ trials are not necessarily unethical in their ‘use of subjects’, although they may offer poor value for transferable resources. Detailed discussion on this topic can be found elsewhere (Edwards *et al.*, 1997).

Deciding when to stop

Just as there are moral complications associated with recruiting too few patients in under-powered trials, so there are with recruiting too many. Some trials are approved simply in the hope of persuading practitioners to take up ‘proven’ effective treatments on the basis of greater statistical precision. However, in the case of ISIS-2, previous results had not even been published in standard texts, thereby cultivating a culture of ignorance (Altman and Gardner, 1992). While emphasis must be placed on dissemination and education through collaborative effort (e.g. Cochrane Collaboration and York Centre for Reviews and Dissemination), there remains the problem of when investigators should stop a trial. Beneficial treatments need to be made widely available as soon as possible and it could be argued that trials should be stopped at the earliest opportunity even before the ‘full’ sample has been accrued. Trials might be stopped for other reasons such as evidence of toxicity or a prediction that a conclusive result will not be forthcoming. The question of when to stop a trial gives birth to a number of other questions, for example deciding which stopping rules should be used, and if and how external data should be incorporated. A fundamental problem remains however: any trial has the potential to destroy the equipoise that it relies on to be ethical. Furthermore, enthusiasm to stop trials early must be tempered by an awareness that the medical community may remain unconvinced in light of potentially misleading data and may call

for replication if equipoise persists. Commonly, it is the DMC that must decide if and when to halt (or at least recommend halting) recruitment. Referring physicians are kept ignorant of any preliminary data as they are bound by the therapeutic obligation, whereas the DMC is at liberty to take account of societal interests in addition without violating any obligations to the individual participant. However, it could be argued that this solution is too contrived and that simply pretending that data do not exist in order to maintain equipoise may only be acceptable if there is no better alternative, that is, if it is the least worst option. 'Feedback' trials (where preliminary data, though not treatment assignment, is disclosed) are one such alternative, but there has been little practical experience with these hitherto. Indeed, many see the *prima facie* advantages of another design, called 'adaptive' designs, according to which the ratio of randomisation changes during the course of the trial along with how the preliminary results look. However, adaptive designs are not a perfect solution to the problem since they do not necessarily maximise individual expected utility – this would be achieved simply by opting for the therapy showing the most promise of the moment. Controversially, we favour feedback trials because: (1) we do not think that it is fair either on DMC members or the public to weigh societal interests against those of future potential participants behind closed doors and (2) it is inappropriate to dichotomise the decision to continue or terminate the trial. Again, the decision is **personal**, as it turns on individual values and how those interact with probabilities (Thornton and Lilford, 1996). Consequently, people with a value system that may have made them ineligible for trial entry at the outset may wish to participate on the basis of interim data and vice versa.

Placebo-controlled trials

It is unethical to conduct placebo-controlled trials in the face of a known advantageous treatment (Rothman, 1987), because equipoise cannot be present. We would argue that this only applies for treatments that would otherwise be freely available. If a technology were not generally available, say because the local health service does not have enough money, then randomisation may offer the best opportunity to get the preferred therapy. There is still the issue, however, of what to do once the trial has come to term. A particular issue arises when a trial is funded from a richer country to be hosted by a poorer one. Here, the above logic holds good, with the proviso that investigators ensure such research is not perceived as exploitation (see below).

Replication

It is important that the research question has not already been answered and ethics committees should avail themselves of a relevant systematic review to ensure that the protocol in question is sufficiently original. Research that has been carried out before may not be interesting even scientifically, though conversely some would argue for repeated attempts at refuting hypotheses in the Popperian tradition. By using Bayesian statistics, however, issues of repetition only arise where there is some doubt over a previous result.

The null hypothesis

The null hypothesis would seem a poor basis for statistical tests in (the frequent) circumstances where trade-offs must be made due to side-effects or 'costs'. Under these circumstances, participants in the trial would have had prior expectation of benefit sufficient to compensate for the expected costs, if they were entered ethically. The most interesting hypothesis is therefore whether or not the data are compatible with this expected benefit – the null hypothesis is not then the default position.

Informed consent

The invitation to participate, or (informed) consent, is fundamental to the ethics of conducting trials. Numerous authors point out that, for consent to be valid, it must be competent, voluntary (not only technically but also in spirit), and all relevant information must be divulged. The requirement that consent be informed applies to research subjects, but not whenever consent is sought, say in routine practice. This tradition runs counter to the Hippocratic one which is essentially paternalistic. Paternalistic choices are ones that override otherwise autonomous decisions (whether or not information is disclosed), whereas a proxy decision is made in the absence of competence. However, it is now widely accepted that a (competent) person is in the best position to know where his/her personal best interests lie and, in any case, that his/her autonomy should be respected. Since patient equipoise turns on personal values, its presence or absence can only be determined through detailed discussion. Some authors add that clinical investigators have a **potential** conflict of interests (between the individual and society) and, by eliciting the patient's own values, the risk of this becoming a real conflict is minimised – 'full' disclosure acts as a safeguard against overzealous scientists. Many authors have argued that the goal of disclosing all relevant information is imperfectly realised in practice, but we still have to decide what ought to be done. There are nevertheless many

situations where it may be argued that the goal of full disclosure should be relaxed.

When consent cannot be obtained. One such special circumstance arises when the potential participant is not competent because he/she is unconscious due to cognitive impairment. In these circumstances, a surrogate (patient, partner, etc.) is the best source of values for we might (or insofar as we might) reasonably assume parity of interests and he/she may have insight into what the patient would have wanted to boot. The patient is not thereby excluded from the opportunity to help others. However, in the absence of a surrogate or in an emergency, some have argued that randomisation should be avoided (Kapp, 1994), notwithstanding the large societal costs of doing so. Others, including the MRC, the Royal College of Physicians, and the FDA, have argued that, since normal practice must proceed on the basis of 'assumed' preferences (i.e. those of the 'average' patient) or 'implied consent', randomisation may be ethical, but only if clinicians are equipoised with respect to their best guess as to where the patient's best interests lie. In some cases, it is possible to elicit consent in advance of a situation which may arise some time in the future. For example, a pregnant woman may give consent for scenarios that may arise in labour or the early neonatal period. In addition, the presence of a proxy may serve as a further safeguard.

Cluster RCTs and consent. The best interests of the individual may be served by trial participation even in the absence of competent consent where the unit of randomisation is the group, for example, a school or general practice, instead of the individual. If the intervention is likely to be considered risky by the community, it may be appropriate to widen such surrogate consent. A decision not to seek individual consent may also be taken for logistical reasons when an intervention is delivered to a defined community or geographic area. In such circumstances, a surrogate in the form of a cluster 'guardian' (a head teacher or general practitioner) is responsible for determining what is in the best interests of the group and can consent to participation and randomisation. Not all cluster trials preclude individual consent to the intervention in question – we distinguish between trials conducted out of pragmatically necessary (for example, fluoridation of water) and those conducted for scientific reasons (for example, to avoid contamination) where the unit of randomisation is the cluster, yet the intervention is implemented at the level of the individual. The latter category includes many educational interventions where

consent typically would only be elicited from individuals in the intervention group.

Behavioural interventions and consent. The goal of full disclosure may sometimes undermine the objective of a trial, whether randomised at the level of the individual or cluster. When participants cannot be blinded, knowledge of the treatment comparison can introduce bias through differential changes in the behaviour or attitudes of the treatment groups. This situation often occurs with education interventions which are typically evaluated by clusters to avoid the aforementioned problem of contamination. Knowledge of the intervention amongst control subjects can lead them to seek the intervention outside the trial, reducing the difference observed between groups, or resulting in demoralisation, which is likely to depress outcomes for the controls and result in an exaggerated difference between groups. A randomised consent design can be used in these situations, although it has been criticised. Here, randomisation is carried out prior to seeking consent and consent is usually sought only for the treatment to which an individual is allocated, that is, without disclosing the treatment comparison. Another alternative is to elicit consent to take part as a control without fully divulging the nature of the intervention.

Can consent be needlessly cruel? A somewhat different situation arises when it is the fear of causing distress, rather than logistics which may inhibit free disclosure. Indeed, on occasion, there may be a trade-off between beneficence and autonomy (see below). In the West, the obligation to respect autonomy is afforded paramount importance and doctors are increasingly opting for 'full' disclosure on the grounds that patients cannot choose between options without knowing what these entail. It has been cogently argued by Dworkin (1988), however, that the option to relegate the decision remains a valid one; that is, the patient may ask the doctor to choose on his/her behalf.

Where equipoise need not apply

There may be circumstances where equipoise need not apply for a trial to be ethical. When a preferred experimental treatment is restricted and is only available within a trial, then the only route to the preferred treatment is through randomisation. This is intuitively appealing when resources are scarce, but not when access is not limited by a central authority. Of course, there are wider issues concerning distributive justice and, given a specific healthcare need, randomisation may indeed be a

fair form of triage. Even without resource limitations, it may be inappropriate to ask individual practitioners to be the principal gate-keepers of medical innovations and it may therefore be ethical for a central authority to proscribe the use of new treatments outside a trial, pending a license or a legal purchasing decision. In this way, the decision about which treatment is 'best' can be hedged, given the existence of collective equipoise, and the narrow window of opportunity can thus be exploited.

However, some have argued that in some cases, it is unethical to restrict potentially life-saving treatments to trials when there is no effective standard (Minogue *et al.*, 1995). The ECMO and AIDS trials are examples thereof. Minogue *et al.* (1995) and Truog (1992) argue that randomisation is unethical, in such cases, and that observational studies are desirable. Another option would be to use the Zelen design, and so avoid potential distress to controls, though this is highly controversial; anticipation of distress was the rationale for using this design in the Harvard ECMO trial, but the hospital's Institutional Review Board (IRB) received a rare reprimand from the National Institutes of Health (Truog, 1992). Such distress was, indeed, demonstrated among controls in a later British trial where pre-randomisation consent was obtained, but where availability of ECMO was restricted to the treatment group (Snowdon *et al.*, 1997). Others argue for the implementation of preference trials in which patients receive their treatment of choice (see patient equipoise, page 22), though the data from such trials may be difficult to interpret (Kadane, 1996). Indeed, It could be argued that patients have a 'consumer' right to use whatever therapy they like (regardless of whether or not they can pay for it). However, not all demands could be met and resource distribution, in one form or another, is an inevitable part of health care. Indeed, Logue and Wear (1995) has argued that restricting strongly preferred treatments to trials does not impinge on a patient's autonomy, since it merely limits the options open to the patient and is not coercive as a result.

Compensation

At the moment, for a research patient to gain compensation for some injury due to participation in a trial, he/she will have to bring an action in negligence. We believe that informed consent to receive potentially dangerous therapies without the promise of compensation in the event of injury may take away any obligation on society to compensate. However, as a mark of respect, it could be argued that patients should be offered the results of the

trial when published and regulatory checks on the trial process should be made throughout.

Conclusion

We conclude from the above that patient equipoise is a necessary basis for the ethical conduct of RCTs and, as equipoise should include patient's values, it can only be determined through detailed discussion. In this way, practitioners might respect a patient's autonomy in the spirit of Kantian ethics. That said, there are situations where informed consent should be relaxed, though in cases of incompetence a proxy should be consulted. Patient equipoise should not be seen as the only safeguard however, and is no substitute for ethics committee approval.

What are the physical effects of participating in trials?

Results

Type of non-trial control

Thirteen of the 15 studies used non-randomised concurrent controls. The exceptions used randomised concurrent controls (Mahon *et al.*, 1996) or historical control data from disease registers (Reiser and Warner, 1985). Of those studies using concurrent non-trial controls, one study, Mahon *et al.* (1996), was actually a randomised trial of doing or not doing n of 1 randomised trials, and was, therefore, fundamentally different. Three studies used patients who had been offered trial entry but who had denied consent (Antman, 1983; CASS Principal Investigators and their Associates, 1984; Schmoor *et al.*, 1996), while the remainder obtained non-trial controls who had not been offered trial entry. One study compared (mainly) trial and concurrent and historical non-trial patients by district of residence (Karjalainen and Palva, 1989).

Type of therapy

Ten articles involved cancer therapy and examined the effect of trial entry on survival/disease-free survival (Antman *et al.*, 1983; Bertelsen, 1991; Davis *et al.*, 1985; Karjalainen and Palva, 1989; Lennox *et al.*, 1979; MRC Working Group on Leukaemia in Childhood, 1971; Schmoor *et al.*, 1996; Stiller and Draper, 1989; Stiller and Eatock, 1994; Ward *et al.*, 1992), of which four (Lennox *et al.*, 1979; MRC Working Group on Leukaemia in Childhood, 1971; Stiller and Draper, 1989; Stiller and Eatock, 1994) involved childhood cancer. Two articles addressed the effect of clinical trials on survival from cardiovascular disease: the CASS Principal Investigators and their Associates (1984) and Jha *et al.* (1996).

Two studies, Mahon *et al.* (1996) and Reiser and Warner (1985), examined the effect of respiratory clinical trials on morbidity. One study was concerned with post-operative care (Williford *et al.*, 1993). Thus, 12 of the 15 studies examined effects on survival.

Methods and interobserver agreement

The list of authors, outcome measures, description of non-trial controls, main results and whether or not an attempt was made to measure and allow for any difference in prognostic variables are summarised in *Tables 2a* and *2b*. The studies were also tabulated according to quality of evidence (see *Tables 2a* and *2b*). There were two cases when the observers (SE and JT) disagreed on an extracted data item, but both instances were resolved by re-scrutinising the original papers. One study was rejected by JT on the grounds that the n of 1 trial itself was an intervention (Mahon *et al.*, 1996); it was included in the results tables for completeness, but was excluded from the graph. Data sets from these studies were then categorised (see *Table 4a*) and listed (see *Table 4b*) by DAB with a view to plotting the HRs for individual trials and strata within studies.

Survival as outcome

In seven of the 12 studies addressing survival, survival was reported as being statistically significantly higher among trial participants than among non-trial controls (Davis *et al.*, 1985; Lennox *et al.*, 1979; MRC Working Group on Leukaemia in Childhood, 1971; Stiller and Draper, 1989; Stiller and Eatock, 1994; Jha *et al.*, 1996; Karjalainen and Palva, 1989). Three of the five studies where the result failed to reach statistical significance nevertheless reported a favourable trend in association with trial entry (Antman, 1983; Schmoor *et al.*, 1996; Ward *et al.*, 1992), while the remainder did not find any noteworthy difference (Bertelsen, 1991; CASS Principal Investigators and their Associates, 1984).

Morbidity as outcome

Morbidity was included as an outcome measure in three studies. In two studies, there was a significantly better outcome (statistically speaking) among trial participants than among non-trial controls (Mahon *et al.*, 1996; Williford *et al.*, 1993). The other study, Reiser and Warner (1985), showed an improvement in symptoms for patients both in the treatment and control arms of the three asthma trials. The authors claim that this exceeded that which would be expected outside the trial context according to the natural history of the disease but had no formal non-trial control group.

Prognostic variables

One study conducted a randomised trial of a n of 1 trial, in other words, they randomised patients to take part, or not in an n of 1 trial (Mahon *et al.*, 1996). With this exception, the others cohorts of trial and non-trial patients (and could therefore have been confirmed by systematic differences between people who were entered into trials and those who were not). Five of these studies compared trial patients with non-trial patients who had similar prognoses to those in the trial (Bertelsen, 1991; CASS Principal Investigators and their Associates, 1984; Schmoor *et al.*, 1996; Ward *et al.*, 1992), while Davis *et al.* (1985), Jha *et al.* (1996), Lennox *et al.* (1979), MRC Working Group on Leukaemia in Childhood (1971), Stiller and Draper (1989), and Stiller and Eatock (1994) all attempted to make statistical allowance for such confounders, and, in each case apart from two (MRC Working Group on Leukaemia in Childhood, 1971; Schmoor *et al.*, 1996), the original significant differences were maintained after appropriate adjustment had been made. Indeed, in the trial reported by Lennox *et al.* (1979), the difference in survival was even more pronounced after making this adjustment. In one study, the original statistically significant difference disappeared after adjustment (Williford *et al.*, 1993). Two studies simply failed to make a suitable adjustment for a known prognostic imbalance between the trial and non-trial groups (Antman, 1983; Williford *et al.*, 1993), while the remainder could not comment on the distribution of prognostic factors because of the informal nature of the non-trial control group (Reiser and Warner, 1985) or because survival rates were not compared on a case-by-case basis – a district with a high recruitment rate to clinical trials was simply compared with a control district (Karjalainen and Palva, 1989).

Trial effects

In order to make possible a visual comparison of the various studies (*Figure 3*), we have extracted estimates, or data, from the published papers, where possible. We have used published estimates and confidence intervals, or data, corresponding to the most adjusted comparison reported by the authors, but this has not been possible in all cases (see *Table 4b*). Three of the 15 studies were excluded from the graph because the authors had not performed appropriate statistical adjustment for known prognostic imbalances (Antman, 1983; Reiser and Warner, 1985; Williford *et al.*, 1993) and one because the trial itself was an intervention – an n of 1 trial (Mahon, 1996). For Davis *et al.* (1985), the HR (though reported as ‘RR’) and 95% confidence interval reported by the authors

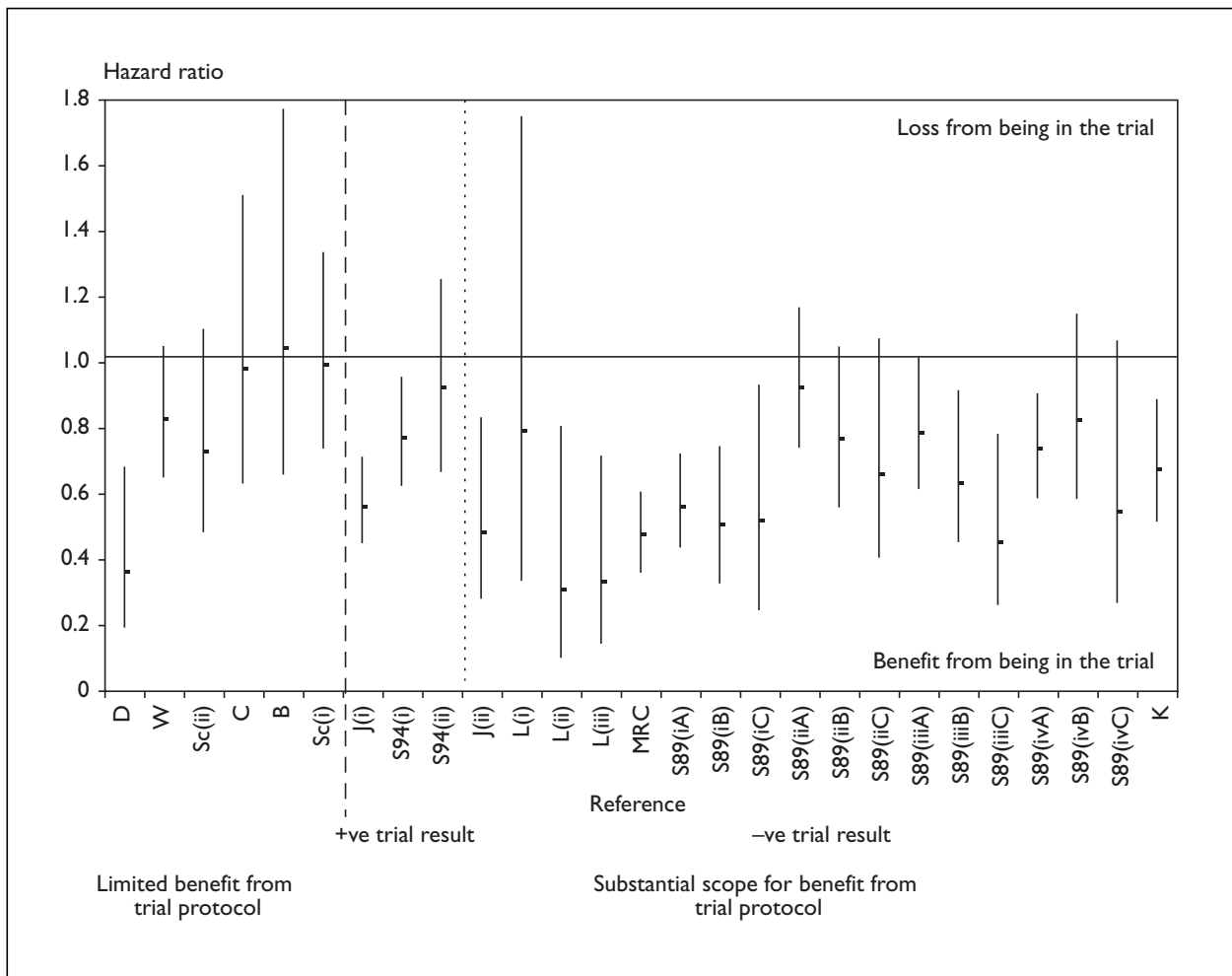


FIGURE 3 Median HRs (95% confidence intervals). The figure is discussed in full in the main text. It shows, with some exceptions, Bayesian credible intervals for the HR comparing those in a trial with those not in a trial. Keys to the labels are given in Table 4b. For all the intervals plotted, a ratio of less than 1 means an advantage to those in trials

from a Cox regression has been plotted, while Jha *et al.* (1996) reported ORs (and 95% confidence intervals), and we have been plotted those. In both these cases, the estimates and intervals can be interpreted essentially in the same way as the Bayesian intervals described below. For the remaining studies, relevant estimates and confidence intervals were not given, so we have had to ‘extract’ the numbers of patients at risk, and the number (or proportion) who survived etc (i.e. have not failed, in statistical terms) for some exposure period. Where data were available for a variety of periods, a period with minimal loss to follow up and a failure probability of as close to 0.5 as possible was selected. In many cases these numbers were estimated, for example by measuring from published Kaplan–Meier survival curves. These numbers can be used to estimate ORs, risk ratios (RRs), absolute risk differences, or HRs. The latter seem to us to be more basic – more likely to be stable – than the other measures. For instance, an

HR that is stable over time will not lead to the OR or RR being stable over time. This is relevant here as we are comparing studies with very different probabilities of failure. Nevertheless, plotting a graph of ORs or RRs should lead to similar broad conclusions.

Making the assumption that during the period of risk the instantaneous hazards are proportional and fairly constant, it is easily shown that the HR is equal to the ratio of the logs of the proportions P not failing, that is,

$$HR = \frac{\ln(P \setminus \text{in trial})}{\ln(P \setminus \text{not in trial})}$$

We have used the (Bayesian) software package BUGS (Gilks *et al.*, 1994) to estimate 95% credible intervals (CIs) for the HRs – which are plotted in Figure 3. There is a 95% chance that the true HR lies in the CI, given the modelling and prior assumptions. We assumed independent uniform

priors on the proportions failing – though (limited) sensitivity analyses suggest the results do not depend strongly on the priors used. For Karjalainen and Palva (1989) we have plotted a (Bayesian) estimate and CI for the ratio of HRs (for trial versus non-trial areas), during and preceding the trials.

For all the intervals plotted, a ratio of less than 1 means an advantage to those in trials. To attempt to draw useful conclusions as to when a trial is likely to prove beneficial, we have categorised each data set plotted according to four criteria:

- Was there included in the trial protocol a pre-existing treatment already known (or presumed) to be effective?
- Was the impact of differences in the treatments, and/or regimens, between trial/non-trial patients possibly large (or very probably small)?
- Did the trial show no advantage for the ‘experimental’ (or ‘new’) treatment (if applicable)?
- Was there large scope for bias due to unadjusted differences in prognostic factors between trial and non-trial groups? (Notes: (1) if the scope for bias was thought **very** large, the data set has not been plotted in the figure; (2) in the remainder of this section, bias is used in this sense of unadjusted differences in prognostic factors between trial and non-trial groups.)

These inevitably somewhat subjective judgements were made before any systematic data ‘extraction’ or plotting. Although subjective, we believe it succeeds in making useful distinctions between data sets. For example, if trials have their putative beneficial effect through better quality of care, then a difference in outcome is only likely to arise when an effective treatment is available. The categories are set out in *Table 4a*, and given together with other relevant information relating to each data set in *Table 4b*, which also includes the ‘key’ to *Figure 3*. *Table 4c* contains all the data plotted in *Figure 3*, as well as the data extracted from the studies.

The data sets in *Figure 3* have been ordered according to the four criteria given above. The dashed vertical line divides data sets (to the left) with apparently limited possibility of extra benefit to trial patients arising from the trial protocol, from the remainder (to the right). Within the data sets with potential protocol benefits to the trial participants, the dotted line separates those with positive trial results (the three to the left) from the remainder with ‘statistically’ negative trial results.

Thus, D and W (see *Table 4b* or *4c* for the key) have been judged to have no prior effective treatment in the protocol, whereas those from Sc(ii) onwards do. Sc(ii), C and, to a lesser extent, B and Sc(i), are judged very likely to have only small differences in outcome caused by differences in treatments or regimens between trial and non-trial groups. By chance, all the data sets from D to Sc(i) had no significant trial effect, and were thought by DAB to be only moderately subject to bias.

A priori, one might hypothesise that data sets such as D–Sc(i) would show little or no difference in benefit between trial and non-trial patients – and this is broadly the picture, with the clear exception of D. To us, the findings in D are sufficiently surprising to warrant being labelled an outlier. Although the authors have apparently adjusted in their analysis for all relevant factors, it is possible to think of possible remaining prognostic biases (albeit on a *post hoc* basis). It is also possible, as is true for data set W (personal communication), that the surgery, performed before randomisation, was nevertheless performed in the knowledge that a particular patient was likely or not to be randomised. This might conceivably have affected the surgery, benefiting trial patients. Perhaps the most likely explanation is a form of publication bias – the authors were only prompted to undertake the trial/non-trial survival comparison **after** noticing the remarkably good trial survival rate.

Data sets J(i), S94(i) and S94(ii) all had significant trial results in favour of the experimental treatment. The S94 data sets were thought possibly subject to large biases. One might expect to see some benefit to trial participants in these trials, if only from the beneficial new treatment. The remaining data sets J(ii)–K all showed no ‘statistically significant’ advantage to the experimental treatment (where applicable), though J(ii) had a strong trend in that direction. J(ii)–L(iii) were judged moderately subject to bias, while MRC–K were thought possibly subject to large biases. These data sets are all ones in which one might expect some benefit to trial participants arising from the development and use of a protocol for trial patients for **pre-existing effective treatments**. Broadly, it seems that there is benefit to trial participants under these conditions. Data sets S89(iA)–S89(ivC) come from the same paper (Stiller, 1989), and are potentially subject to large biases. However, any biases might be expected to be similar for all the S89 data sets. S89(i.) refers to the period 1971–1973, similarly ii, iii and iv refer to later periods. S89(.A) refers to patients treated in

hospitals treating six or more acute lymphoblastic leukaemia (ALL) patients per year, similarly B and C to those treating 1–6, and < 1 ALL patients per year. Hospitals treating many ALL patients are probably more likely to have and use up to date protocols for all ALL patients, not just those in trials. The benefit of being in a trial in an ‘A’ hospital might therefore be expected to be less than that in a ‘B’ hospital. In fact, one would expect to see a trend of increasing benefit from ‘A’ to ‘B’ to ‘C’ hospitals within each period. This is clearly seen here by visual inspection (and was, of course, noted by Stiller (1989)).

Drawing firm, general, conclusions from *Figure 3* would be ill-advised, as the trials studied are not a random sample of trials, may be subject to considerable ‘publication’ bias, and the ‘data extraction’ and categorisation processes were far from perfect (though the best that could be achieved with the resources available). We did not produce an overall estimate of effect, or conduct a quantitative ‘sensitivity’ analysis because, in our view, the data were not of high enough quality to warrant such precision. Nevertheless, we feel that *Figure 3* lends some support to the already plausible hypothesis that RCTs tend to be good for you if there is a pre-existing effective treatment that is included in the trial protocol, or if it turns out that the experimental treatment is more effective.

Outcome in trial control versus non-trial control patients

Three studies (CASS Principal Investigators and their Associates, 1984; Schmoor *et al.*, 1996; Reiser and Warner, 1985), further subdivided outcome among trial patients, so the control arm in the trial itself could be compared to non-trial patients. Two of the three studies did not find any significant difference between the two groups (who received similar treatments) in terms of actuarial and 5 year disease-free survival (CASS Principal Investigators and their Associates (1984) and Schmoor *et al.* (1996), respectively). The remaining study simply inferred that the trial controls receiving a placebo did better in terms of morbidity than non-trial patients (Reiser and Warner, 1985). Four studies (Davis *et al.*, 1985; Ward *et al.*, 1992) reported no evidence of treatment difference for the clinical trials themselves, i.e. outcome for trial controls was not significantly different from that of the ‘experimentally’ treated patients or that the experimental treatment was less effective than the standard (Karjalainen and Palva, 1989; Stiller and Draper, 1989). Four studies showed a non-significant treatment advantage for one of the treatments in a trial (Bertelsen, 1991; Jha *et al.*, 1996; Lennox

et al., 1979; Stiller and Eatock, 1994). The trial results in one study were statistically significant which suggests that the significant difference which they observed between trial and non-trial patients could be partially attributed to the superior experimental treatment (Jha *et al.*, 1996). The remaining studies did not supply data which might make possible a comparison between the outcomes of trial versus non-trial control patients (Antman, 1983; Williford *et al.*, 1993).

Excluded study of some relevance

In addition to the 13 studies which set out to investigate a possible trial effect for randomised/non-randomised patients, there was another paper (Olschewski *et al.*, 1992) which did not seek to establish a ‘trial effect’, although it did provide some information on the survival of trial participants (Coronary Artery Surgery Study) and similar non-trial patients. They merely reported that there was no significant difference in survival between trial and non-trial patients.

Discussion

Possible bias

The comparison of physical outcome in clinical trials, compared to that of non-trial cases, is potentially confounded in many ways which could lead to a spurious ‘trial effect’.

The study of Reiser and Warner (1985), which did not use a control group running concurrently with the trial, could be confounded by a trend with time in the condition of the children selected for the trial – perhaps seasonal or due to regression to the mean. Considerable bias is a risk with all historical control studies (Sacks *et al.*, 1982).

However, the use of concurrent controls (as in the remaining 14 studies) does not protect the analysis from all possible biases. The underlying assumption behind the use of concurrent controls is that the prognosis for the control patients is not systematically different from those in the study group, that is, those included in the trial. However, there are important prognostic variables which may distribute themselves unequally between non-trial and trial patients, leading to a biased comparison. Put another way, participants may tend to be healthier than their non-trial counterparts and so have a better prognosis. Eleven studies made an attempt to adjust statistically for this potential bias, to a greater or lesser extent, or observed that the trial and non-trial groups were similar in important respects. Even when formal statistical adjustment is carried out (six studies) or when the comparator groups appear similar (five studies), important

biasing factors affecting outcome may remain, since it is not possible to record or measure all relevant variables and hence account for them in the analysis. Those who carry out randomised trials and proselytise their advantages would be the first to concede that non-randomised concurrent controls are subject to bias, even after carrying out multivariate or other statistical analyses to allow for confounding variables. As a result, it is now widely accepted that randomised clinical trials are epistemologically superior to both historical and non-randomised concurrent designs.

Where non-trial controls who were not offered trial entry are used, patients who refuse to participate should be followed along with those consenting to trial entry. This is because refusers may have a different prognosis to acceptors, thereby biasing the comparison with those not offered trial entry. Analysis should ideally be both by the offer of entry (i.e. by 'intention') and by whether or not the patient participated. However, in four studies, the only control group was made up of people who denied consent (Antman, 1983; CASS Principal Investigators and their Associates, 1984; Schmoor *et al.*, 1996; Williford *et al.*, 1993) and, in the remainder, no attempt was made to differentiate refusers from consenters among those offered trial entry.

In light of the methods used, we must not be overzealous when interpreting the data and the only way to resolve this issue completely would be to randomise sufficient people to take part in clinical trials or to receive non-trial treatment, as in the study of Mahon *et al.* (1996), who randomised patients to n of 1 trials or standard practice and observed their comparative physical morbidity. Put another way, the perfect study design would be a randomised study of being invited or not to participate in a range of trials, themselves selected (ideally) at random from all such trials. In short, we are never likely to have unassailable evidence from prospective studies that large trials *per se* provide physical benefit.

Summary of findings

Six of the 12 studies examining survival with concurrent controls suggested improved survival for people treated within prospective trials. However, statistical adjustment for known and recorded confounding variables was not possible in one case. In the remaining five cases, improved outcome for trial cases remained (or was enhanced) after such adjustment. Although Stiller's review produced a higher proportion of significant findings in terms of survival (6/8 compared to our 8/13 studies

achieved significant outcomes after adjustment for prognostic variables), our more recent review, based on a greater number of papers, is broadly supportive of his conclusions. We feel that a tentative conclusion can be drawn from *Figure 3* – that RCTs tend to be good for you if there is a pre-existing effective treatment that is included in the trial protocol, or if it turns out that the experimental treatment is more effective. This latter condition is, of course, hard to predict – though there may be historical evidence as to whether past experimental trials in a particular area of medicine have tended to be effective or not (Gilbert *et al.*, 1977). In any case, it seems from *Figure 3* that the former condition may be more important, and it is clearly one that trialists have some influence over. For example, in trials of adjuvant therapy after surgery for cancer, trialists might include the surgery in the protocol. By doing this they could expect to improve survival of participants irrespective of whether the treatment proved effective, or which arm a patient was randomised to. This might, however, cause a reduction in 'generalisability' of the trial results in the presence of an interaction (e.g. synergy) between pre-existing treatment and the experimental treatment. It would be a transgression of deontological ethics to make a deliberate attempt to improve treatment for trial patients above that available outside the trial by including an effective treatment in the protocol solely in order to improve outcome for trial participants, rather than, say, to make the trial arms more comparable and hence increase statistical power.

Possible explanation of findings

Even if there is no bias, a beneficial effect for trial participants has two explanations: (1) the effect of a particularly successful intervention in the trial, or (2) a 'side-effect' of the trial itself. The putative benefit is most commonly ascribed to a general improvement in care, resulting from attention to detail inherent in following the trial protocol (Hawthorne effect) rather than because a proportion of patients receive superior treatment (Karjalainen and Palva, 1989). However, improved physical prognosis when new treatments are compared with old, would also arise if the former were systematically better than pre-existing alternatives. If this were the case, then study patients in the trial should do better in terms of physical outcome than both the trial controls and similar patients treated outside the clinical trial. Such a comparison was possible in six studies but only two (CASS Principal Investigators and their Associates, 1984; Reiser and Warner, 1985) analysed study and control patients explicitly. The others simply reported a non-

significant treatment effect, thereby indicating that the survival rate of the trial controls was indistinguishable, in a statistical sense, from that of the experimentally treated patients, or else reported that the experimental treatment was significantly less effective than the standard. The explicit three-way comparison by Reiser and Warner (1985), showed that both study and trial controls did better than non-trial patients but this finding was not duplicated by the CASS Principal Investigators and their Associates (1984), where there were no significant improvements in either the experimental or trial control arms over the non-trial controls. The remaining four studies which did not report a trend (significant or otherwise) in favour of the experimental treatment within the trial (Davis *et al.*, 1985; Karjalainen and Palva, 1989; Stiller and Draper, 1989; Ward *et al.*, 1992) all found that trial patients, as a whole, did better than those outside a trial. This suggests a general (non-specific) trial effect, rather than a systematic benefit from experimental/new treatments given in trials.

It has been noted by (Benson *et al.*, 1991) that some physicians make use of strict protocols without actually entering their patients into a trial. The use of protocols outside trials may have similar physical benefits to those seen above. A study of Schmoor *et al.* (1996) examined survival rates of non-randomised patients who had declined trial entry but who had nevertheless been treated in accordance with the trial protocol, and had found no significant difference between this group and those who underwent randomisation. This approach is otherwise known as a 'comprehensive cohort study'. Indeed, a systematic review of clinical guidelines by Grimshaw and Russell (1993) showed that they tend to result in improved medical care. The extra attention to detail and compliance with agreed standards associated with guidelines has advantages over less formalised practice (Lilford *et al.*, 1995). Overall, the evidence seems to favour the idea that participating in clinical trials is beneficial, thanks to the enhanced attention to detail contingent on the need to follow a trial protocol and the expectation of benefit which available effective treatments afford.

Conclusion

Of course, the studies, from which the meta-analytic graph is derived, are few in number, of variable quality, and are not a random sample from the population of all trials. Nevertheless, it offers some support for the plausible belief that well-researched treatment protocols, as used in many trials, bring benefits to patients.

It could be argued that because the apparent benefit to patients of being in a trial is not intended, that is, it is merely incidental, there are no ethical implications to the use of non-protocol treatments outside trials. However, an ethical imperative (in the spirit of the Helsinki Declaration) demands that physicians do their best for each individual patient under the ambit of their care, in which case, it could be argued, patients outside trials should not systematically receive inferior care as a **direct or indirect** consequence of their non-trial status. If we espouse this view, then there are two possible ways of redressing the balance between trial and non-trial patients. The first option is predicated on the observed benefit being an intrinsic property of the trial, for example a treatment effect. In that case, we might offer all eligible patients entry into trials so that trials become routine 'treatments' and all eligible patients have access to the both the risks and benefits that trials offer if they so choose (Segelov *et al.*, 1992). However, if the 'trial effect' is really a 'protocol effect', then a second, though not mutually exclusive, option appears preferable – that all treatments, whether trial or non-trial, should be carried out under protocol regimens. A patient who did not want to enter a trial would not thereby be disadvantaged and would still receive all the benefits associated with care under protocol. In the meantime, we may, as scientists, gain confidence that well-conducted trials tend to benefit the participants on average.

What are the psychological effects of participating in trials?

Results

Three studies provided data on the psychological effect participating in trials.

The lists of studies, outcome measurement, main results and quality of data assessment are summarised in *Table 6*.

The first study, by Cassileth *et al.* (1986), examined psychological effects in two cancer trials. The remaining studies were based on single placebo-controlled trials of treatments for hypertension (Mann, 1977) and HIV/AIDS (Robiner *et al.*, 1993).

The study of Cassileth *et al.* (1986) compared study and control groups in two cancer trials and also compared one trial with another – the difference between the trials was in the type of chemotherapy used. However, a non-trial control group, which

would be needed to establish a trial effect *per se*, was not used. They found no significant or consistent trends in anxiety between trials. However, the control (observation only) group showed significantly higher levels of anxiety than those receiving adjuvant therapy and this difference was persistent over time.

The two remaining studies measured patients' psychological state before and after enrolment and compared these scores with a concurrent non-trial control group (see *Figure 1*). Using this design, both Mann (1977) and Robiner *et al.* (1993) reported that there was no difference in psychological scores for trial participants and non-trial controls at the baseline. However, improved psychological scores were seen among trial participants at 3 months and 1 year later in the study of Mann (1977). Robiner *et al.* (1993), however, found that there was no significant difference in measures of depression or distress between trial participants and non-trial controls, and that both groups improved with time. That said, non-trial controls differed in their relative patterns of distress over a 6 month period: there was an initial decrease in distress at 2 months but an increase by 6 months, whereas, for trial participants, there was a consistent decrease in distress from entry to 6 months.

Discussion

The ideal study to examine the psychological effects of participating in clinical trials would invoke repeated psychological measures from patients randomised to be offered or not offered trial entry in a wide range of clinical trials (ideally, themselves, representing a random sample of all possible trials). The analysis should be by 'intention to treat', since those who refuse to participate might have different experiences. None of the studies considered people who refused to participate. Moreover, psychological outcome should be measured in the trial control group and compared with that in non-trial controls, so that any psychological advantage inherent in participating in trials *per se* can be distinguished from the effects of hope engendered by innovative treatments in the study arm of the trial (Robiner *et al.*, 1993).

All three studies used well validated psychometric scales. A disadvantage of not using such a scale is that patients may have difficulty articulating their emotions or may not do so consistently. Several different psychological instruments for measuring psychological well-being are used but there is no obvious agreement among the scales due to the use of different psychological concepts, for example

anxiety, psychiatric morbidity, or depression, and time of administration.

It is important to differentiate between trait and state anxiety (Spielberger, 1988). In attempting to determine the specific effects of trial participation and the immediate effects of different informed consent procedures, the state measure is, *prima facie*, a more useful outcome because a patient's state will be affected by information, whereas his/her trait score should not. However, a patient's trait anxiety may have wider implications for the conduct of clinical trials. Physicians must be sensitive to the fact that some patients will need a greater degree of caring attention than others during informed consent and thereafter, irrespective of what information is given to them. In addition, patients scoring high on trait anxiety scales may be selectively excluded from trial participation due to reluctance on the part of the physician to broach the subject of trial entry. Thus, it is doubly important for the such patients to be advised that they have nothing to lose by trial entry, and that their physician is equipoised.

Response rate to the outcome measurements is another potential problem; indeed, two studies, Cassileth *et al.* (1986) and Mann *et al.* (1977), failed to achieve a response rate of 70% or above.

Conclusion

There is some evidence to suggest that participants in clinical trials have better psychological outcomes than non-trial patients – a result which is sustainable for up to 1 year following trial entry. However, as there are only a few studies in this area, the above result requires replication before it can be regarded as conclusive.

What is the 'best' method for obtaining informed consent?

Results

Studies under review

There were 14 studies providing data on different methods of obtaining informed consent of which all except three (Dal-re, 1991; Levene *et al.*, 1996; McLean, 1980) used RCT designs, that is, they were trials of methods to get consent for trials. In terms of outcome, 11 studies examined recruitment rates to the clinical trial in question, eight studies examined understanding, and five studies looked at psychological well-being (four studies examined all three outcomes). Seven studies were based on hypothetical scenarios and seven studied patients

who were offered entry into 'real' trials. Randomised designs were used five former and six of the latter.

Seven studies involved patients who were offered entry into real trials: cancer trials (Aaronson *et al.*, 1996; Davis *et al.*, 1990; Simes *et al.*, 1986), an AIDS trial (Tindall *et al.*, 1994), a cardiovascular disease trial (Mayers *et al.*, 1987), a trial for mentally ill patients (McLean, 1980), and trials for critically ill premature babies (Levene *et al.*, 1996).

Lists of studies using real trials, main results and evaluation of quality are summarised in *Table 8a*.

Respondents in studies, based on hypothetical scenarios, were either patients in hospital, or were members of the general public. Patients took part in four of these hypothetical studies (Fetting *et al.*, 1990; Llewellyn-Thomas *et al.*, 1995; Simel and Feussner, 1991; White *et al.*, 1984), but they were aware that they were taking part in a psychological experiment. The other three studies asked members of the general public to make a hypothetical decision about entry to an RCT (Epstein and Lasagna, 1969; Gallo *et al.*, 1995) or to a Phase 1 trial (Dal-re, 1991).

Lists of studies using hypothetical trial scenarios, main results and evaluation of quality are summarised in *Table 8b*.

Inter-reviewer reliability

All studies were reviewed by the first author and one in two studies were analysed independently by the last author; there were four discrepancies between the reviewers according to the quality of evidence checklist (see *Table 7*), all of which were resolved by re-analysis of the studies.

Recruitment rates

Eleven studies examined the effect of different methods of obtaining informed consent on recruitment rates to trials. Seven of these studies looked at the effect of quantity of information on willingness to consent and all except two (Davis *et al.*, 1990; McLean, 1980) found that more information was associated with a lower rate of consent (Aaronson *et al.*, 1996; Dal-re, 1991; Epstein and Lasagna, 1969; Simes *et al.*, 1986). However, only two of these studies reported a statistically significant association (Dal-re, 1991; Simes *et al.*, 1986). The two exceptions found no statistically significant difference in terms of willingness to consent between patients receiving a supplementary information booklet and those who did not (Davis *et al.*, 1990), and between patients receiving an explanation of the concept

of randomisation (in addition to baseline information) and those who did not (McLean, 1980). In sum, more information was associated with either a lower or an unchanged consent rate.

Levene *et al.* (1996) found that the greater the time between presentation of information and decision, the lower the willingness to participate. However, this observation was based on a comparison of two separate trials, where, not only the urgency, but also the type of therapy, was different. Very tentatively, one might conclude that the more time patients have to consider their position and the better informed they are, so the more likely they are to select their treatment and eschew randomisation.

One study examined the effect of pre- versus post-randomisation consent on recruitment rates and found that those who were assigned to post-randomisation consent were less likely to consent to standard treatment than those who were offered experimental treatment (Gallo *et al.*, 1985). Moreover, the consent rate seen in the post-randomisation consent group was lower than that in the pre-randomisation group but only when the standard, not the experimental, treatment was offered, even when they understood that equipoise applied. This is interesting as it suggests that patients do not like finding themselves in a control group when they were not party to the randomisation process.

One study examined the effect of different types of information on recruitment rate and found that information given in a descriptive rather than a numerical vignette was associated with significantly higher rate of consent (Fetting *et al.*, 1990) – much remains hidden when words are used to convey quantitative data. The remaining study, which examined the effect of framing probabilistic information on recruitment, found no statistically significant difference between formats, though the 'neutral frame' was associated with a slightly higher consent rate (Llewellyn-Thomas *et al.*, 1995). In the 'negatively framed' version, side-effects were presented in terms of morbidity and mortality rates, while the positively framed version enumerated freedom from side-effects and survival rates. The 'neutrally framed' version attempted to give a balanced description of both.

Knowledge and understanding

The effect of quantity of information. Five studies examined the effect of quantity of information provided at consent on patient understanding and they produced apparently conflicting results:

- **Research value of treatment.** The study of Simes *et al.* (1986) found that the ‘total disclosure’ group was more knowledgeable about the research nature of the study than the group receiving only limited information. Aaronson *et al.* (1996) corroborated this: the concept of the trial and the particular objective were understood statistically significantly better by those receiving a supplementary interview with a nurse than those who underwent the standard consent procedure.
- **The voluntary nature of participation.** One study, Davis *et al.* (1990), reported that patients receiving a supplementary information booklet were significantly more aware of the voluntary nature of their participation.
- **Right to withdraw.** Aaronson *et al.* (1996) reported the proportion of respondents who understood that they could withdraw at any time from the trial was significantly larger in the statistical sense in the group receiving a supplementary interview with a nurse on top of the standard consultation.
- **Equipoise.** White *et al.* (1984) found no significant difference between the three groups who received varying levels of informational detail in terms of understanding of the ‘uncertainty’ associated with the treatments offered in their trial.
- **Available alternative treatments.** One study, Aaronson *et al.* (1996), asked respondents if they knew of any alternative treatments and found that those who received a supplementary interview with a nurse were statistically significantly more knowledgeable about available alternatives.
- **Side-effects.** Three studies, Davis *et al.* (1990), Epstein and Lasagna (1969) and Simes *et al.* (1986), looked at the effects on understanding of different quantities of information on side-effects. Whereas **less** detailed information was associated with greater knowledge in the study of Epstein and Lasagna (1969), a **higher** level of disclosure resulted in better understanding in the study of Simes *et al.* (1986). In the latter study, patients were allocated to ‘total disclosure’ (which mentioned an average of 12 side-effects) or an ‘individual approach’ which resulted in an average disclosure of seven side-effects. The short form in the study of Epstein and Lasagna (1969) mentioned eight side-effects, making it comparable with Simes’s ‘individual approach’. However, both the intermediate and long forms in the study of Epstein and Lasagna (1969) provided substantially more information than was given in Simes’s ‘total’ disclosure method. Davis *et al.* (1990) did not report a significant difference, but the trend was in favour of greater understanding with more information. There may be an optimal level of information such that more information is associated with greater understanding, until perhaps the quantity is so great that boredom or confusion set in.
- **Concept of randomisation.** Different quantities of information about method of treatment allocation (concept of randomisation) were examined by three studies: Simes *et al.* (1986) found that respondents in the ‘total disclosure’ group understood the concept of randomisation significantly better than those in the individual approach (the concept was actually relayed, on average 68%, of the time during the individual approach interviews as compared with 96% for the total disclosure group); neither Davis *et al.* (1990) nor White *et al.* (1984) replicated this result. Davis *et al.* (1990) reported that respondents who received a supplementary information booklet gave significantly more incorrect responses or were undecided about the meaning of the concept, and White *et al.* (1984) found no significant difference between forms of different length, even though the only form to mention randomisation was the long form.
- **Overall understanding.** One study reported significantly better overall understanding of respondents receiving a supplementary interview with a nurse (Aaronson *et al.*, 1996).

Oral versus written information

Two studies were concerned with the effect of oral versus written, or descriptive versus numerical information on understanding. Fetting *et al.* (1990) showed that presenting numerical as opposed to descriptive information (about disease-free survival) produced more accurate recall, while Tindall *et al.* (1994) reported that respondents increased their knowledge scores at a greater rate if they received both oral and written information.

Timing of consent

One study examined the timing of consent on understanding (i.e. before versus after randomisation), but found that misunderstanding rates were independent of this aspect of the consent procedure (Gallo *et al.*, 1995).

Anxiety and other complaints (or side-effects)

Four of the five studies examined the effect of different quantities of information on anxiety: two studies showed that less information was associated with less anxiety (Simes *et al.*, 1986; Epstein and Lasagna, 1969), whereas Davis *et al.* (1990) found

that patients receiving a supplementary booklet were significantly more likely to feel 'somewhat' or 'more relieved'. The other study, by Aaronson *et al.* (1996), reported no effect of consent format on patient anxiety.

One study, by Mayers *et al.* (1987), found that gastrointestinal side-effects were reported significantly more often if the possibility of these effects had been disclosed at the consent stage, irrespective of whether the patients were assigned to the treatment or placebo arm of the trial.

Interactions

Four of the 14 studies conducted a multivariate analysis to see how the dependent variables themselves were related. Two studies sought interactions between recruitment rates and level of understanding, irrespective of the method for obtaining informed consent. Consent was associated with significantly higher mean scores for understanding (Epstein and Lasagna, 1969). Those who expected the experimental treatment to be superior to the standard treatment displayed a higher rate of consent than those who understood that trial entry was based on individual equipoise (Gallo *et al.*, 1995). Another study (Fetting *et al.*, 1990) gave a breakdown of consent rates by expressed optimism and found that those who gave more optimistic estimates of 10 year disease-free survival were less likely to consent to trial entry. The remaining study reported that patients who exhibited good overall understanding were also significantly less anxious, irrespective of consent method (Aaronson *et al.*, 1996).

Discussion

Methods

The studies we have reviewed were mostly (11/14) RCTs of different methods of obtaining informed consent. The exceptions were Dal-re (1991) who did not provide details of the method of allocation, McLean (1980) who used historical controls (with possible time bias), and Levene *et al.* (1996) who compared the same participants offered entry into separate trials requiring different periods of reflection, (with possible confounding by differences in the treatments on trial).

Six of the RCTs were based on hypothetical scenarios whose results must be extrapolated to the 'real life' situation with care (King, 1986); patients faced with difficult decisions may be more concerned to ensure that they understand the issues when those affect them in reality, and/or they may make different trade-offs.

Several different instruments were used to measure anxiety, but only one administered a formal psychometric scale (Aaronson *et al.*, 1996), while the others simply relied on patients' accounts of how they felt. Psychometric scales, such as the Spielberger State-Trait Anxiety Inventory (STAI), possess a high degree of validity and give results which can be compared from place to place.

Some studies sought to measure how much information was understood by the respondents. Simple recall of information is potentially misleading, since memory *per se* is an imperfect indicator of understanding and different methods for testing how well a concept can be understood may give different results. For example, recall that the treatment was allocated on a random basis was rated 'good' by Aaronson *et al.* (1996), while more in-depth understanding of the part that 'chance' has to play was less satisfactory in the study by Howard *et al.* (1981); this could reflect differences between people in the studies, but equally, it could reflect differences in how the question was phrased. Other tools used to test knowledge and understanding were multiple choice questionnaires, true/false responses, open-ended interviews, and patients' perceptions of their own understanding. The latter method is particularly likely to over-estimate understanding since self-assessment of ignorance requires knowledge of topics or what information may be available.

Most of the studies using real trials included only a sub-population of eligible patients and any attempt to generalise the results should proceed with caution as there could be systematic differences between those who participated in the follow-up and those who did not. However, the response rates were reasonably high (> 75%) in nine studies, so that inferences based on their results are less questionable (response rates were not given in the five remaining studies).

Findings

The results of the various studies suggest that giving people more information is associated with a lower consent rate and that consent in emergency situations is more often forthcoming than in circumstances where patients have time to absorb what has been said to them and reflect on how they feel.

However, the data on the effects of quantity of information on understanding are not so straightforward. Data on understanding of the concept of

the clinical trial and the research nature of the treatments was only reported by two studies and both found that the more information the greater the understanding (Aaronson *et al.*, 1996; Simes *et al.*, 1986). As understanding that one is participating in a formal experiment is often perceived to be one of the most important aspects of consent (Siminoff and Fetting, 1991), it is surprising that the studies, as a whole, did not bring this out. Likewise, the studies did not fully investigate the effect of quantity of information on other aspects of the consent procedure. It could be that the authors considered such information to be 'simple' facts and relayed them as such without elaboration. For example, one intervention (a supplementary interview with a nurse) was found to yield significantly more awareness of the voluntary nature of participation and the allied right to withdraw among respondents, though this does not necessarily reflect quantity, so much as quality of communication (Aaronson *et al.*, 1996). The same study was the only one to report knowledge of alternative treatments as an outcome in its own right – this could reflect a lack of real available alternatives in the other studies or a reluctance to report negative results (e.g. Simes *et al.* (1986) reported disclosing different levels of information on relevant alternatives, but failed to report knowledge of this as an outcome). Finally, there was only one study which addressed the effect of informational quantity on understanding of the concept of equipoise (White *et al.*, 1984).

In terms of information on side-effects, there seems to be an optimal amount of information, such that patients are not over-burdened by detail but are nevertheless informed of the more important risks. However, in terms of understanding the concept of randomisation, the literature is apparently contradictory: in some studies suggesting that providing information on randomisation is associated with better understanding of this concept and in others suggesting the reverse. This lack of consistency between studies cannot easily be explained by differing educational and socio-demographic characteristics of the populations studied since the respective samples appeared comparable. It may, however, reflect differences in how the concept was actually explained (Corbett *et al.*, 1996). However, rather than investigating different ways of explaining the concept, the studies simply compared groups who were given an explanation of randomisation with those where no attempt was made. Interestingly, White *et al.* (1984) reported that, although there was no difference between groups in terms of their understanding of randomisation (even though only one group had the concept

explained), > 75% understood this issue, suggesting that they had previously encountered the concept.

The data on anxiety, when taken alongside that of understanding, suggest that how much a patient understands is more important than how that understanding is achieved. This claim is substantiated by a multivariate analysis conducted by Aaronson *et al.* (1996) who found that knowledge was significantly associated with less anxiety, irrespective of consent method.

The effects of different formulations of the same information on patient understanding have not been fully investigated in a comparative study. However, we have conducted an analysis of 24 observational and comparative studies auditing the amount patients in real trials had understood about their trial (Aaronson *et al.*, 1996; Bergler *et al.*, 1980; Daughterty *et al.*, 1995; Davis *et al.*, 1990; DCCT Research Group, 1989; DeLuca *et al.*, 1995; Gallet *et al.*, 1994; Harth and Thong, 1995; Harrison *et al.*, 1995; Hassar and Weinstein, 1976; Howard *et al.*, 1981; Jensen *et al.*, 1993; Lynoe *et al.*, 1991; Marini *et al.*, 1976; Maslin, 1994; Miller *et al.*, 1994; Oddens *et al.*, 1992; Olver *et al.*, 1995; Penman *et al.*, 1984; Postlewaite *et al.*, 1995; Rodebhuis *et al.*, 1984; Simes *et al.*, 1986; Tomamichel *et al.*, 1995; Tindall *et al.*, 1994). This study showed that medical details (particularly concrete information such as side-effects) are well understood by patients: eight studies reported that > 65% of respondents were familiar with the side-effects associated with their trial (Davis *et al.*, 1990; DCCT Research Group, 1989; Harrison *et al.*, 1995; Howard *et al.*, 1981; Jensen *et al.*, 1993; Marini *et al.*, 1976; Maslin, 1994; Simes *et al.*, 1986), while three studies reported 35–57% of respondents were so informed (Gallet *et al.*, 1994; Hassar and Weinstein, 1976; Miller *et al.*, 1994; Olver *et al.*, 1995), and one study reported as few as 28% (Bergler *et al.*, 1980). Other factual information such as right to withdraw and available alternatives was also familiar to respondents. However, more conceptual information, such as the concept of randomisation, seems to be less accessible to patients, for example the concept of randomisation was understood by 65% or more patients in three studies (Aaronson *et al.*, 1996; DCCT Research Group, 1989; Jensen *et al.*, 1993), but only 24–45% of patients in a further four studies (Davis *et al.*, 1990; Gallet *et al.*, 1994; Howard *et al.*, 1981; Simes *et al.*, 1986). There is evidence elsewhere to suggest that patients are happy to accept their physician's treatment recommendations, except when it comes to clinical trials (Siminoff and Fetting, 1991), and this might be explained in part by the abstract concepts involved

(though the factors highlighted by the authors included: amount and specificity of information, perceived strength of recommendation, educational level and risk-aversion attributes). It is possible that, for such abstract material which is particularly troublesome, some formulations of the same concept may facilitate understanding whereas others may simply generate obscurity. More research into what it is about conceptual information such as 'randomisation' patients find hard to grasp. Indeed, it has already been shown in one study that people generally prefer descriptions of the concept of 'randomisation' which play down the role of 'chance' (Corbett *et al.*, 1996). Whether this preference simply reflects an emotional inclination or whether it shows that some phrases were more comprehensible than others is uncertain – respondents preferred the long form in the study of White *et al.* (1984) which was, in fact, less comprehensible to them.

Conclusion

The moral imperative of informed consent is an ideal where patients are given full details of the trial procedure so that a person can determine what is or is not done to him/her. In theory, if autonomy is the foundation of informed consent, a patient should be asked whether or not they wish any information upon which to base a decision, and then, given an expressed desire for information, the patient should make a considered decision about trial entry. Practice, as ever, falls short of this ideal and there is a myriad of reasons why this should be so, not least of which is the logical point that patients cannot easily judge whether or not they want information until that have received it. Additionally, time to give full information about treatments is limited; patients do not always read the consent information, may avoid discussing their queries with the physician, or may have only partial or no understanding of what is put to them. That is not to say, however, that informed consent can never be valid, but rather that physicians must do their best to give as much information as a patient can use in a form which maximises understanding. This review shows reasonably clearly that, provided overload is avoided, giving patients more information results in greater knowledge (albeit at the possible cost of a transient increase in anxiety). It seems to result in reduced willingness to be randomised and this is consistent with the notion that people are only likely to wish to participate in trials when equipoised (see the results section, page 29).

Lastly, we should not rely solely on the informed consent process to educate patients about trials –

baseline knowledge in the community should be enhanced by more open discussion of the topic in the media and elsewhere, because the more people understand the subject, the less anxious they are when given detailed information as part of their invitation to participate.

What is the quality of informed consent in practice?

Quantitative results

Of the 24 studies included in the audit, 23 were quantitative. Ten of these studies examined understanding of cancer trials (three were explicitly Phase 1 studies), four were concerned with cardiovascular trials, two with HIV/AIDS trials (one was a vaccine trial), one with a trial of growth hormone, one with an asthma drug trial, one with a diabetes control trial, one with an arthritis drug trial, one with common analgesic drugs trial, one with a trial related to reproduction and one with a psychiatric drug trial.

Lists of the studies, along with their methods, main results and an assessment of the quality of the data are summarised in *Table 10*.

Of the 23 quantitative studies, one examined the transcripts of consent discussions between patients and physicians to find out what information had actually been given to patients irrespective of their understanding (Tomamichel *et al.*, 1995), nine assessed understanding of eligible patients who had not yet consented to trial entry (Aaronson *et al.*, 1996; Davis *et al.*, 1990; DCCT Research Group, 1989; DeLuca *et al.*, 1995; Harrison *et al.*, 1995; Jensen *et al.*, 1993; Rodebuis *et al.*, 1984; Simes *et al.*, 1986; Tindall *et al.*, 1994) and the remainder examined the understanding of those already participating in a trial or those who had completed their trial.

The study assessing the information actually given to patients reported that complete information about the Phase 1 drug which had been identified as important in prospect (lack of known treatments of proven efficacy, anti-tumour effect still unknown and probably non-existent, limited knowledge of side-effects, and the logistics of the study) was given to 78% or more patients, though specific information concerning right to withdraw or refuse treatment was given to < 40% (Tomamichel *et al.*, 1995).

Of the 22 quantitative studies examining patient understanding, five observed that complete or

adequate information* was understood by 80% or more patients (Daughterty *et al.*, 1995; DeLuca *et al.*, 1995;† Postlewaite *et al.*, 1995;‡ Rodebuis *et al.*, 1984; Tindall *et al.*, 1994).

Specific knowledge and understanding of various elements of the trial process was examined by 18 studies.

Nine studies addressed understanding of the scientific purpose of trials, and all apart from two (Daughterty *et al.*, 1995; Gallet *et al.*, 1994) reported that most patients understood the scientific objectives of their trial or were aware of the research nature of their trial (Aaronson *et al.*, 1996; DCCT Research Group, 1989; Harth and Thong, 1995; Howard *et al.*, 1981; Lynoe *et al.*, 1991; Marini *et al.*, 1976; Miller *et al.*, 1994; Penman *et al.*, 1984; Simes *et al.*, 1986). The exceptions observed that 40% or less respondents were able to state the scientific purpose of a Phase 1 trial (Daughterty *et al.*, 1995) and a placebo-controlled trial (Gallet *et al.*, 1994). Additionally, Harth and Thong (1995) reported that, while nearly 100% of parents were clear about the aim of determining drug efficacy, less than 15% were aware that their trial was designed to assess safety as well.

Seventeen studies examined knowledge of potential side-effects, and all apart from seven (Aaronson *et al.*, 1996; Bergler *et al.*, 1980; Gallet *et al.*, 1994; Hassar and Weinstein, 1976; Maslin, 1994; Miller *et al.*, 1994; Olver *et al.*, 1995) reported that more than 60% patients were, at least, aware of the possibility of side-effects (Davis *et al.*, 1990; DCCT Research Group, 1989; Harrison *et al.*, 1995; Howard *et al.*, 1981; Jensen *et al.*, 1993; Marini *et al.*, 1976; Maslin, 1994; Penman *et al.*, 1984; Postlewaite, 1995; Simes *et al.*, 1986). Despite patients being aware of the possibility of side-effects, Jensen *et al.* (1993) and Marini *et al.* (1976) showed that more detailed recall of the particular nature of specific side-effects was, in fact, poor. The exceptions observed that 48% or less respondents could correctly recall possible side-effects (Bergler *et al.*, 1980; Gallet *et al.*, 1994; Hassar and Weinstein, 1976; Maslin, 1994; Miller *et al.*, 1994; Olver *et al.*, 1995) and that, on average, patients receiving a supplementary interview with a nurse were

aware of 77.5% of the potential side-effects as compared with 60.7% for patients not receiving the intervention (Aaronson *et al.*, 1996).

Seven studies examined understanding of the randomisation procedure, of which three found that the concept was understood by 65% or more patients (Aaronson *et al.*, 1996; DCCT Research Group, 1989; Jensen *et al.*, 1993). Davis *et al.* (1990), Gallet *et al.* (1994), Howard *et al.* (1981), and Simes *et al.* (1986), by contrast, reported that only 24–45% of patients understood that the allocation of treatment was based on ‘chance’.

Six studies reported data on patient’s knowledge of their right to withdraw from the trial. Although most patients were aware of this right (Aaronson *et al.*, 1996; Bergler *et al.*, 1980; Gallet *et al.*, 1994), 40% or more respondents did not appreciate the fact that they could withdraw at any time even before the trial was over (Davis *et al.*, 1990; Lynoe *et al.*, 1991; Maslin, 1994).

Four studies observed that > 60% of respondents were aware that their physician did not know which treatment they had been allocated to, that is, that their trial was ‘double-blind’ (Bergler *et al.*, 1980; Gallet *et al.*, 1994; Hassar and Weinstein, 1976; Howard *et al.*, 1981).

Three studies showed that > 70% of respondents knew that they could receive a placebo in their placebo-controlled trial (Harrison *et al.*, 1995; Howard *et al.*, 1981; Marini *et al.*, 1976).

Two studies found that 65% or more respondents were aware of the availability of alternative treatments outside their trial (Aaronson *et al.*, 1996; Jensen *et al.*, 1993).

One study reported that 53% of respondents understood that standard treatments are not always inferior to experimental treatments (Davis *et al.*, 1990).

Qualitative results

One of the 23 studies was a qualitative study. Snowdon *et al.* (1997) found that parents of babies participating in the ECMO Trial had difficulty

* Adequate information for medical research, as specified by the Nuremberg Code, comprises: the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; and the effects upon his health or person which may possibly come from his participation in the experiment.

† The author did not state exactly what material was needed to satisfy each level of understanding.

‡ Postlewaite measured children’s understanding as well as that of their parents (cited here) and found that > 35% were unable to recall the information.

understanding the concept of a trial and failed to appreciate that their baby might receive a control treatment, thereby equating the trial with the single experimental treatment. There was particular difficulty understanding what randomisation means, why it is used and how it is actually carried out – recall was vague and responses were sometimes inconsistent.

Discussion

The studies

The studies we have reviewed all dealt with different samples and different methods of assessment; generalisation from these results therefore requires caution. Studies used a mix of designs but were all based on recruitment to real trials.

There are many difficulties associated with measuring understanding as an outcome of psychosocial research. By employing recall of information as a device for evaluating patient's knowledge and comprehension, there is a reliance on memory which may fade over time. The longer the recall test is administered after consent, the more prone to error are the results. Furthermore, recall *per se* does not necessarily reflect understanding, as can be seen from the apparently inconsistent results concerning patient's recall and understanding of the concept of 'randomisation'. While recall of the randomisation procedure, that is, that the treatment was allocated on a random basis, was rated 'good' (Aaronson *et al.*, 1996), understanding of the part that 'chance' has to play was less satisfactory (Howard *et al.*, 1981). Other methodological tools used were multiple choice questionnaire, true/false responses, open-ended interviews, and patients' attitudes to their own understanding. However, to ask the respondents whether or not they thought that they had understood the information given may over-estimate understanding since patients may not be aware of what there is to know (Olver *et al.*, 1995).

Qualitative studies are important in this subject as they can provide some insight into what people really understand by allowing the respondent to determine the structure of the conversation. However, there are problems associated with encoding qualitative responses, so making it especially important to conduct inter-rater reliability tests. We think that an approach combining qualitative and quantitative methods would be particularly appropriate for this topic.

Another difficulty for the audit arises when those who decline to participate in a real clinical trial are excluded from the psychosocial research since refusers might be systematically different to those

who consent (refusers might have refused trial entry **because** they failed to understand the information or **because** they understood that equipoise did not apply). Eleven out of the 24 studies in the audit assessed patients who had not consented to trial entry or cited the recruitment rates of the trials, thereby providing a degree of reassurance that all those approached to participate were enumerated in the result.

Any attempt to generalise the results should proceed with caution as there could be systematic differences between those patients who participated in the audit and those who did not. However, if the response rates to the psychosocial surveys in question are reasonably high, inferences based on their results are less questionable.

It is evident that the level of patient's knowledge and understanding of their clinical trial varies according to two separate factors, that is, type of information within the same trial, and type of trial. The first factor, the type of information within the same trial, is best illustrated by the result that the possibility of incurring side-effects is easier for patients to grasp (> 60% of respondents were aware of the possibility of side-effects though more detailed recall was less good) than the concept of randomisation, e.g. the concept of randomisation was understood by only 24–45% of patients in four studies (Davis *et al.*, 1990; Gallet *et al.*, 1994; Howard *et al.*, 1981; Simes *et al.*, 1986), and by 65% or more patients in three studies (Aaronson *et al.*, 1996; DCCT Research Group, 1989; Jensen *et al.*, 1993). This can be explained by the notion that patient's understanding is facilitated by concrete rather than abstract information. Abstract information may be particularly troublesome for children and adolescents given that cognitive functioning develops in stages and begins with thinking in terms of concrete information and then progresses to more abstract conceptualisations (Piaget, 1926). The second factor, a possible corollary of the first, is that patients understand some trials more easily than others and Phase 1 trials seem to produce particular barriers to understanding (Daughterty *et al.*, 1995). The high level of scientific sophistication associated with the Phase 1 trial and its consequent richness of abstract conceptualisations may explain why patients find the information more incomprehensible.

Implications for the doctrine of informed consent

The moral imperative of informed consent is an ideal where patients are given full details of the trial procedure so that a competent person can

determine what is done with him/her. Thus, if material information were withheld from patients or if they were deceived into harbouring mistaken beliefs about the consequences of a decision, the informed consent process may be invalidated. However, patients do not always grasp what information is disclosed to them, resulting in partial or even no understanding of the trial. Difficulties relaying esoteric (especially scientific) knowledge are not due to its technical and precise vocabulary alone, as our everyday language can be, though is by no means always, as precise or well defined. That said, some concepts do take on a more technical and specific meaning in science and consequently some terms are not familiar to patients at all. More importantly, however, the meaning of scientific concepts becomes increasingly inter-dependent (or paradigmatic), so that it is difficult to relay a concept in isolation to the patient (unless he/she understands the whole theory). Misunderstanding may also result from a reluctance to discuss queries with the physician, or even from failure to read the consent form (Olver *et al.*, 1995). Potential problems do not stop there, for, even if patients think that they understand individual concepts, they may take away a very different idea (from that of the physician) of what is going on, making different inferences on the basis of apparently well-understood shared information. Defects in reasoning which are within the agent's control can likewise limit autonomous decision-making (Savalescu and Momeyer, 1997). That is not to say that informed consent can only be valid if a patient has perfect understanding of his/her trial, rather that legally valid consent should be based on a pre-determined minimum grasp of the details as was set out in the audit. What seems to be important is that patients have a realistic grasp of how they can expect to benefit from participation, since we have found that more people seem to choose to participate on the basis of self-interest than altruism (see the following section). Decision analysis can provide a rational platform for informed consent, so that any lack of equipoise is transparent. In order for a physician to respect a patient's autonomy in a Kantian sense, he/she must discharge a 'perfect' duty to transmit material information, without obscuring concepts. Deciding exactly what is 'material' may vary somewhat from patient-to-patient, however. In addition, a judgement concerning patient comprehension should be made and the physician should repeat or elucidate specific points if necessary. It is worth pointing out that the languages of the medical profession and the laity are not incommensurable, and the informed consent consultation is a process of two-way communication aimed at reaching mutual understanding.

Conclusion

We conclude that competent patients should be given 'material' information, though we cannot always expect full understanding. The poor quality of informed consent in some cases does not necessarily invalidate the procedure, though practitioners should check a patient's understanding and be prepared to repeat or explain points where necessary. Patients should be encouraged to ask questions when they do not understand what is said to them.

How do patients, the public and healthcare professionals view RCTs?

Quantitative and qualitative studies Studies under review

Fifty-eight articles provided data on attitudes to clinical trials, of which 51 were quantitative and eight were qualitative (one study used both methods – Marsden *et al.*, unpublished). Thirty-four of the quantitative studies examined the opinions of the public or patients, of which 19 addressed patients who had been invited to participate in clinical trials and 17 addressed patients or the public in hypothetical trial scenarios (one study examined both patients in real trials and members of the public responding hypothetically – Bevan *et al.*, 1993). Twenty studies examined the opinions of healthcare professionals (four studies examined both: Epstein and Lasagna, 1969; Marsden *et al.*, unpublished; Oakley, 1990; Penman *et al.*, 1984). Professionals' views were generally based on real trials, though five studies looked at views on clinical trials in general and two studies looked at the views of members of trial review committees (Dal-re, 1990; Kodish *et al.*, 1992).

Interobserver reliability

Interobserver reliability testing for the views of patients and the public showed 21 examples of disagreement among reviewers (SE and JH) over the quality of evidence. The majority of disagreement (16 cases) was over the 'validity' of the study design used, and reflected the fact that validity can be used to mean different things. We resolved these disagreements by clarifying the definition of external validity, so that we were concerned with how clearly the target population was defined, a population to which the sample results could in theory be generalised. Discrepancies in the response rate to the survey in question or the type of sampling employed occurred five times, for example JH noted that the study of Mattson *et al.* (1985) had used random sampling of the

population in question while SE did not – all such cases were resolved through re-analysis of the original papers.

Quantitative study results

Views of patients and the public

Real trial scenarios. Five of the 19 real trial scenario studies provided data on patients' views on cancer trials, of which two were Phase 1 studies. Five studies were related to cardiovascular disease, two to AIDS trials, three were studies of views on trials concerning abortion and reproduction (including hormone replacement), two were studies concerning childhood asthma, one involved a placebo-controlled study for arthritis and one did not give details of the trials in question (Bevan *et al.*, 1993).

Table 12a lists the above real trial scenarios along with sampling information, the instruments used for assessing patients' attitudes, the main results and comments on the quality of the study design as described by the authors.

Common questions put to the respondents in various studies concerned what motivates patients to participate, the perceived benefits or disadvantages to the patient, who they thought stood to benefit most from the trial, satisfaction with the medical attention they received whilst participating in the trials, and whether or not they would be willing to enter future trials.

Thirteen of the studies (summarised in *Table 12c*) addressed the question of what motivates patients to participate in trials, but the phrasing of the questions differed from study to study. Overall, there were ten studies based on real trials which reported altruistic motivations and the frequency with which such inclinations were cited by respondents in those studies was: over 60% of respondents in three studies (Bevan *et al.*, 1993; Harth and Thong, 1990; Mattson *et al.*, 1985), between 40 and 60% in four studies (Hassar and Weinstein, 1976; Jensen *et al.*, 1993; Lynoe *et al.*, 1991; Penman *et al.*, 1984), and under 40% in three studies (Henzlova *et al.*, 1994; Vogt *et al.*, 1986; Wilcox and Schroer, 1994). Thirteen studies reported self-interested motivations for participation in real trials. The frequency with which self-interest was expressed by respondents was over 70% in four studies (Daughterty *et al.*, 1995; Harth and Thong, 1990; Mattson *et al.*, 1985; Penman *et al.*, 1984), between 30 and 55% in eight studies (Barofsky and Sugarbaker, 1979; Bevan *et al.*, 1993; Hassar *et al.*, 1976; Jensen *et al.*, 1993; Lynoe *et al.*, 1991; Rodebhuis *et al.*, 1984; Vogt *et al.*, 1986; Wilcox, 1994) and under 20% in

one study (Henzlova *et al.*, 1994). Ten of the above studies reported both altruism and self-interest as motivating factors. The percentage of patients citing altruistic reasons was greater than that citing self-interested motivations in five of these ten studies (Bevan *et al.*, 1993; Harth and Thong, 1990; Henzlova *et al.*, 1994; Jensen *et al.*, 1993; Lynoe *et al.*, 1991).

Nine studies reported the perceived benefits or disadvantages to the patients of participation in trials: Daughterty *et al.* (1995), Harth and Thong (1995), Henzlova *et al.* (1994), Mattson *et al.* (1985), Penman *et al.* (1984), Rodebhuis *et al.* (1984), Ross *et al.* (1993), Vogt *et al.* (1986), and Wilcox (1994). The proportion of respondents expecting physical therapeutic benefit varied according to the type of trial in which the patients enrolled, from 78% in Phase 2 and 3 trials (Penman *et al.*, 1984) to 20% in a Phase 1 study (Rodebhuis *et al.*, 1984). However, most participants were hopeful of gaining some psychological benefit (Henzlova *et al.*, 1994) even in these Phase 1 trials (Daughterty *et al.*, 1995). Only three studies, Henzlova *et al.* (1994), Mattson *et al.* (1985) and Vogt *et al.* (1986), reported some perceived disadvantages to trial participation (in 11–37% of respondents), and these were of a practical rather than health-related nature. One study (Harth and Thong, 1995) reported that 79% of parents thought that there was no or only a low risk associated with placing their children in a clinical trial.

Two studies asked respondents who they thought stood to benefit most from the trial (Mattson *et al.*, 1985; Ross *et al.*, 1993). In both cases, scientists rather than participants were more frequently rated as being the major beneficiaries, notwithstanding confirmation of perceived therapeutic benefit to the participants themselves.

Seven studies gave some measure of the patient's satisfaction with the medical attention they received in their trials (Bevan *et al.*, 1993; Henzlova *et al.*, 1994; Henshaw *et al.*, 1993; Hassar and Weinstein, 1976; Jensen *et al.*, 1993; Mattson *et al.*, 1985; Wilcox and Schroer, 1994). Over 77% of patients in four studies expressed a willingness to participate in future studies or the same trial again (Henzlova *et al.*, 1994; Henshaw *et al.*, 1993; Jensen *et al.*, 1993; Mattson *et al.*, 1985). Wilcox and Schroer (1994) found that 88% of respondents would enter the same study again, but only 58% would be interested in future studies of a different nature. Hassar and Weinstein (1976) reported that no respondent thought that the quality of their care had suffered during the trial period, while 54% of respondents

in the study of Bevan *et al.* (1993) were happy with every aspect of the trial.

Four of the studies gave an indication of who patients thought had the most influence over their decision to participate in the trial. They reported that no less than 80% of patients felt that they had made an autonomous decision whether or not to participate in the trials, and did not feel that they had relegated this decision to their physician (Harth and Thong, 1995; Lynoe *et al.*, 1991; Penman *et al.*, 1984; Rodebuis *et al.*, 1984). One study compared the responses of consenters and refusers and found that there was no statistically significant difference between these groups with respect to wanting shared decision-making with their physician (Marsden *et al.*, unpublished).

One study, Tindall *et al.* (1994), found that 79% of responding AIDS patients thought that unproved medications should be available to sufferers outside the trial procedure.

Another study, Bevan *et al.* (1993), reported that 83% of respondents thought that they had been given sufficient time to consider the informed consent material.

One final study, Marsden *et al.* (unpublished) gave limited raw data, but indicated that there was no statistically significant difference between those who consented to be randomised and those who refused with respect to concerns about the medical 'uncertainty' surrounding hormone replacement therapy (HRT). However, 4% of those who refused were, in fact, equipoised, yet still declined randomisation, while the remainder cited perceived side-effects as a reason for refusing.

Hypothetical trial scenarios. There were seventeen studies which used hypothetical scenarios to elicit views on trials. Nine of the 17 studies presented respondents with a specific (mock trial) scenarios conditions with varying degrees of medical severity: Corbett *et al.* (1996), Epstein and Lasagna (1969), Flanery *et al.* (1978), Johnson *et al.* (1991), Kemp *et al.* (1974), Llewellyn-Thomas *et al.* (1991), Saurbrey *et al.* (1984), Simel and Feussner (1991), Slevin *et al.* (1995) and White *et al.* (1984). The remainder ascertained views of patients and the public to clinical trials in general.

All studies using hypothetical trial scenarios are summarised in *Table 12b*.

Common questions posed were what would motivate patients to participate, what information

should be provided during the consent process, how the concept of equipoise is regarded, who should participate in trials, and willingness to participate.

Eleven studies asked respondents what factors might motivate them to accept or decline to take part in a hypothetical clinical trial. Nine of the 11 studies asked about the specific motivations of altruism and self-interest and are summarised in *Table 12c*. Eight of the nine studies reported altruistic motivations and the frequency with which such inclinations were cited by respondents was over 65% in four studies (Alderson, *et al.*, 1994; Autret *et al.*, 1993; Cassileth *et al.*, 1982; Flanery *et al.*, 1978), between 20 and 60% in three studies (Bevan *et al.*, 1993; Millon-Underwood, 1993; Slevin *et al.*, 1995), and under 15% in one study (Kemp *et al.*, 1974). Self-interested motivations were reported by seven of the nine studies, and the frequency with which self-interest was expressed by respondents was over 50% in two studies (Cassileth *et al.*, 1982; Flanery, 1978), and between 25 and 50% in the remaining five studies (Alderson, *et al.*, 1994; Autret *et al.*, 1993; Bevan *et al.*, 1993; Millon-Underwood, 1993; Slevin *et al.*, 1995). One study (Gerard *et al.*, 1995) showed that severity of illness, rather than remuneration, was most influential in the decision to participate, though it is unclear whether this was due to altruistic or self-interested motives. Another study, Autret *et al.* (1993), reported that the most frequently cited reason (75%) for refusing trial entry was risk of side-effects, while 19% of potential refusers disagreed with the RCT on principle.

Six studies examined perceptions of the information that should be provided during the consent process: Corbett *et al.* (1996), Epstein and Lasagna (1969), Oakley *et al.* (1992), Saurbrey *et al.* (1984), Simel and Feussner (1991), White *et al.* (1984). The first study reported that respondents generally preferred written over verbal information, and favoured explanations of the concept of randomisation which were less explicit about the play of chance. Both the first two studies reported that some respondents expected a degree of distress contingent on the very offer of trial entry (Corbett *et al.*, 1995, Epstein and Lasagna, 1969). Saurbrey *et al.* (1984) and White *et al.* (1984) reported that > 80% and 68% of respondents respectively preferred longer consent forms or 'full' information despite the observation by Simel and Feussner (1991) that only 62% of their respondents would take quantitative information into account when deciding whether or not to participate. One study (Alderson *et al.*, 1994) reported that nearly 70% of respondents

would want to know that there was uncertainty surrounding treatments in an RCT and whether or not they had been assigned to the control arm. Finally, Saurbrey *et al.* (1984) found that 75% of respondents thought that patients who are unable to give consent (e.g. they were unconscious) could be included in a trial nevertheless.

Four studies made reference to the concept of equipoise in the reported views of patients and the public. Corbett *et al.* (1995) showed that 83% of respondents considered clinical trials to be ethical in principle given equipoise, while Johnson *et al.* (1991) investigated the extent to which the public regarded equipoise among experts as important, and reported that 97% of respondents would consider a trial unethical if equipoise was disturbed above 80:20, that is, if 80% or more of the experts thought that one treatment offered more benefit than its comparators. In the studies of Cassileth *et al.* (1982) and Millon-Underwood (1993), 30 and 74% of respondents, respectively, thought it likely that physicians enter their patients in trials only when equipoised.

Two studies examined the issue of whether the severity of a patient's disease should affect the offer to participate in trials. Cassileth *et al.* (1982) remarked that respondents who had not before participated in a trial thought that the offer of trial entry should be restricted by the patient's medical status, whereas those who had participated in trials previously thought any patient should be allowed to enter. Likewise, Millon-Underwood *et al.* (1993) showed that a large proportion of respondents thought that any patient, regardless of medical status, should be given the opportunity to participate.

In the studies of Corbett *et al.* (1996), Johnson *et al.* (1991) and Kemp *et al.* (1984), views were seen to change according to the type of trial under consideration. Johnson *et al.* (1991) reported that the required level of collective equipoise was higher if the issues were highly emotive, for example if infants were involved or if the prognosis were grave. The remaining two studies were consistent with this: more respondents stated that they would prefer to choose their own treatment (thereby refusing randomisation) as the clinical condition described became increasingly grave (Corbett *et al.*, 1996; Kemp *et al.*, 1984).

In five studies, respondents were asked whether they would wish to participate in the proposed trial should the described scenario be realised (Bevan *et al.*, 1993; Flanery *et al.*, 1978; Gerard *et al.*, 1995; Mettlin *et al.*, 1985; Slevin *et al.*, 1995).

Affirmative responses were received from 50 to 90% of respondents except in the study of Flanery *et al.* (1978) which found that only 41% of respondents would be willing to consent.

Views of healthcare professionals

Fifteen of 21 articles in this category examined views of physicians to oncology trials. One study hinged on a particular hypothetical trial of early versus delayed delivery for preterm foetuses (Lilford, 1994), while one study used an HRT pilot trial (Marsden *et al.*, unpublished). Five studies looked at the views of committee members, academics or chairpersons when reviewing Phase 1 studies (Kodish *et al.*, 1992), trials involving children (Mammel and Kaplan, 1995) or trials in general (Blum *et al.*, 1987; Dal-re, 1990, 1993).

Table 13 provides a summary of the reported attitudes to the various trials, the sample population, the method of assessing the attitudes and comments on the quality of the data.

Common issues studied were: to what extent are physicians prepared to participate in trials, what are their views on the principle and practice of informed consent, do their patients stand to benefit from participation, what effect does participation have on the physician-patient relationship, and, finally, are clinical trials ethical given equipoise?

Seven of the 15 studies sketched a general picture of the extent to which physicians would be prepared to participate in trials: Alderson *et al.* (1994), Benson *et al.* (1991), Langley *et al.* (1987), Spaight *et al.* (1984), Taylor (1992), Taylor and Kelner (1987b), and Taylor *et al.* (1984). With one exception (Oakley *et al.*, 1992), the studies found that over 60% of responding physicians commonly enter some or all of their eligible patients in clinical trials. The exception (Alderson *et al.*, 1994) reported that 23–53% of physicians, depending on the trial in question, expressed a willingness to participate. However, two studies showed that some physicians were more reluctant to enter patients when placebo controls are used (Benson *et al.*, 1991), or when one of the comparator treatments is toxic and/or has substantial side-effects (Spaight *et al.*, 1984). With only two exceptions (Alderson *et al.*, 1994; Langley *et al.*, 1987), the studies examined views of professionals from specialist centres who were sometimes already involved with research.

Fourteen studies examined views on the informed consent process. Although informed consent was

regarded as a necessary precursor to randomisation by over 91% of respondents (Benson *et al.*, 1991; Dal-re, 1990, 1992e, 1993), up to 22% of respondents in the studies of Williams and Zwitter (1994) and Taylor and Kelner (1987b) regularly entered patients without obtaining informed consent. Approximately 60% of responding IRB members thought that parental consent was required for (hypothetical) trials involving children, though 85% thought that parental consent could be waived when the risk was minimal (Mammel and Kaplan, 1995). Dal-re (1990) reported that nearly 70% of responding committee members thought it permissible for an investigator to administer trial drugs without informed consent but only under 'special circumstances', while 39% of respondents in the study of Blum *et al.* (1987) agreed that the law should permit research under such circumstances. If the requirement of informed consent were abandoned, some physicians stated that they would enter more patients (Taylor and Kelner, 1987a,b). There was some disagreement over how informed consent should be obtained; not more than 32% of respondents in the studies of Blum *et al.* (1987) and Williams and Zwitter (1994) felt that it should always be obtained in writing, whereas Dal-re (1990, 1993) reported that > 64% of respondents thought that written consent should always be sought. There was also some disparity among physicians over the amount of information they thought should be given to their patients before entry in a trial. Indeed, Taylor and Kelner (1987b), showed that some physicians had difficulty in assessing their patients' desire for detailed information, and, while most physicians routinely disclosed full details of the trial (Williams and Zwitter, 1994), 83% thought it possible to give more information than the patients actually wanted (Benson *et al.*, 1991). The study of Penman *et al.* (1984) estimated this to be the case for 41% of patients. In light of such uncertainty, two studies reported favourable attitudes to a more individualised approach to the consent process: Benson *et al.* (1991) and Taylor and Kelner (1987a). However, one study found that 90% of respondents thought that a 'minimum' amount of information should always be disclosed. The quality of the informed consent process in practice was addressed in five studies. Forty-seven per cent of physicians thought that their patients were never aware that they were participants in an experiment when they signed the consent form (Taylor and Kelner, 1987b), while most physicians believed that informed consent was obtained more rigorously in Phase 1 trials than in Phase 2 or 3 studies (Kodish *et al.*, 1992), and in trials of supportive care rather than in trials testing curative or palliative therapies (Williams and

Zwitter, 1994). Eighty-six per cent of respondents thought that patients rarely understand the information given to them (Blum *et al.*, 1987), and nearly 75% of respondents thought that randomisation, in particular, is impossible to explain adequately to patients (Spaight *et al.*, 1984). Two studies reported that 67 and 55% of respondents thought the decision to participate should be shared or left to the patient rather than it be the sole responsibility of the physician (Alderson *et al.*, 1994; Taylor, 1992).

Five studies addressed views on possible benefits for their patients of participating in trials (Benson *et al.*, 1991; Daughterty *et al.*, 1995; Kodish *et al.*, 1992; Penman *et al.*, 1984; Richardson, 1986), of which two also highlighted the risks of toxicity in Phase 1 studies (Daughterty *et al.*, 1995; Kodish *et al.*, 1992). Therapeutic benefit from all active treatments (both experimental and standard) was considered probable by most respondents in all studies except for those based on Phase 1 trials. Despite the concern over the real risk of toxicity in Phase 1 trials, the majority of responding physicians in the two studies above thought that participants would, nevertheless, benefit psychologically.

Five studies reported views on the effect of offering trial entry on the physician-patient relationship: Benson *et al.* (1991), Blum *et al.* (1987), Spaight *et al.* (1984), Taylor and Kelner (1987b), and Taylor *et al.* (1984). All studies except Spaight *et al.* (1984) showed that there was considerable concern among physicians over the effect of discussing trial entry on the trusting relationship with their patients. The exception (based on a small sample) found that over 75% of respondents thought that randomisation did not, in fact, lessen patient's trust in their physician (Spaight *et al.*, 1984).

Finally, four studies examined physician's views on equipoise. Lilford (1994), using hypothetical scenarios, established that obstetricians were frequently in personal and collective equipoise over the effects of two treatments which were to be compared in a proposed trial. Taylor and Kelner (1987a) reported that 36% of respondents would be prepared to enter their patients in a trial even when personal (effective) equipoise did not apply, while Alderson *et al.* (1994) reported that only 25% of physicians thought that they could ever be in equipoise. Interestingly, only 28% of surgeons in one study (Marsden *et al.*, unpublished) were 'uncertain' about whether or not HRT could cause a recurrence of cancer, while 73% of the same sample thought that a trial would be ethical.

Qualitative study results

Studies under review

There were eight studies of a more qualitative nature which sought to produce in-depth opinions through more open-ended inquiry. Three studies examined the views of healthcare professionals (Garcia, 1987; Madden, 1994; Twomey, 1994) while the remainder solicited views of patients and the public (two studies examined both: Madden, 1994; Twomey, 1994).

Views of patients and the public

Two studies reported that ethnic minority groups considering enrolment in a hypothetical trial and participants in a real trial for multiple sclerosis tended to have altruistic motivations (Roberson, 1994 and Wynne, 1989) but also expected psychological and physical benefit (Wynne, 1989).

Another study showed that pregnant women, who were offered entry into a trial of holding their own obstetric case notes versus liaising with a number of different healthcare professionals who were privy to their notes, were pleased to enrol and mostly felt pleased to help others; none expressed concern that they were part of an RCT (Elbourne, 1987). This was supported by the study of Madden (1994) who showed that women with breast cancer expressed positive views on the abstract notion of research but were less motivated when it came to personal participation in trials because of concerns about uncertainty, randomisation, and loss of control. This concern was echoed by the remaining two studies which sought to obtain views of parents whose children had been entered in the ECMO (artificial lung) (Snowdon *et al.*, 1997) or AIDS (Twomey, 1994) trials. In both cases, there was some concern over randomisation as a method of allocating treatment (involving 'desperate' patients), given the lack of effective standard treatments as alternatives to more experimental methods. However, respondents recognised that, when equipoise applies, randomisation may resolve an otherwise difficult (finely balanced) decision. Another study discussed (by focus groups) a trial where the new therapy was only available within a trial and found that, even when the patients were not desperate, they would still prefer a three-way choice, that is, treatment A, treatment B, or a trial of A versus B (Marsden *et al.*, unpublished).

Views of healthcare professionals

Two of the three studies showed that health professionals, while expressing positive views on the abstracted notion of research, were concerned about uncertainty, randomisation and loss of control (Madden, 1994), especially when the patients

are desperate (Twomey, 1994). The remaining study asked professionals whether or not trial results should be shared with the participating patients after trial completion and uncovered mixed views: the offer of such information might encourage recruitment and serve as a 'reward' for participation, while, at the same time, there was doubt over the patient's capacity to understand the data, especially if the treatment which turned out to be less effective or harmful had been given (Garcia, 1987).

Discussion

The methods used by the various studies we have reviewed to evaluate the views of patients, physicians and the public to clinical trials might be flawed in a variety of ways.

Firstly, there has been methodological concern over the use of hypothetical scenarios in such studies for some time (King, 1986), and it has been suggested that respondents answering hypothetically may be more prone to tailor their answers in a direction that they consider socially desirable. We included studies using both hypothetical scenarios and those based on patients in real trials. In the event, we found little difference between these groups, for example the proportion of respondents citing altruistic reasons for participating in trials was only slightly (and not significantly) higher among those in hypothetical scenarios. Nevertheless, actually taking part in a trial may change a person's views.

Some studies of patients in real trials confined their attention to those who had actually participated whereas it is important to obtain the views of all patients offered entry in the trial, whether or not they consented to take part. The effect of offering trial entry among consenters may be systematically different from that among refusers.

The framing of questions and the order in which they are presented differed from study to study. Although some ideal methodological standards can be specified, others are open to debate. Face-to-face interviewing, telephone interviewing and self-administered questionnaires may elicit different responses. That said, the methodological rigour of the studies was generally suboptimal, for example only a handful reported that they had conducted a pilot test (Benson *et al.*, 1991; Cassileth *et al.*, 1982; Slevin *et al.*, 1995; Spaight, 1984; Taylor *et al.*, 1984, 1987; Taylor and Kelner, 1987a; Wilcox and Schroer, 1994) and only one study assessed their questionnaire for readability (Corbett *et al.*, 1996).

Response to the surveys (especially those using postal questionnaires) is also a potential problem: 13 studies failed to achieve a response rate of 70% or above. In addition, 16 studies did not state the response rate. If the response rate is low, then there is a risk of introducing systematic bias since non-respondents may have different views.

In addition, only five studies used random sampling techniques to achieve as representative a sample as possible. However, 15 studies used 'quota' sampling and deliberately took certain numbers from specified groups, sometimes with a mind for comparison. An example of 'quota' sampling is the study of Corbett *et al.* (1996) who selected respondents from three different groups, that is, medical secretaries, students and the general public. Even though the consequences of haphazard sampling are not easily determined, we would have more confidence in the data if random sampling techniques were more common.

Qualitative studies are important in this subject because they provide some insight into what people are really thinking. This is especially valuable in establishing what the main issues are so that a tight set of questions can be devised for subsequent study. However there are problems associated with encoding qualitative responses. We think that a combined approach using qualitative and quantitative methods would be particularly appropriate for this complex topic.

There is an interesting issue concerning framing effects which is particularly pertinent for studies using hypothetical scenarios. The context within which a survey is conducted might have some effect on the responses given. For example, Kemp *et al.* (1984) described hypothetical treatment choices in a non-trial context prior to the questions concerning trial entry and this 'priming' may have resulted in lower stated willingness to accept randomisation than would have occurred had the trial been mentioned at the outset.

As a final methodological point, it is impossible to tell, in many cases, whether the respondents understood the same thing as the investigators by the term 'clinical trial'. However, some of the quantitative studies and qualitative studies examined knowledge and understanding as well as views on clinical trials which go some way to resolving the issue (see the conclusion, page 51). These studies found that the more scientific aspects of trials such as the concept of randomisation were, in general, poorly understood (DeLuca *et al.*, 1995; Penman, 1984; Rodebuis *et al.*, 1984; Tindall *et al.*, 1994) though specific details of the therapies such as

side-effects seemed to be more clearly understood (Daughterty *et al.*, 1995; Harth and Thong, 1995; Hassar and Weinstein, 1976; Jensen *et al.*, 1993; Lynoe *et al.*, 1991). Both the qualitative studies also reported a limited grasp of the concept of a trial (particularly the concept of randomisation) and sometimes missed the whole idea of comparison (Madden, 1994; Snowdon *et al.*, 1997). Misunderstanding and ignorance might affect recruitment or uninformed compliance, so it is very important that patients and the general public are given accurate and comprehensible information.

The majority of studies sought only to elicit views of respondents and did not attempt to produce a scale that might serve as a measure of views in other sample populations. However, the series of studies by Taylor and colleagues sought to draw up a 'physician orientation profile' from the results of physician views on clinical trials but omitted to assess the properties of such measures by conventional psychometric methods.

Despite a considerable range in the findings, 5–99% of respondents, overall slightly more people participate for personal gain than for altruistic reasons, even in Phase 3 studies. In six out of 14 studies (where both types of motivation were measured), the number of self-interested respondents outweighed the number of altruistic respondents. Patients in Phase 3 studies only stand to benefit clinically individually if their overall care is better or if one of the treatments is superior to the other(s), in prospect. Since we think that standards of care should be independent of trial participation and since comparator treatments should offer equal expected utilities to patients (Brewin and Bradley, 1989; Lilford and Jackson, 1995), personal gain should not be an aim of participation in a trial, given free availability of treatments. The finding that so many people hope to gain from trial entry, therefore, makes us uneasy. It is important that patients both understand and accept that, provided equipoise applies, they stand neither to lose nor gain by participation. Patients who have nothing to lose or gain, in prospect, are exhibiting a form of altruism, albeit a weak form, by their participation. We think that well informed people, if accepting trial entry, should do so for altruistic reasons, or because they are indifferent between participating and declining, and not because they expect to gain clinically in prospect. If they expect to lose, but nevertheless wish to enter a trial, we would say they are manifesting a strong form of altruism. It is dangerous for healing professions to encourage this. However, it seems entirely appropriate at least to give people an opportunity to

manifest a weak form of altruism (or indifference), given equivalent expected utilities from the various comparator treatments. In the philosophical literature there is an order of both chronology and emphasis on the self, with the concept of Christian concern for one's fellow men taking second place. Even in the religious teachings, where the latter gained most currency, 'loving thy neighbour' was foreshadowed by a love of God. The possibility of genuine altruism has been hotly debated, some arguing that, at best, altruism is a form of self-realisation (in the Hegelian sense) and, at worst, self-indulgent martyrdom. Others such as David Hume are more sympathetic to the notion. Indeed, Kant would object to using oneself merely as the means to an end just as much as using someone else, though it seems to us that this 'formula of humanity' does not rule out the possibility of altruistic behaviour. This substantiates the notion that the classical act-utilitarianism doctrine which requires of an individual that he/she always promotes **overall** happiness (not just his/her own) is too burdensome. Rather, we believe that, in order to respect a patient's autonomy, the expected consequences of entering a trial for that patient should be underlined and that any altruism could be factored into a decision analysis to determine whether equipoise applies.

The proportion of patients/members of the public who thought that doctors would put people in trials even if equipoise was not present ranged from 26 to 70% according to Millon-Underwood (1993) and Cassileth *et al.* (1982), respectively; both studies used hypothetical trial scenarios. Such variation might be explained, in part, by the people sampled: an exclusively African American sample was used by Millon-Underwood (1993) who produced the more promising figure, and a sample from the general public was used by Cassileth *et al.* (1982). This brings out the issue of trans-cultural applicability of studies, which could reflect different levels of familiarity with, and understanding of, the trials in question. Without more data, this issue cannot be resolved. Still more worrying, however, some physicians themselves confessed that they would be prepared to enter patients even when not equipoised but when the trial treatment were freely available (Taylor and Kelner, 1987a). Here, the duty of physician-scientist seems to take precedence over the duty of care – a situation we deplore.

Even when altruism was the main motivating factor, most respondents actually expected some tangible benefit despite viewing themselves as secondary to the major beneficiary, the scientists. Patients, the

public and physicians in the studies reviewed all expected trial participants to benefit therapeutically from all active treatments except for those in Phase 1 trials. Even in the latter case, participants were still expected to benefit psychologically from the trial experience. Interestingly, the proportion of altruistic respondents was not greater in the Phase 1 studies than in the others.

The issue of informed consent was dealt with by many of the studies. The uncertainty expressed by the physicians over how to approach the informed consent procedure was mainly born of perceived variation in the quantity of material desired by the patients themselves. Even when the information was provided, it was not a foregone conclusion that the patients would actually base their decision on the material given. Surprisingly, physicians were more cavalier about obtaining informed consent than is demanded by the Declaration of Helsinki (1964). Sometimes physicians reported not even telling patients they were in a trial, let alone giving them sufficient information, and, in one study, 47% of physicians thought that their patients were never aware that they were about to participate in an experiment when signing the consent form (Taylor and Kelner, 1987b). This result could be attributed to the variation of practice across countries, but it engenders concern nevertheless. Views on the amount of information required to make patients' consent morally significant are varied but our results suggest that much more care is needed.

Finally, some studies solicited views on whether experimental treatments should only be available within the trial mechanism. Minogue *et al.* (1995) has recently highlighted the plight of the 'desperate volunteer', in the context of AIDS where the absence of standard and effective treatment favours the experimental therapies. Since most patients participate in trials out of self-interest, Minogue suggests that prospective participants should be provided with the choice to participate in the trial or to receive the experimental treatment. Indeed, a large proportion of AIDS patients in one study (Tindall *et al.*, 1994) and parents of very ill children in two others (Snowdon *et al.*, 1997; Twomey, 1994) thought that unproved medications should be available to sufferers without their having to participate in a trial.

Conclusion

More people participate in trials out of self-interest than altruism. Professionals and the public alike see informed consent as a necessary safeguard in trials, though sometimes they have a lax attitude in practice.

Chapter 5

Recommendations

- The caring professions must articulate clear, ethical justification for trials if public confidence is to be retained. Currently, this is confusing and contradictory.
- 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, a situation sometimes described as patient equipoise.
- 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 (and hence respect their autonomy), even though this may increase anxiety temporarily and depress recruitment rates.
- Patients are least alarmed and understand the issues most clearly when they have encountered the concept of comparative trials before. Since hundreds of thousands of patients are entered in trials each year in a country like the UK, the rationale for conducting trials and the concept of patient equipoise should become part of the public understanding of science.
- Practitioners should pay particular attention to explaining abstract ideas (especially that of randomisation) during the invitation to participate, since it is the conceptual scientific basis of trials rather than details of the treatments themselves which patients find hard to grasp.
- Small trials of existing therapies are not necessarily unethical in terms of the participants themselves, provided that they are in equipoise – small trials may be poor value for transferable resources, however.
- Clinical trials should start early in the life of a new treatment (even if further refinement is likely in prospect) since equipoise may be lost quickly on the basis of observational data, and the results may be analysed after stratifying by treatment variables.
- The much quoted 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.

Chapter 6

Questions for future research

Areas in ethics of conducting RCTs which have attracted little or no attention, and so 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 (topics in quantitative ethics) which also need to be addressed, and these include:

- What is it about abstract trial concepts such as randomisation that patients find difficult to grasp? (See the results section, page 36.)
- How might patient understanding be maximised in a cost-effective way? (See the results section, page 36.)
- In particular, how might practitioners best use decision analysis (or techniques derived therefrom) to make the choice to participate or

not more explicit and what effects would this have on (different groups of) patients? (See the results section, pages 41 and 44.)

- How do practitioners (and others) form prior beliefs about treatment effects and how accurate do they turn out to be? (See the results section, page 41.)
- How do the public view post-randomisation consent in circumstances where a promising new treatment is not available outside a trial? (See the results section, page 41.)
- How do the general public view cluster trials and interventions? (See the results section, page 41.)
- How does disclosure of interim trial data (or externally published data) affect recruitment rates to trials? (See the results section, page 41.)
- What are the public views on the obligations of data monitoring committees? (See the results section, page 41.)
- What principles do data monitoring committees follow when deciding if and when to stop a trial early? (See the results section, page 41.)



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References

- Aaronson NK, Visserpol E, Leenhouts GHMW, Muller MV, Vanderschot ACM, Vandam FSAM, *et al.* Telephone-based nursing and intervention improves the effectiveness of the informed consent process in cancer clinical trials. *Journal of Clinical Oncology* 1996;**14**(3):984–96.
- Abraham EP, Chain E, Fletcher CM. Further observations on penicillin. *Lancet* 1941;**ii**:177–88.
- Ackermann TF. Medical research, society and health care ethics. In: Gillon R, editor. Principles of health care ethics. Chichester: Wiley, 1994:873–84.
- Albert R, Raiffa H. A progress report on the training of probability assessors. Unpublished findings. Harvard University, 28 August 1969.
- Alderson P. Equipoise as a means of managing uncertainty: personal, communal, and proxy. *Journal of Medical Ethics* 1996;**22**:135–9.
- Alderson P, Madden M, Oakley A, Wilkins R. Women's views of breast cancer treatment and research: report of pilot project 1993. London: SSRU, 1994.
- Altman DG. Statistics and ethics in medical research III. How large a sample? *British Medical Journal* 1980;**281**:1336–8.
- Altman DG. Size of clinical trials. *British Medical Journal* 1983;**286**:1842–3.
- Altman DG, Gardner MJ. Confidence intervals for research findings. *British Journal of Obstetrics and Gynaecology* 1992;**99**(2):90–1.
- Ambroz A, Chalmers TC, Smith H. Deficiencies of randomised controlled trials. *Clinical Research* 1978;**26**:280a.
- Anderson B, Baden. The controlled clinical trial in surgery. *Scandinavian Journal of Gastroenterology* 1971;**6**(9):23–9.
- Anderson RP. Standards for surgical trials. *Annals of Thoracic Surgery* 29:192, 1980.
- Anello C, Fleiss J. Exploratory or analytic meta-analysis: should we distinguish between them? *Journal of Clinical Epidemiology* 1995;**48**(1):109–16.
- Angell M. Patients' preferences in randomized clinical trials. *New England Journal of Medicine* 1984;**310**:1385–7.
- Anonymous. Controlled clinical trials: planned deception? *Lancet* 1979;**i**:534–5.
- Anonymous. Positive discrimination for surgery? *Lancet* 1990;**336**:151.
- Anscombe F. Sequential medical trials. *Journal of the American Statistical Association* 1963;**58**:365–83.
- Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomized controlled trials and recommendations of clinical experts. Treatment for myocardial infarction. *JAMA* 1992;**268**:240–8.
- Antman K. A comparison of randomized vs concurrent controls. *Proceedings of the American Association of Cancer Research* 1983;**24**:146.
- Armitage P. Sequential medical trials: some comments on FJ. Anscombe's paper. *American Statistical Association Journal* 1963;**58**:384–7.
- Armitage P. Sequential medical trials. Oxford: Blackwell, 1975.
- Ashby D, Machin D. Stopping rules, interim analysis and data monitoring committees. *British Journal of Cancer* 1993;**68**:1047–50.
- Ashcroft JJ, Leinster SJ, Slade PD. Breast cancer – patient choice of treatment: preliminary communication. *Journal of the Royal Society of Medicine* 1985;**78**:43–6.
- Autret E, Dutertre JP, Barbier P, Jonville AP, Pierre F, Berger C. Parental opinions about biomedical research in children in Tours, France. *Developmental Pharmacology and Therapeutics* 1993;**20**(1–2):64–71.
- Avorn J, Soumerai SB. Improving drug therapy decisions through educational outreach: a randomized controlled trial of academically based 'detailing'. *New England Journal of Medicine* 1983;**308**:1457–63.
- Avorn J, Chen M, Hartley R. Scientific versus commercial sources of influence on the prescribing behaviour of physicians. *American Journal of Medicine* 1982;**3**:4–8.
- Banta HD, Thacker SB. The case for reassessment of health care technologies. Once is not enough. *JAMA* 1990;**364**:235–46.
- Barnard GA. Must clinical trials be large? The interpretation of *p*-values and the combination of test results. *Statistics in Medicine* 1990;**9**:601–14.
- Barofsky I, Sugarbaker PH. Determinants of nonparticipation in randomized clinical trials for the treatment of sarcomas. *Cancer Clinical Trials* 1979;**2**:237–46.
- Barry M, Molyneux M. Ethical dilemmas in malaria drug and vaccine trials: a bioethical perspective. *Journal of Medical Ethics* 1992;**18**(4):189–92.
- Bartlett RH, Cornell RG. Comment on ethics and statistics in randomized clinical trials. *Statistical Science* 1991;**6**(1):63–5, 1991.

- Baum M. Commentary on the practical and ethical defects of surgical randomized prospective trials. *Journal of Medical Ethics* 1983;**9**:92–3.
- Baum M. The ethics of clinical research. In: Byrne P, editor. *Ethics and law in health care 1*. Chichester: Wiley, 1990.
- Baum M. Clinical trials – a brave new partnership: a response to Ms. Thornton. *Journal of Medical Ethics* 1994;**20**:23–5.
- Baum M. The ethics of clinical trials. *Israel Journal of Medical Science* 1995;**31**:197–200.
- Baum M, Houghton J, Abrams K. Early stopping rules – clinical perspectives and ethical considerations. *Statistics in Medicine* 1994;**13**:1459–69 and 1471–2.
- Beauchamp TL, Childress JF. *Principles of biomedical ethics*. New York: Oxford University Press, 1989.
- Beecher HK. Ethics and clinical research. *New England Journal of Medicine* 1966;**274**:1354–60.
- Bellissant E, Benichou J, Chastang C. A comparison of methods for phase ii cancer clinical trials: advantages of the triangular tests, a group sequential method. *Lung Cancer* 1994;**10**(1):S105–15.
- Benson AB, Pregler JP, Bean JA, Rademaker AW, Eshler B, Anderson K. Oncologists reluctance to accrue patients onto clinical trials: an Illinois center study. *Journal of Clinical Oncology* 1991;**9**(11):2067–75.
- Bergler JH, Pennington AC, Metcalfe M, Freis ED. Informed consent: how much does the patient understand? *Clinical Pharmacology and Therapeutics* 1980;**27**(4):435–40.
- Berglund CA. Children in medical research: Australian ethical standards. *Child: Care, Health, and Development* 1995;**21**(2):149–59.
- Berkowitz S. Ethical issues in the case of surgical repair of cleft palate. *Cleft Palate – Cranial Facial Journal* 1995;**32**(4):271–81.
- Berry DA, Chih-Hsiang Ho. One-sided sequential stopping boundaries for clinical trials: a decision-theoretic approach. *Biometrics* 1988;**44**:219–27.
- Berry DA, Wolff MC, Sack D. Public health decision-making: a sequential vaccine trial. *Bayesian Statistics* 1992;**4**:79–96.
- Bertelsen K. Protocol allocation and exclusion in two Danish randomized trials in ovarian cancer. *British Journal of Cancer* 1991;**64**:1172–6.
- Bevan EG, Chee LC, McGhee SM, McInnes GT. Patients' attitudes to participation in clinical trials. *British Journal of Clinical Pharmacology* 1993;**35**(2):204–7.
- Blackwelder WC. 'Proving the null hypothesis' in clinical trials. *Controlled Clinical Trials* 1982;**3**:345–53.
- Bleich HL. Experimentation on human subjects. In: Rosner F, Bleich JD, editors. *Jewish bioethics*. New York: Sanhedrin Press, 1979:384–5.
- Bleich HL. The science and ethics of the randomized clinical trial. *MD Computing* 1995;**12**(1):5–6.
- Block JB, Elahoff RM. The randomized clinical trial in evaluation of new cancer treatment. *Methods in Cancer Research* 1979;**xvii**:259–75.
- Blum A.L, Chalmers TC, Deutch E, Koch-Weser J, Rosen A, Tygstrup N, *et al.* The Lugano statement on controlled clinical trials. *Journal of International Medical Research* 1987;**15**:2–22.
- Blumgart HL. The medical framework for viewing the problem of human experimentation. In: Freund PA, editor. *Experimentation with human subjects*. 1970:39–65.
- Boissel JP. Impact of randomized clinical trials on medical practice. *Controlled Clinical Trials* 1989;**10**:1205–345.
- Bonchek LI. Sounding board: are randomized trials appropriate for evaluating new operations? *New England Journal of Medicine* 1979;**301**:44–5.
- Botros S. Equipoise, consent, and the ethics of randomised controlled trials. In: Byrne P, editor. *Ethics and law in health care*. Chichester: Wiley, 1990:9–24.
- Bracken MB. Clinical trials and the acceptance of uncertainty. *British Medical Journal* 1987;**294**:1111–2.
- Bradley C. Designing medical and educational intervention studies. A review of some alternatives to conventional randomised controlled trials. *Diabetes Care* 1993;**16**:509–18.
- Brewin CR, Bradley C. Patient preferences and randomized clinical trials. *British Medical Journal* 1989;**229**:313–5.
- Brown B. Statistical controversies in the design of clinical trials – some personal views. *Controlled Clinical Trials* 1980;**1**:13–27.
- Brown BW, Herson J, Atkinson EN, Rozell ME. Projection from previous studies: a Bayesian and frequentist compromise. *Controlled Clinical Trials* 1987;**8**:29–44.
- Bruera E. Ethical issues in palliative care research. *Journal of Palliative Care* 1994;**10**:7–9.
- Bulpitt CJ. *Randomised controlled clinical trials*. The Hague: Nijhoff, 1983.
- Burkhardt R, Kienle G. Controlled clinical trials and medical ethics. *Lancet* 1978;1356–9.
- Burkhardt R, Kienle G. Basic problems in controlled trials. *Journal of Medical Ethics* 1983;**9**(2):90–3.
- Buyse M. Randomized clinical trials in surgical oncology. *European Journal of Surgical Oncology* 1991;**17**(5):421–8.
- Byar DP. The necessity and justification of randomized clinical trials. In: Tagnon, Staquet, editors. *Controversies in cancer*. New York: Masson, 1979:15–20, 75–82.
- Byar DP. Problems with using observational databases to compare treatments. *Statistics in Medicine* 1991;**10**:663–6.

- Byar DP, Simon RM, Friedewald WT, *et al.* Randomized clinical trials. Perspectives on some recent ideas. *New England Journal of Medicine* 1976;**295**:74–80.
- Byar DP, Schoenfield DA, Green SB, *et al.* Design considerations for AIDS trials. *New England Journal of Medicine* 1990;**323**:1343–8.
- Byer A. The practical and ethical defects of surgical randomised prospective trials. *Journal of Medical Ethics* 1983;**9**:90–3.
- Campbell KA. Knots in the fabric: Richard Pearson Strong and the Bilbid Prison vaccine trials, 1905–1906. *Bulletin of the History of Medicine* 1994;**68**:600–38.
- Canner PL. In: Freund, PA, editor. Experimentation with human subjects. New York: George Braziller, 1970.
- Canner PL. Further comment on “statistical inference from clinical trials: choosing the right *p*-value”. *Controlled Clinical Trials* 1983;**4**(1):35.
- Caplan A. Is there a duty to serve as a subject in biomedical research? *IRB: Human Subjects Research* 1984;**6**:1–5.
- Cappelleri JC, Trochim WM. Ethical and scientific features of cutoff-based designs of clinical trials. *Medical Decision Making* 1995;**15**:387–94.
- Cappelleri JC, Ioannidis JP, Schmid CH, de Ferranti SD, Aubert M, Chalmers TC, *et al.* Large trials vs meta-analysis of smaller trials: how do their results compare? *JAMA* 1996;**276**:1332–8.
- Capron AM. Human experimentation: basic issues. In: Reich, editor. Encyclopedia of bioethics. New York: Free Press, 1978:692–9.
- Capron AM. Protection of research subjects: do special rules apply in epidemiology? *Journal of Clinical Epidemiology* 1991;**44**:184–90.
- CASS Principal Investigators and their Associates. Coronary Artery Surgery Study (CASS): a randomized trial of coronary artery bypass surgery. Comparability of entry characteristics and survival in randomized and non-randomized patients meeting the randomization criteria. *Journal of the American College of Cardiology* 1984;**3**:114–28.
- Cassel CK. Research in nursing homes: ethical issues. *Journal of the American Geriatrics Society* 1985;**33**:795–9.
- Cassileth BR, Lusk EJ, Miller DS, Hurtwitz S. Attitudes toward clinical trials among patients and the public. *JAMA* 1982;**248**:968–70.
- Cassileth BP, Knuiman MW, Abeloff MD, Falkson G, Ezdinli EZ, Mehta CR. Anxiety levels in patients randomized to adjuvant therapy vs observation for early breast cancer. *Journal of Clinical Oncology* 1986;**4**:972–4.
- Cavan DH. Ethics of clinical trials of ineffectual therapies. *IRB: A Review of Human Subjects Research* 1981;**3**(5):10–11.
- Challah S, Mays NB. The randomised controlled trial in the evaluation of new technology: a case study. *British Medical Journal* 1986;**292**:877–8.
- Chalmers I. Letter to the editor. *New England Journal of Medicine* 1991;**21**:1514.
- Chalmers I, Chalmers TC. Randomisation and patient choice. *Lancet* 1994;**344**:892–3.
- Chalmers I, Silverman WA. Professional and public double standards on clinical experimentation. *Controlled Clinical Trials* 1987;**8**:388–91.
- Chalmers I, Sinclair JC. Promoting perinatal health: is it time for a change of emphasis in research? *Early Human Development* 1985;**10**:171–91.
- Chalmers TC. When should randomization begin? *Lancet* 1968:858.
- Chalmers TC. Impact of controlled trials on practice of medicine. *Mount Sinai Journal of Medicine* 1974;**41**:753–9.
- Chalmers TC. Randomization of the first patient. *Medical Clinics of North America* 1975a;**59**:1035–8.
- Chalmers TC. Ethical aspects of clinical trials. *American Journal of Ophthalmology* 1975b;**79**:753–8.
- Chalmers TC. Randomized clinical trials in surgery. In: Delaney JP, editor. Controversy in surgery. Philadelphia: Saunders, 1976:3–11.
- Chalmers TC. Invited remarks on terminating a long-term clinical trial. *Clinical Pharmacology and Therapeutics* 1979;**25**(5):649–50.
- Chalmers TC. A potpourri of RCT topics. *Controlled Clinical Trials* 1982;**3**:285–98.
- Chalmers TC. Ethical implications of rejecting patients for clinical trials. *JAMA* 1990;**263**:865.
- Chalmers TC, Lau J. Meta-analytic stimulus for changes in clinical trials. *Statistical Methods in Medical Research* 1993;**2**(2):161–72.
- Chalmers TC, Lau J. Changes in clinical trials mandated by the advent of meta-analysis. *Statistics in Medicine* 1996;**15**(12):1263–8,1269–72.
- Chalmers TC, Block JB, Lee S. Controlled studies in clinical cancer research. *New England Journal of Medicine* 1972;**287**:75–8.
- Chalmers TC, Levin H, Sacks HS, Reitman D, Berrier J, Nagalingam R. Meta-analysis of clinical trials as a scientific discipline. I: control of bias and comparison with large co-operative trials. *Statistics in Medicine* 1987;**6**:315–28.
- Chalmers TC, Hewett P, Reitman D, Sacks HS. Selection and evaluation of empirical research in technology assessment. *International Journal of Technology Assessment in Health Care* 1989;**5**:521–36.
- Chard JA, Lilford RJ. The use of equipoise in clinical trials. *Social Science and Medicine* 1998;**47**(7):891–8.
- Charlton BG. Randomized clinical trials: the worst kind of epidemiology? *Nature Medicine* 1995;**1**:1101–2.

- Chipman JJ. Study design for final height determination in Turner syndrome: pros and cons. *Hormone Research* 1993;**39**(2):18–22.
- Clarke A. Problems of clinical research in dementia. In: Wilcock GK, editor. *The management of Alzheimer's disease*. Petersfield: Wrighton Biomedical Publishing, 1993:161–73.
- Clayton D. Ethically optimized designs. *British Journal of Clinical Pharmacology* 1982;**13**:469–80.
- Cleophas TJ. Clinical trials: specific problems associated with the use of a placebo-control group. *Journal of Molecular Medicine* 1995;**73**:421–4.
- Cohen J. Clinical trial monitoring: hit or miss? *Science* 1994;**264**:1534–7.
- Collier J. Confusion over the use of placebos in clinical trials. *British Medical Journal* 1995;**311**:821–2.
- Collins R, Gray R, Godwin J, Peto R. Avoidance of large biases and large random errors in the assessment of moderate treatment effects: the need for systematic overviews. *Statistics in Medicine* 1987;**6**:245–50.
- Collins R, Doll R, Peto R. Ethics of clinical trials. In: Williams CJ, editor. *Introducing new treatments for cancer: practical and legal problems*. Chichester: Wiley, 1992:49–66.
- Corbett F, Oldham J, Lilford R. Offering patients entry in clinical trials: preliminary study of the views of prospective participants. *Journal of Medical Ethics* 1996;**22**:227–31.
- Cornfield J. Sequential trials, sequential analysis and the likelihood principle. *American Statistician* 1966;**20**:18–23.
- Coulehan JL, Schaffner KF, Block M. Ethics of clinical trials in family medicine. *Journal of Family Practice* 1985;**21**:217–22.
- Cowan DH. The ethics of clinical trials of ineffectual therapy. *IRB: A Review of Human Subjects Research* 1981;**3**(5):10–11.
- Crisp R. *Routledge philosophy guidebook to Mill on utilitarianism*. London: Routledge, 1997.
- Crowley J, Green S, Lui P Y, Wolf M. Data monitoring committees and early stopping guidelines: the Southwest Oncology Group experience. *Statistics in Medicine* 1994;**13**:1391–9.
- Curran WJ. Reasonableness and randomization in clinical trials: fundamental laws and government regulations. *New England Journal of Medicine* 1979;**300**:1273–5.
- Cutler SJ, Greenhouse SW, Cornfield J, *et al.* The role of hypothesis testing in clinical trials. *Journal of Chronic Diseases* 1966;**19**:857–82.
- Dagan R. Clinical studies in pediatric respiratory-tract infections: what is desirable, feasible, or simply misleading? *Chemotherapy* 1992;**38**:18–24.
- Dal-re R. Informed consent in clinical research with drugs in Spain: perspectives of clinical trials committee members. *European Journal of Clinical Pharmacology* 1990;**38**:319–24.
- Dal-re R. Clinical trial of drugs: a study of the influence of information on adverse reactions on obtaining of informed consent. *Medicina Clinica* 1991;**96**(15):566–9.
- Dal-re R. Elements of informed consent in clinical research with drugs: a survey of Spanish clinical investigators. *Journal of Internal Medicine* 1992;**231**(4):375–9.
- Dal-re R. Good clinical practice in clinical trials: the responsibilities of the investigator. A survey of 827 hospital physicians (and II). Patient consent. *Medicina Clinica* 1993;**100**(11):423–7.
- Daughterty C, Ratain MJ, Grochowski E, Stocking C, Kodish E, Mick R, *et al.* Perceptions of cancer patients and their physicians involved in phase I trials. *Journal of Clinical Oncology* 1995;**13**(5):1062–72.
- Davis S, Wright PW, Schulman SF, Hill LD, Pinkham RD, Johnson LP, *et al.* Participants in a prospective, randomized clinical trials for resected non-small cell lung cancer have improved survival compared with non-participants in such trials. *Cancer* 1985;**56**:1710–8.
- Davis S, Seay J, Stone J, Bagley C, Johnson J, Speyer J, Smith S. Does knowing about clinical trials increase participation? *Proceedings of the American Society of Clinical Oncology* 1990;**9**:A232.
- Davis S, Seay J, Stone J, *et al.* Final report of 'Does knowing about clinical trials increase participation?' Unpublished.
- Day NE. Two-stage designs for clinical trials. *Biometrics* 1969;**25**:111–18.
- DCCT Research Group. Implementation of a multi-component process to obtain informed consent in a diabetes control and complications trial. *Controlled Clinical Trials* 1989;**10**:83–96.
- De Bono M, Fawdry RDS, Lilford RJ. Size of trials for evaluation of antenatal tests of fetal well-being in high risk pregnancy. *Journal of Perinatal Medicine* 1990;**18**:77–87.
- De Deyn PP. On the ethical acceptability of placebo application in neuropsychiatric research. *Acta Neurologica Belgica* 1995;**95**:8–17.
- de Groot JM, Kennedy SM. Integrating clinical and research psychiatry. *Journal of Psychiatry and Neuroscience* 1995;**20**(2):150–4.
- DeLuca SA, Korcusk LA, Oberstar BH, Rosenthal ML, Welsh PA, Topol EJ. Are we promoting true informed consent in cardiovascular clinical trials? *Journal of Cardiovascular Nursing* 1995;**9**(3) 54–61.
- Detsky AS, Naylor CD, O'Rourke K, McGeer AJ, L'abbe KA. Incorporating variation of the quality of individual randomized trials into meta-analysis. *Journal of Clinical Epidemiology* 1992;**45**:255–65.

- Donner A. The use of auxiliary information in the design of a clinical trial. *Biometrics* 1977;**33**(2):305–14.
- Dudley HAF. The controlled clinical trial and the advance of reliable knowledge: an outsider looking in. *British Medical Journal* 1983;**287**:957–60.
- Dudley HAF. Stones, lithotripters, trials, and arguments. *British Medical Journal* 1986;**292**:846–7.
- Duley L. Magnesium sulphate regimens for women with eclampsia: messages from the Collaborative Eclampsia Trial. *British Journal of Obstetrics and Gynaecology* 1996;**103**:103–5.
- Duley L, Johanson R. Magnesium sulphate for pre-eclampsia and eclampsia: the evidence so far. *British Journal of Obstetrics and Gynaecology* 1994;**101**:565–7.
- Dupont HL. Importance of collaborative research to improve world health. *Journal of Infectious Diseases* 1991;**163**(5):946–50.
- Dupont WD. Randomised vs historical clinical trials: are the benefits worth the costs? *American Journal of Epidemiology* 1985;**122**:904–46.
- Dutertre JP, Barbier P, Jonville AP, Autret E, *et al.* Children's participation in biomedical research. A planned survey of 541 parents. *Archives Francaises de Pediatrie* 1993;**50**(6):533–8.
- Dworkin G. Law and medical experimentation: of embryos, children and others with limited capacity. *Monash University Law Review* 1987;**13**:186–206.
- Dworkin G. The theory and practice of autonomy. Cambridge: Cambridge University Press, 1988.
- Eclampsia Trial Collaborative Group. Which anti-convulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. *Lancet* 1995;**345**:1455–63.
- Editorial. Ethics, philosophy and clinical trials. *Journal of Medical Ethics* 1983;**9**:59–60.
- Editorial. Evaluation of emerging technologies for coronary revascularization. *Circulation* 1992;**85**(1):357–61.
- Editorial. Clinical trials and clinical practice. *Lancet* 1993;**342**:877–8.
- Editorial. Your baby is in a trial. *Lancet* 1995;**345**:805–6.
- Edwards SJL. Ethical issues in the design and conduct of cluster randomised controlled trials. In preparation.
- Edwards SJL, Lilford RJ, Braunholtz DA, Jackson JC. Why 'underpowered' trials are not necessarily unethical. *Lancet* 1997;**350**:804–7.
- Edwards SJL, Lilford RJ, Braunholtz D. Advantages of trials units for clinical trials. In preparation.
- Eichler HG. Hazards of misguided ethics committees. *Lancet* 1995;**346**:1115–6.
- Eick TJ, Kofoed L. An unusual indication for a single-subject clinical trial. *Journal of Nervous and Mental Disease* 1994;**182**:587–90.
- Elander G, Hermon G. Placebo effect and randomized clinical trials. *Theoretical Medicine* 1995;**16**(2):171–82.
- Elbourne D. Subjects' views about participation in a randomised controlled trial. *Journal of Reproductive and Infant Psychology* 1987;**5**:3–8.
- Elks ML. The right to participate in research studies. *Journal of Laboratory and Clinical Medicine* 1993;**122**:130–6.
- Ellenberg SS, Cooper E, Eigo J, Finkelstein DM, Hoth DF, Nusinoff-Lehrman S, *et al.* Studying treatments for AIDS: new challenges for clinical trials – a panel discussion at the 1990 annual meeting of the Society for Clinical Trials. *Controlled Clinical Trials* 1990;**13**:272–92.
- Elliott GR. Dilemmas facing clinicians and researchers using anti-depressants to treat adolescents with depression. *Journal of Child and Adolescent Psychopharmacology* 1992;**2**:7–9.
- Emrich LJ, Sedrank N. Whether to participate in a clinical trial: the patient's view. In: Kadane JB, editor. Bayesian statistics and ethics in a clinical trial design. Chichester: Wiley, 1996:267–309.
- Engelhart HT. Diagnosing well and treating prudently: randomized clinical trials and the problem of knowing truly. In: Spicker SF, Alon I, de Vries A, Engelhart HT, editors. The use of human beings in research. Dordrecht: Kluwer, 1988:123–41.
- Epstein LC, Lasagna L. Obtaining informed consent: form or substance. *Archives of Internal Medicine* 1969;**123**:682–8.
- Ernst E, Resch KL. Clinical trials – methodological gold standard or naive reductionism? *Wiener Medizinische Wochenschrift* 1995;**145**(1):9–12.
- Ernst E, Resch KL. The clinical trial – gold standard or naive reductionism? *European Journal of Physical Medicine and Rehabilitation* 1996;**6**(1):26–7.
- Fagot-Largeault AM. Epistemological presuppositions involved in the programs of human research. In: Spicker SF, Alon I, de Vries A, Engelhart HT, editors. The use of human beings in research. Dordrecht: Kluwer, 1988:161–88.
- Fayers P, Armitage T. Towards an international register for cancer trials: the UKCCCR register of UK trials. *European Journal of Cancer* 1993;**29A**: 907–12.
- Fayers PM, Machin D. Sample size: how many patients are necessary? *British Journal of Cancer* 1995;**72**:1–9.
- Feenberg A. On being a human subject: interest and obligation in the experimental treatment of incurable disease. *Philosophical Forum* 1992;**23**(3):213–30.
- Feinstein AR. Clinical biostatistics XXIII. The role of randomization in sampling, testing, allocation and credulous idolatry. *Clinical Pharmacology and Therapeutics* 1973;**14**:898–915, 1035–51.
- Ferner U, Neumann N. Active control equivalence trials: some methodological aspects. *Psychopharmacology* 1992;**106**:S93–5.

- Fethé C. Beyond voluntary consent: Hans Jonas on the moral requirements of human experimentation. *Journal of Medical Ethics* 1993;**19**:99–103.
- Fetter MS, Feetham SL, Apolito K, *et al.* Randomized clinical trials: issues for researchers. *Nursing Research* 1989;**38**(2):117–20.
- Fetting JH, Siminoff LA, Piantadosi S, Abeloff MD, Damron DJ, Sarsfield AM. Effect of patients' expectations of benefit with standard breast cancer adjuvant chemotherapy on participation in a randomized clinical trial: a clinical vignette study. *Journal of Clinical Oncology* 1990;**8**:1476–82.
- Fisher RL, Fisher S. Anti-depressants for children. Is scientific support necessary? *Journal of Nervous and Mental Disease* 1996;**184**:99–102.
- Flanery, Gravdal, Hendrix, Hoffman, King, May, *et al.* Just sign here. *South Dakota Journal of Medicine* 1978;**31**:33.
- Fleming TR. Historical controls, data banks, and randomized trials in clinical research: a review. *Cancer Treatment Reports* 1982;**66**(5):1101–6.
- Fleming TR. Data monitoring committees and capturing relevant information of high quality. *Statistics in Medicine* 1993;**12**(5–6):565–70, 571–3.
- Fleming TR, DeMets DL. Monitoring of clinical trials: issues and recommendations. *Controlled Clinical Trials* 1993;**14**(3):183–97.
- Fleming TR, Waterlet LF. Approaches to monitoring clinical trials. *Journal of the National Cancer Institute* 1989;**81**:188–93.
- Fortin PR, Lew RA, Liang MH, Wright EA, Beckett LA, Chalmers TC, *et al.* Validation of a meta-analysis: the effects of fish oil in rheumatoid arthritis. *Journal of Clinical Epidemiology* 1995;**48**:1379–90.
- Fox TF. The ethics of clinical trials. *Medico-legal Journal* 1960;**28**:132–41.
- Freedman B. Equipoise and ethics of clinical research. *New England Journal of Medicine* 1987;**317**:141–5.
- Freedman B. Suspended judgement. AIDS and the ethics of clinical trials: learning the right lessons. *Controlled Clinical Trials* 1992;**13**(1):1–5.
- Freedman B, *et al.* Non-validated therapies and HIV Disease. *Hastings Center Report* 1989;**19**(3):14–20.
- Freedman B, Fuks A, Weijer C. In loco parentis: minimal risk as an ethical threshold for research upon children. *Hastings Center Report* 1993;**23**(2):13–19.
- Freedman LS. The size of clinical trials in cancer research – what are the current needs? *British Journal of Cancer* 1989;**59**:396–400.
- Freedman LS, Spiegelhalter DJ. Comparison of Bayesian with group sequential methods for monitoring clinical trials. *Controlled Clinical Trials* 1989;**10**:357–67.
- Freedman LS, Spiegelhalter DJ. Application of Bayesian statistics to decision making during a clinical trial. *Statistics in Medicine* 1992;**11**:23–35.
- Freedman LS, Lowe, Macaskill. Stopping rules for clinical trials incorporating clinical opinion. *Biometrics* 1984;**40**:575–86.
- Freedman LS, Spiegelhalter DJ, Parmar MKB. The what, why and how of Bayesian clinical trials monitoring. *Statistics in Medicine* 1994;**11**:23–35.
- Freedman N. A response to a purported ethical difficulty with randomised clinical trials involving cancer patient. *Journal of Clinical Ethics* 1992;**3**(3):231–4.
- Freeman PR. The role of *p*-values in analysing trial results. *Statistics in Medicine* 1993;**12**:1443–52.
- Freiman JA, Chalmers TC, Smith H Jr, Kuebler RR. The importance of beta. The type II error, and sample size in the design and interpretation of the RCT. *New England Journal of Medicine* 1978;**299**:690–4.
- Freireich EJ, Gehan EA. The limitations of the randomized clinical trial. *Methods in Cancer Research* 1979;**XVII**: 277–310.
- Freston JW. Dose ranging in clinical trials. Rationale and proposed use with placebo or positive controls. *American Journal of Gastroenterology* 1986;**81**:307–11.
- Freund PA. Introduction. Legal frameworks for human experimentation. In: Freund PA, editor. *Experimentation with human subjects*. New York: George Braziller, 1970: xii–1, 105–15.
- Fried C. *Medical experimentation: personal integrity and social policy*. Amsterdam: North-Holland, 1974.
- Friedman L, Wenger NK, Knatterud GL. Impact of the Coronary Drug Project findings on clinical practice. *Controlled Clinical Trials* 1983;**4**:513–22.
- Gallet M, Aupetit JF, Servan E, Lestaevl M, Lopez M, Chassoux G. Informed consent, what information is left after a therapeutic trial? *Archives des Maladies du Coeur et des Vaisseaux* 1994;**87**(1):39–45.
- Gallo C, Perrone F, De Placido S, Giusti C. Informed vs randomized consent to clinical trials. *Lancet* 1995;**346**:1060–4.
- Ganz PA. Do we need a new end point in clinical trials today? *Journal of the National Cancer Institute* 1989;**81**:1105–6.
- Ganz PA. Clinical trials. Concerns of the patient and the public. *Cancer* 1990;**65**:2394–9.
- Garcia J. Sharing research results with patients: the views of care-givers involved in a randomized controlled trial. *Journal of Reproductive and Infant Psychology* 1987;**5**:9–13.
- Gehan EA. Design of controlled clinical trials: use of historical controls. *Cancer Treatment* 1982;**66**:1089–93.
- Gehan EA, Freireich EJ. Non-randomized controls in cancer clinical trials. *New England Journal of Medicine* 1974;**290**:198–203.

- Geller NL. Planned interim analysis and its role in cancer clinical trials. *Journal of Clinical Oncology* 1987;**5**(9):1485–90.
- Geller NL, Pocock SJ. Interim analyses in randomized controlled trials: ramifications and guidelines for practitioners. *Biometrics* 1987;**43**:213–23.
- George SL. Discussion of “sequential methods based on the boundaries approach for the clinical trial comparison of survival times”. *Statistics in Medicine* 1994;**13**:1369–70.
- George SL, Chengchang LI, Berry DA, Green MR. Stopping a clinical trial early: frequentist and Bayesian approaches applied to a CALGB trial in non-small-cell lung cancer. *Statistics in Medicine* 1994;**13**:1313–27.
- Gerard MJ, Rouillon F, Miller HD, Dreyfus JP. Consent for clinical trials in psychiatry – results of a population survey. *Clinical Research and Regulatory Affairs* 1995;**12**(3):193–209.
- Gerard-Coue MJ, Rouillon F, Dreyfus JD. Enquete sur la participation aux essais therapeutiques en psychiatrie. *Encephale* 1994;**20**:421–6.
- Gerbarg SB, Horwitz RI. Resolving conflicting clinical trials. Guidelines for meta-analysis. *Journal of Clinical Epidemiology* 1988;**41**:503–90.
- Giertz G. Ethics of randomized clinical trials. *Journal of Medical Ethics* 1980;**6**:55–7.
- Gifford F. The conflict between randomized clinical trials and the therapeutic obligation. *Journal of Medicine and Philosophy* 1986;**11**:347–66.
- Gifford F. Community equipoise and the ethics of RCTs. *Bioethics* 1995;**9**(2):127–48.
- Gilbaldi M. Meta-analysis. A review of its place in therapeutic decision making. *Drugs* 1993;**46**(5):805–18.
- Gilbert JP. Patients must be told that treatment will be randomised. *British Medical Journal* 1995;**310**:125.
- Gilbert JP, McPeck B, Mosteller F. Statistics and ethics in surgery and anesthesia. *Science* 1977;**198**:684–9.
- Gilks WR, Thomas A, Spiegelhalter DJ. A language and programme for complex Bayesian modelling. *Statistician* 1994;**43**:169–78.
- Gillett GR. Ethics and dental research. *Journal of Dental Research* 1994;**73**(11):1766–72.
- Gillon R. Philosophical medical ethics. Chichester: Wiley, 1985.
- Gillon R. Recruitment for clinical trials: the need for public professional co-operation. *Journal of Medical Ethics* 1994;**20**:3–4.
- Glasser SP, Clark PI, Lipicky RJ, Hubbard JM, Yusuf S. Exposing patients with chronic, stable, exertional angina to placebo periods in drug trials. *JAMA* 1991;**265**(12):1550–4.
- Glasziou PP, Irwig Les M. An evidence-based approach to individualizing treatment. *British Medical Journal* 1995;**311**:1356–8.
- Goldberg HI, McGough H. The ethics of ongoing randomization trials. Investigation among inmates. *Medical Care* 1991;**29**(7):JS41–8.
- Goldman AI. Issues in design and sequential stopping rules for monitoring side-effects in clinical trials. *Controlled Clinical Trials* 1987;**8**:327–37.
- Goodare H, Smith R. The rights of patients in research. *British Medical Journal* 1995;**310**:1277–8.
- Goodman SN, Berlin JA. The use of predicted confidence intervals when planning experiments and the misuse of power when interpreting results. *Annals of Internal Medicine* 1994;**121**:201–6.
- Goodyear M, Levine M. From methodological to ethical issues in randomized trials, unpublished, 1987.
- Gore SM. The consumer principle of randomisation. *Lancet* 1994;**343**:58.
- Gracia D. Between the clinical trial and clinical ethics: good clinical practices. *Medicina Clinica* 1993;**100**(9):333–6.
- Grady C. Ethical issues in clinical trials. *Seminars in Oncology Nursing* 1991;**7**(4):288–96.
- Green S, Fleming TR, O’Fallon JR. Policies for study monitoring and interim reporting of results. *Journal of Clinical Oncology* 1987;**9**:1477–84.
- Greenhouse JB. On some applications of Bayesian methods in cancer clinical trials. *Statistics in Medicine* 1992;**11**:37–53.
- Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice: a systematic review of rigorous evaluations. *Lancet* 1993;**342**:1317–22.
- Gross M. Innovations in surgery. A proposal for phased clinical trials. *Journal of Bone and Joint Surgery* 1993;**75**(3):351–4.
- Grunkemeier GL, Starr A. Alterations to randomization in surgical studies. *Journal of Heart Valve Disease* 1992;**1**(2):142–51.
- Guyatt G, Sackett D, Taylor DW, Chong J, Roberts R, Pugsley S. Determining optimal therapy-randomized trials in individual patients. *New England Journal of Medicine* 1986;**314**:889–92.
- Guyatt GH, Jaeschke R. N of 1 randomized trials: where do we stand? *Weston Journal of Medicine* 1990;**152**:67.
- Guyatt GH, Heyting A, Jaeschke R, Keller J, Adachin JD, Roberts RS. N of 1 randomized trials for investigating new drugs. *Controlled Clinical Trials* 1990a;**11**:88–100.
- Guyatt GH, Keller JL, Jaeschke R, Rosenbloom D, Adachi JD, Newhouse MT. The N-of-one randomized controlled trial – clinical usefulness: our three year experience. *Annals of Internal Medicine* 1990b;**112**:293–9.
- Haines SJ. Randomized trials in the evaluation of surgical innovation. *Journal of Neurosurgery* 1979;**51**:5–11.

- Hall JC. The other side of statistical significance: a review of type II errors in the Australian medical literature. *Australian and New Zealand Journal of Medicine* 1982;**12**:7–9.
- Hamilton M. On informed consent. *British Journal of Psychiatry* 1983;**143**:416–8.
- Hammett TM, Dubler NN. Clinical and epidemiological research on HIV infection and AIDS among corrective inmates: regulations, ethics, and procedures. *Evaluation Review* 1990;**14**:482–501.
- Harrington D, Crowley J, George SL, Pajak T, Redmond, Wieand S. The case against independent monitoring committees. *Statistics in Medicine* 1994;**13**:1411–14.
- Harrison H. Neonatal intensive care: parents' role in ethical decision making. *Birth* 1986;**13**:165–75.
- Harrison K, Vlahov D, Jones K, Charron K, Clements ML. Medical eligibility, comprehension of the consent process, and retention of injection drug users recruited for an HIV vaccine trial. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology* 1995;**10**:386–90.
- Harth SC, Thong YH. Socio-demographic and motivational characteristics of parents who volunteer their children for clinical research: a controlled study. *British Medical Journal* 1990;**300**:1372.
- Harth SC, Thong YH. Parental perceptions and attitudes about informed consent in clinical research involving children. *Social Science and Medicine* 1995;**40**:1573–7.
- Hassar M, Weinstein M. "Uninformed" consent and the wealthy volunteer: an analysis of patient volunteers in a clinical trial of a new anti-inflammatory drug. *Clinical Pharmacology and Therapeutics* 1976;**20**(4):379–86.
- Hasselbald V, Mosteller F, Littenberg B, Chalmers TC, Hunink MG, Turner JA, *et al.* A survey of current problems in meta-analysis. Discussion from the Agency for Health Care Policy and Research inter-PORT Work Group on Literature Review/Meta-Analysis. *Medical Care* 1995;**33**:202–20.
- Hegel GWF. In: Wo AW, editor. Elements of the philosophy of right. Cambridge: Cambridge University Press, 1991.
- Heitjan DF, Houts PS, Harvey HA. A decision-theoretic evaluation of early stopping rules. *Statistics in Medicine* 1992;**11**(5):673–83.
- Hellman S. Editorial: randomised clinical trials and the doctor–patient relationship. An ethical dilemma. *Cancer Clinical Trials* 1979;**2**:189–93.
- Hellman S, Hellman DS. Of mice but not men. *New England Journal of Medicine* 1991;**324**:1585–9.
- Hennekens CH, Buring JE. Epidemiology in medicine. Boston: Little, Brown, 1987.
- Henry D, Hill S. Comparison should be against active treatments rather than placebos. *British Medical Journal* 1995;**310**:1279.
- Henshaw RC, Naji SA, Russell IT, Templeton AA. Comparison of medical abortion with surgical vacuum aspiration: women's preferences and the acceptability of treatment. *British Medical Journal* 1993;**307**:714–7.
- Henzlova MJ, Blackburn GH, Bradley EJ, Rogers WJ. Patient perception of a long-term clinical trial: experience using a close-out questionnaire in the studies of Left Ventricular Dysfunction (SOLVD) Trial. *Controlled Clinical Trials* 1994;**15**:281–93.
- Hilden J, Block JE, Andresson B, Visfeldt J. Ethics and decision theory in a clinical trial involving severe disfigurement. *Theoretical Surgery* 1987;**1**:183–9.
- Hilden J, Habbema JDF. The marriage of clinical trials and clinical decision science. *Statistics in Medicine* 1990;**9**:1243–57.
- Hill AB. The experimental approach in preventative medicine. *Journal of the Royal Institute of Public Health* 1958;**21**:177–218.
- Hill AB. Statistical methods in clinical and preventive medicine. London: Oxford University Press, 1962.
- Hill AB. Medical ethics and controlled trials. *British Medical Journal* 1963;**1**:1043–9.
- Hill C, Sancho-Garnier H. Interim analysis and early results in clinical trials. In: Tagnon HJ, Staquet MJ, editors. Controversies in cancer: design of trials and treatment. New York, 1979:51–3.
- Hobbes T. Leviathan: or the matter, form, and power of a commonwealth ecclesiastical. Oxford: Blackwell, 1946.
- Holden G, Rosenberg G, Barker K, Tuhirim S, Brenner B. The recruitment of research participants: a review. *Social Work and Health Care* 1993;**19**:1–44.
- Hollenberg NK, Dzau VJ, Williams GH. Letter to the editor: are uncontrolled clinical studies ever justified? *New England Journal of Medicine* 1980;**303**:1067.
- Horwitz RI. Large-scale randomised evidence: large, sample trials and overviews of trials: discussion. A clinician's perspective on meta-analyses. *Journal of Clinical Epidemiology* 1995;**48**(1):41–4.
- Howard JM, Demets D, BHAT Research Group. How informed is informed consent? The BHAT experience. *Controlled Clinical Trials* 1981;**2**:287–304.
- Hughes MD. Reporting Bayesian analysis of clinical trials. *Statistics in Medicine* 1993a;**12**:1651–65.
- Hughes MD. Stopping guidelines for clinical trials with multiple treatments. *Statistics in Medicine* 1993b;**12**:901–15.
- Hughes MD, Freedman LS, Pocock SJ. The impact of stopping rules on heterogeneity of results in overviews of clinical trials. *Biometrics* 1992;**48**:41–53.
- Hume D. Enquiries concerning human understanding and concerning the principles of morals, 3rd edn. Oxford: Clarendon Press, 1975.

- Hutchins SA, Eckes R. HIV infection. Clinical research. Considerations for prospective participants. *Nursing Clinics of North America* 1996;**31**:125–35.
- Hutton JL. Statistics is essential for professional ethics. *Journal of Applied Philosophy* 1995;**12**:253–61.
- Hutton JL. The ethics of randomized controlled trials: a matter of statistical belief? *Health Care Analysis* 1996;**4**:146, 1–146, 8.
- Illich I. Medical nemesis. New York: Pantheon Press, 1976.
- Ingelfinger FJ. The randomized clinical trial. *New England Journal of Medicine* 1972;**287**:100–1.
- Institute of Medical Ethics Working Party. AIDS, ethics, and clinical trials. *British Medical Journal* 1992;**305**:699–701.
- ISIS-2 Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both or neither among 17187 cases of acute myocardial infarction. *Lancet* 1988;**349**:53.
- Jaeschke R, Cook D, Sackett DL. The potential role of single-patient randomized controlled trials (N-of-1 RCTs) in clinical practice. *Journal of the American Board of Family Practice* 1990;**5**:227–9.
- Jaeschke R, Adachi JD, Guyatt GH, Keller JL, Wong B. Clinical usefulness of amitriptyline in fibromyalgia: the results of 23 N of 1 randomized controlled trials. *Journal of Rheumatology* 1991;**18**:447–51.
- Jensen AB, Madsen B, Anderson P, Rose C. Information for cancer patients entering a clinical trial: evaluation of an information strategy. *European Journal of Cancer* 1993;**29**:2235–8.
- Jha P, Deboer D, Sykora K, Naylor CD. Characteristics and mortality outcomes of thrombolysis trial participants and non-participants: a population-based comparison. *Journal of the American College of Cardiology* 1996;**27**:1335–42.
- Johannessen T. Controlled trials in single subjects. 1. Value in clinical medicine. *British Medical Journal* 1991;**303**:173–4.
- Johannessen T, Fosstvedt D, Petersen H. Combined single subject trials. *Scandinavian Journal of Primary Health Care* 1991;**9**:23–7.
- Johnson N, Lilford RJ, Brazier W. At what level of collective equipoise does a clinical trial become ethical. *Journal Medical Ethics* 1991;**17**:30–4.
- Jonas H. Philosophical reflections on experimenting with human subjects. *Daedalus* 1969;**98**:219–47.
- Jones B, Jarvis P, Lewis JA, Ebbutt AF. Trials to assess equivalence: the importance of rigorous methods. *British Medical Journal* 1996;**313**:36–9.
- Kadane JB. Progress toward a more ethical method for clinical trials. *Journal of Medicine and Philosophy* 1986;**2**:385–404.
- Kadane JB. Bayesian methods and ethics in a clinical trial design. Chichester: Wiley, 1996:3–19.
- Kadane JB, Seidenfeld T. Statistical issues in the analysis of data gathered in the new designs. In: Kadane JB, editor. Bayesian statistics and ethics in a clinical trial design. Chichester: Wiley, 1996:115–29.
- Kairys D. The law of clinical testing with human subjects. In: Kadane JB, editor. Bayesian statistics and ethics in a clinical trial design. Chichester: Wiley, 1996:223–51.
- Kant I. Groundwork of the metaphysic of morals. Translated and analysed by Paton HJ. London: Routledge, 1991.
- Kapp MB. Proxy decision making in Alzheimer disease research. *Alzheimer Disease Association* 1994;**8**(4):28–37.
- Kardinal CG. Ethical issues in cancer clinical trials. *Journal of the Louisiana State Medical Society* 1994;**146**(8):359–61.
- Karjalainen S, Palva I. Do treatment protocols improve end results? A study of survival of patients with multiple myeloma in Finland. *British Medical Journal* 1989;**299**:1069–72.
- Kassirer JP. Adding insult to injury: usurping patients' prerogatives. *New England Journal of Medicine* 1983;**308**:898–901.
- Katz J. Randomized clinical trials: am I my brother's keeper? *Journal of Clinical Gastroenterology* 1981;**3**:141–6.
- Katz J. Ethics and clinical research revisited: a tribute to Henry K. Beecher. *Hastings Center Report* 1993;**23**:31–9.
- Katz KD. Commentary on "the law of clinical testing with human subjects". In: Kadane JB, editor. Bayesian statistics and ethics in a clinical trial design. Chichester: Wiley, 1996:257–63.
- Kauffman RE. Drug trials in children: ethical, legal, and practical issues. *Journal of Clinical Pharmacology* 1994;**34**:296–9.
- Kaufman D. Cancer therapy and the randomized clinical trial: good medicine? *A Cancer Journal for Clinicians* 1993;**44**:109–14.
- Kemp N, Skinner E, Toms J. Randomized clinical trials of cancer treatment – a public opinion survey. *Clinical Oncology* 1984;**10**:155–61.
- Kennedy I. The law and ethics of informed consent and randomized controlled trials. In: Treat me right: essays in medical law and ethics. Oxford: Clarendon Press, 1988:213–24.
- King J. Informed consent: a review of the empirical evidence. Institute of Medical Ethics Bulletin Dec. 1986.
- Kleijnen J, Gotsche P, Chalmers I. So what's so special about randomization? In press.
- Klimt CR. The conduct and principles of randomised clinical trials. *Controlled Clinical Trials* 1981a;**1**:283–93.

- Klimt CR. Terminating a long-term clinical trial. *Controlled Clinical Trials* 1981b;1:319–25.
- Klimt CR, Canner PL. Terminating a long-term clinical trial. *Clinical Pharmacology and Therapeutics* 1979;25:641–6.
- Kodish E, Stocking C, Ratain MJ, Kohrman A, Siegler M. Ethical issues in phase in oncology research: a comparison of investigators and institutional review board chairpersons. *Journal of Clinical Oncology* 1992;10(11):1810–6.
- Kopelman L. Estimating risk in human research. *Clinical Research* 1981;29:1–8.
- Kopelman L. When is the risk minimal enough for children to be research subjects? In: Kopelman L, Moskop J, editors. *Children and health care: moral and social issues*. Dordrecht: Kluwer, 1989:89–102.
- Korn EL, Baumind S. Randomized clinical trials with clinician preferred treatment. *Lancet* 1991;337:149–52.
- Korsgaard CM. *Creating the kingdom of ends*. Cambridge: Cambridge University Press, 1991.
- Kramer M, Shapiro S. Scientific challenges in the application of randomised trials. *Journal of the American Medical Association* 1984;252:2739–45.
- L'abbe KA, Detsky AS, O'Rourke K. Meta-analysis in clinical research. *Annals of Internal Medicine* 1987;107:224–33.
- Lacher MJ. Patients and physicians as obstacles to a randomized trial. *Seminars in Oncology* 1981;8:424–9.
- Lamas GA, Pfeffer MA, Hamm P, Wertheimer J, Rouleau JL, Braunwald E. Do the results of randomized controlled trials of cardiovascular drugs influence medical practice? *New England Journal of Medicine* 1992;327:241–7.
- Langley GR, Sutherland HJ, Wong S, Minkin S, Llewellyn-Thomas HA, Till JE. Why are (or are not) patients given the option to enter clinical trials? *Controlled Clinical Trials* 1987;8:49–59.
- Lantos J. Ethical issues. How can we distinguish between clinical research and innovative therapy? *American Journal of Pediatric Hematology-Oncology* 1994a;16(1):72–5.
- Lantos J. Ethics, randomization and technology assessment. *Cancer* 1994b;74(9):2653–6.
- Larson EB, Ellsworth AJ, Oas J. Randomized clinical trials in single patients during a two year period. *JAMA* 1993;270:2708–12.
- Lasagna L. Special subjects in human experimentation. In: *Experimentation with human subjects*. 1970:262–75.
- Lau J, Chalmers TC. The rational use of therapeutic drugs in the 21st century. Important lessons from cumulative meta-analyses of randomized control trials. *International Journal of Technology Assessment in Health Care* 1995;11(3):509–22.
- Lau J, Schmid CH, Chalmers TC. Cumulative meta-analysis of clinical trials builds evidence for exemplary medical care. *Journal of Clinical Epidemiology* 1995;48:45–57, 59–60.
- Laupacis A. Research by collaboration. *Lancet* 1995;345:938.
- Laupacis A, Connolly SJ, Gent M, Roberts RS, Cairns J, Joyner C. How should results from completed studies influence ongoing clinical trials? The CAFA study experience. *Annals of Internal Medicine* 1991;115:818–22.
- Leading article. Qualms about innovative surgery. *Lancet* 1985;149:149.
- Lebacqz K. The National Commission and research in pharmacology: an overview. *Federation Proceedings* 1977;36(10):2344–8.
- Lebacqz K. Ethical aspects of clinical trials. In: Shapiro SH, Louis TA, editors. *Clinical trials: issues and approaches*. New York: Marcel Dekker, 1983:81–98.
- Lebacqz K, Levine RJ. Respect for persons and informed consent to participate in research. *Clinical Research* 1977;25(3):101–7.
- Lennox EL, Stiller CA, Morris Jones PH, Kinnier Wilson LM. Nephroblastoma: treatment during 1970–3 and the effect on survival of inclusion in the first MRC trial. *British Medical Journal* 1979;567–9.
- Lesser H. Obligation and consent. *Journal of Medical Ethics* 1989;15:195–6.
- Levene M, Wright I, Griffiths G. Is informed consent in neonatal randomized controlled trial ritual? *Lancet* 1996;347:475.
- Levine C. Ethics, epidemiology and women's health. *Annals of Epidemiology* 1994;4(2):159–65.
- Levine C, et al. Building a new consensus: principles and policies for clinical research on HIV/AIDS. *IRB: A Review of Human Subjects Research* 1991;13:1–17.
- Levine R. *Ethics and regulation of clinical research*. Baltimore: Urban and Schwarzenberg, 1981.
- Levine RJ. The use of placebos in randomized clinical trials. *IRB: A Review of Human Subjects Research* 1985;7:1–4.
- Levine RJ. *Ethics and regulation of clinical research*. Baltimore: Urban and Schwarzenberg, 1988.
- Levine RJ. Building a new consensus: principles and policies for clinical research. *IRB: A Review of Human Subjects Research* 1991;13:1–17.
- Levine RJ. Clinical trials and physicians as double agents. *Yale Journal of Biology and Medicine* 1992;65(2):65–74.
- Levine RJ. Ethics of clinical trials. Do they help the patient? *Cancer* 1993;72(1):2805–10.
- Levine RJ, Lebacqz K. Some ethical considerations in clinical trials. *Clinical Pharmacology and Therapeutics* 1979;25:728–41.

- Lewis RJ. An introduction to the use of interim analysis in clinical trials. *Annals of Emergency Medicine* 1993;**22**(9):1463–9.
- Liberati A. The relationship between clinical trials and clinical practice: the risks of underestimating its complexity. *Statistics in Medicine* 1994;**13**:1485–91.
- Liberati A. Meta-analysis: statistical alchemy for the 21st century: discussion. *Journal of Clinical Epidemiology* 1995;**48**(1):81–6.
- Light RJ. Accumulating evidence from independent studies: what we can win and what we can lose? *Statistics in Medicine* 1987;**6**:221–8.
- Lilford RJ. Clinical experimentation in obstetrics. *British Medical Journal* 1987;**295**:1298–300.
- Lilford RJ. Clinical experimentation in obstetrics. *British Medical Journal* 1988;**296**:571.
- Lilford RJ. Evaluating new treatments and technologies in perinatal medicine: practical problems, ethics and solutions. *International Journal of Technology Assessment in Health Care* 1989;**5**:459–72.
- Lilford RJ. Clinical trial numbers. *Lancet* 1990;**335**:483–4.
- Lilford RJ. The rise and fall of chorionic villus sampling. *British Medical Journal* 1991;**303**(6808):936–7.
- Lilford RJ. for the fetal compromise group. Formal measurement of clinical uncertainty: prelude to a trial in perinatal medicine. *British Medical Journal* 1994;**308**:111–12.
- Lilford RJ, Braunholtz D. The statistical basis of public policy: a paradigm shift is overdue. *British Medical Journal* 1996;**313**:603–7.
- Lilford RJ, Jackson JC. Equipoise and the ethics of randomisation. *Journal of the Royal Society of Medicine* 1995;**88**:552–9.
- Lilford RJ, Johnson N. The alpha and beta errors in randomised controlled trials. *New England Journal of Medicine* 1990;**322**:780–1.
- Lilford RJ, Thornton JG. Decision logic in medical practice. *Journal of the Royal College of Physicians* 1992;**26**:400–12.
- Lilford RJ, Thornton JG, Braunholtz D. Clinical trials and rare diseases: a way out of the conundrum. *British Medical Journal* 1995;**311**:1621–5.
- Llewellyn-Thomas HA, McGreal MJ, Theil EC, Fines, Erlichman C. Patients' willingness to enter clinical trials: measuring the association with perceived benefit and preference for decision participation. *Social Science and Medicine* 1991;**32**:35–42.
- Llewellyn-Thomas HA, McGreal MJ, Theil EC. Cancer-patients decision-making and trial entry preferences – the effects of framing information about short-term toxicity and long-term survival. *Medical Decision Making* 1995;**15**(1):4–12.
- Lockwood M, Anscombe GEM. Sins of omission? The non-treatment of controls in clinical trials. *Aristotelian Society* 1983;**57**:207–22.
- Logue G, Wear S. A desperate solution: individual autonomy and the double-blind controlled experiment. *Journal of Medicine and Philosophy* 1995;**20**(1):57–64.
- Love JW, Phil D. Drugs and operations: some important differences. *JAMA* 1975;**232**:37–8.
- Lurie P, Bishaw M, Chesney MA, Cooke M, Fernandes MEL, Hearst N, *et al.* Ethical, behavioural, and social aspects of HIV vaccine trials in developing countries. *JAMA* 1994;**271**(4):295–301.
- Lyons D. Forms and limits of utilitarianism. Oxford: Clarendon Press, 1965:119–60.
- Lynoe N, *et al.* Informed consent: study of the quality of information given to participants in a clinical trial. *British Medical Journal* 1991;**303**:610.
- Machin D. Interim analysis and ethical issues in the conduct of trials. In: Williams CJ, editor. *Introducing new treatments for cancer*. New York: Wiley, 1992.
- Machin D. Discussion of the “What, why and how of Bayesian clinical trial monitoring”. *Statistics in Medicine* 1994;**13**:1385–9.
- Mackillop WJ, Johnston PA. Ethical problems in clinical research: the need for empirical studies of the clinical trials process. *Journal of Chronic Diseases* 1986;**39**(3):177–88.
- McLean PD. The effect of informed consent on the acceptance of random treatment assignment in a clinical population. *Behavior Therapy* 1980;**11**:129–32.
- McPherson K. On choosing the number of interim analyses in clinical trials. *Statistics in Medicine* 1982;**12**:25–36.
- McPherson K. The Cochrane Lecture. The best and the enemy of the good: randomized controlled trials, uncertainty, and assessing the role of patient choice in medical decision-making. *Journal of Epidemiology and Community Health* 1994;**48**:6–15, 423–4.
- Madden M. In: Alderson P, editor. *Breast cancer, randomised controlled trials and consent*. London: SSRY, 1994:62–76.
- Mahon J, Laupacis A, Donner A, Wood T. Randomised study of n of 1 trials vs standard practice. *British Medical Journal* 1996;**312**:1069–74.
- Mahon JL, Feagan BG, Laupacis A. Ethics of N-of-1 trials. *Lancet* 1995;**345**:989.
- Mammel KA and Kaplan DW. Research consent by adolescent minors and institutional review boards. *Journal of Adolescent Health* 1995;**17**:323–30.
- Mann AH. The psychological effect of a screening programme and clinical trial for hypertension on the participants. *Psychological Medicine* 1977;**7**:431–8.

- Mariner. The ethical conduct of clinical trials of HIV vaccines. *Evaluation Review* 1990;**14**:538–64.
- Marini JL, Sheard MH, Bridges CI. An evaluation of informed consent with volunteer prisoner subjects. *Yale Journal of Biology and Medicine* 1976;**427**:434.
- Markman M. Ethical difficulties with randomized clinical trials involving cancer patients. *Journal of Clinical Ethics* 1992;**3**:193–5.
- Marquis D. Leaving therapy to chance. *Hastings Center Report* 1983;**13**(4):40–7.
- Marsden J, Sacks NPD, Baum M, Whitehead MI, Crook D. A pilot study investigating the feasibility of conducting a randomised trial of HRT use in women with a history of breast cancer – preliminary report of findings. Unpublished.
- Maslin A. A survey of the opinions on “informed consent” of women currently involved in clinical trials within a breast unit. *European Journal of Cancer Care* 1994;**3**(4):153–62.
- Mathews D. Comment on ‘clinical experimentation in obstetrics’. *British Medical Journal* 1988;**296**:66.
- Mattson ME, *et al.* Participation in a clinical trial: the patients’ point of view. *Controlled Clinical Trials* 1985;**6**:156–67.
- Mautner T. The Penguin dictionary of philosophy. London: Penguin Books, 1997.
- Meier P. Terminating a trial – the ethical problem. *Clinical Pharmacology and Therapeutics* 1979;**25**:633–40.
- Meinert CL. When and how to stop a clinical trial. *Clinical Pharmacology and Therapeutics* 1979;**25**(5):632.
- Meisel A, Roth L. Toward a informed discussion of informed consent: a review and critique of the empirical studies. *Arizona Law Review* 1983;**25**:265–46.
- Mettlin C, Cummings KM, Walsh D. Risk factor and behavioural correlates of willingness to participate in cancer prevention trials. *Nutrition and Cancer* 1985;**7**:189–98.
- Mike V. Modern medicine: perspectives on harnessing its vast emerging power. *Technology in Society* 1988;**10**:327–38.
- Mike V. Towards an ethics of evidence – and beyond: observations on technology and illness. *Research in Philosophy and Technology* 1989a;**9**:101–13.
- Mike V. Philosophers assess randomized clinical trials: the need for dialogue. *Controlled Clinical Trials* 1989b;**10**(3):244–53.
- Mike V, Krauss AN, Ross GS. Neonatal extracorporeal membrane oxygenation: clinical trials and the ethics of evidence. *Journal of Medical Ethics* 1993;**19**(4):212–8.
- Mill JS. Utilitarianism, 5th edn. London: Longmans, Green, Reader and Dyer, 1874.
- Miller BL. The ethics of cardiac arrest research. *Annals of Emergency Medicine* 1993;**22**(1):118–24.
- Miller C, Searight HR, Grable D, Schwartz R, Sowell C, Barbarash RA. Comprehension and recall of the informational content of the informed consent document: an evaluation of 168 patients in a controlled clinical trial. *Journal of Clinical Research and Drug Development* 1994;**8**:237–48.
- Miller ST, Appelgate WB. Clinical trials in elderly persons. *Journal of the American Geriatrics Society* 1985;**33**:91–2.
- Millon-Underwood. Determinants of participation in state-of-the-art cancer prevention, early detection? screening, and treatment trials. *Cancer Nursing* 1993;**16**(1):25–33.
- Minogue BP, Palmer-Ferandez G, Udell L, Waller BN. Individual autonomy and the double-blind controlled experiment: the case of the desperate volunteer. *Journal of Medicine and Philosophy* 1995;**20**(1):43–55.
- Moore D, Papp AJ. Commentary on “the law of clinical testing with human subjects”. In: Kadane JB, editor. Bayesian statistics and ethics in a clinical trial design. Chichester: Wiley, 1996:251–7.
- Morris RE, Brown B. Commentary: Tacrolimus for prevention of liver allograft rejection: clinical trials and tribulations. *Lancet* 1995;**346**:1310.
- MRC. Medical Research Council series. The ethical conduct of research in children. London: MRC, 1991.
- MRC Working Group on Leukaemia in Childhood. Duration of survival of children with acute leukemia. *British Medical Journal* 1971;**4**:7–9.
- Munir K. Ethical principles governing research in child and adolescent psychiatry. *Journal of the American Academy of Child and Adolescent Psychiatry* 1992;**31**(3):408–14.
- Myers MG, Cairns JA, Singer J. The consent form as a possible cause of side-effects. *Clinical Pharmacology and Therapeutics* 1987;**42**(3):250–3.
- National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: ethical principles and guidelines for the protection of human subjects of research. DHEW Publication No. (OS) 78-0012. Washington, DC: DHEW, 1978.
- Neuberger J. The patient’s view of the patient-health care worker relationship. In: Gillon R, editor. Principles of health care ethics. Chichester: Wiley, 1994:377–86.
- Neugebauer E. Conventional vs laparoscopic cholecystectomy and the RCT. *British Journal of Surgery* 1991;**78**(2):150–4.
- Newell DJ. Type 2 errors and ethics. *British Medical Journal* 1789, 1978.
- Nicholson RH. Replication of clinical trials. *Lancet* 1986;**ii**:518.
- Nowak R. Problems in clinical trials go far beyond misconduct. *Science* 1994;**264**:1538–41.

- Nyapadi TJ. Legal aspects of medical research and the way forward. *The Central African Journal of Medicine* 1995;**41**(3):73–6.
- Oakley A. Who's afraid of the randomised controlled trial? Some dilemmas of the scientific method and "good" research practice. *Women and Health* 1990;**15**:25–59.
- Oakley A. Women's knowledge and experience of breast cancer treatment and research. London: Social Science Research Unit, 1992.
- Oddens BJ, Algra A, van Gijn J. How much information is retained by participants in clinical trials? *Nederlands Tijdschrift voor Geneeskunde* 1992;**136**:2272–6.
- Oettinger W, Berger HG. Commentary on: the rise and fall of the randomized controlled trial in surgery. *Theoretical Surgery* 1989;**4**:170.
- Olschewski M, Schumacher M, Davis KB. Analysis of randomized and non-randomized patients in clinical trials using the comprehensive cohort follow-up study design. *Controlled Clinical Trials* 1992;**13**:226–39.
- Olver IN, Buchanan L, Laidlaw C, Poulton G. The adequacy of consent forms for informing patients entering oncological clinical trials. *Annals of Oncology* 1995;**6**:867–70.
- Palmer CR. Ethics and statistical methodology in clinical trials. *Journal of Medical Ethics* 1993;**19**(4):219–22.
- Palmer CR. Recent advances in adaptive clinical trials. Paper presented at annual meeting of the American Statistical Association, 1995.
- Palmer CR, Rosenberger WF. Ethics and practice: alternative designs for phase 3 randomised controlled trials. In press.
- Parmar MKB, Machin D. Monitoring clinical trials: experience of, and proposals under consideration by, the cancer therapy committee of the British Medical Research Council. *Statistics in Medicine* 1993;**12**:497–504.
- Passamani E. Clinical trials – are they ethical? *New England Journal of Medicine* 1991;**324**:1589–92.
- Pellegrino ED, Thomasma DC. A philosophical basis of medical practice. New York: Oxford University Press, 1981.
- Penman DT, Holland JC, Bahna GF, et al. Informed consent for investigational chemotherapy: patients' and physicians' perceptions. *Journal of Clinical Oncology* 1984;**2**:849–55.
- Peto R. Why do we need systematic overviews of randomized clinical trials? *Statistics in Medicine* 1987;**6**:233–40.
- Peto R, Pike MC, Armitage P, Breslow NE, Cox DR, Howard SV, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. *British Journal of Cancer* 1976;**34**:585–612.
- Pfeffer MR. Ethics and the oncologist. *Medicine and Law* 1993;**12**(3–5):235–40.
- Piaget J. The language and thought of the child. London: Harcourt, Brace, 1926.
- Pignon JP, Arrigada R. Early stopping rules and long-term follow-up in phase iii trials. *Lung Cancer* 1994;**10**(1):S151–9.
- Pocock SJ. The combination of randomized and historical controls in clinical trials. *Journal of Chronic Diseases* 1975;**29**:175–88.
- Pocock SJ. Group Sequential methods in the design and analysis of clinical trials. *Biometrika* 1977;**64**:191–9.
- Pocock SJ. Can sequential methods be used for analysis of cancer clinical trials. In: Controversies in cancer. 1979:63–74.
- Pocock SJ. Current issues in the design and interpretation of clinical trials. *British Medical Journal* 1985;**290**:39–42.
- Pocock SJ. Statistical and ethical issues in monitoring trials. *Statistics in Medicine* 1993;**12**:1459–75.
- Pocock SJ, Hughes MD. Practical problems in interim analysis, with particular regard to estimation. *Controlled Clinical Trials* 1989;**10**:209S–21S.
- Pocock SJ, Hughes MD. Estimation issues in clinical trials and overviews. *Statistics in Medicine* 1990;**9**:657–6.
- Pollock AV. The rise and fall of the random controlled surgery. *Theoretical Surgery* 1989;**4**:163–70.
- Pollock AV. Surgical evaluation at the crossroads. *British Journal of Surgery* 1993;**80**(8):964–6.
- Postlethwaite RJ, Reynolds JM, Wood AJ, Evans JH, Lewis MA. Recruiting patients to clinical trials: lessons from studies of growth hormone treatment in renal failure. *Archives of Disease in Childhood* 1995;**73**(1):30–5.
- Popper KR. Conjectures and Refutations: the growth of scientific knowledge. London: Routledge and Kegan Paul, 1963.
- Powell-Tuck J, Macrae KD, Healy MJR, Lennard-Jones JE, Parkins RA. A defence of the small clinical trial: evaluation of three gastroenterological studies. *British Medical Journal* 1986;**292**:599–602.
- Prentice ED, et al. IRB review of a phase II randomized clinical trial involving incompetent patients suffering from severe closed head injury. *IRB: A Review of Human Subjects Research* 1993;**15**:1–7.
- Prescott RJ. Feedback of data to participants during clinical trials. In: Tagnon HJ, Staquet MJ, editors. Controversies in cancer: design of trials and treatment. New York, 1979:55–61.
- Prestifilippo J. The ethical treatment of cancer: what is right for the patient? *Cancer* 1993;**72**:2817–9.
- Pringle M, Churchill R. Randomized controlled trials in general practice: gold standard or fool's gold? *British Medical Journal* 1995;**311**:1382–3.

- Properit KJ, Dillman RO, Seagren SL, Green MR. Chemotherapy and radiation therapy as compared with radiation therapy in stage 3 non-small cell cancer. *New England Journal of Medicine* 1991;**323**:1136–7.
- Rahimtoola SH. Some unexpected lessons from large multicenter randomized clinical trials. *Circulation* 1985;**72**:449–55.
- Raju TN, Langenberg P, Sen A, Aldana O. How much “better” is good enough? The magnitude of treatment effect in clinical trials. *American Journal of Diseases of Children* 1992;**146**(4):407–11.
- Reber AS. The Penguin dictionary of psychology. London: Penguin Books, 1985.
- Reemtsma K. Experimental surgery: what is it? In: Herter FP, editor. Human and ethical issues in the surgical care of patients with life-threatening disease. Springfield: Charles C Thomas, 1986:183–6.
- Reidenberg M. Should unevaluated therapies be available for sale? *Clinical Pharmacology and Therapeutics* 1987;**42**:6.
- Reiser J, Warner JO. The value of participating in an asthma trial. *Lancet* 1985;**i**:206–7.
- Reiser SJ. Human experimentation and the convergence of medical research and patient care. *Annals of the American Academy of Politics and Social Science* 1978;**437**:8–18.
- Report of an Institute of Medical Ethics Working Party. In: Nicholson R, editor. Medical research with children: ethics, law and practice. Oxford: Oxford University Press, 1986.
- Report to the Health Services and Public Health Review Board. Health technology assessment in surgery: the role of the randomized clinical trial. 1993.
- Richardson JL, Myrtle R, Solis JM, Hiisserich JW, Oliver D. Participation of community medical oncologists in clinical research trials. *Progress in Clinical Biology Research* 1986;**216**:269–80.
- Roberson NL. Clinical trial participation. Viewpoints from racial/ethnic groups. *Cancer* 1994;**74**:2687–91.
- Robiner WN, Melroe H, Campbell S, Rhame FS, Colon E, Chung J, et al. Psychological effects of participation and non-participation in a placebo-controlled zidovudine clinical trial with asymptomatic human immunodeficiency virus-infected individuals. *Journal of Acquired Immune Deficiency Syndromes* 1993;**6**(7):765–808.
- Rockhold FW, Enas GG. Data monitoring committees and the pharmaceutical industry: ethical and logistic considerations. *Statistics in Medicine* 1993;**12**:471–9.
- Rodebuis S, Van den Heuvel WJA, Amyas AA, Koops HS, Sleijfer DTH, Mulder NH. Patient motivation and informed consent in a phase I study of anticancer agent. *European Journal of Cancer Clinical Oncology* 1984;**20**:457–62.
- Ross MW, Jeffords K, Gold J. Reasons for entry into and understanding of HIV/AIDS clinical trials: a preliminary study. *AIDS Care* 1993;**6**(1):77–82.
- Rothman DJ. Ethics and human experimentation. *New England Journal of Medicine* 1987;**317**(19):1195–9.
- Rothman KJ. Placebo mania. *British Medical Journal* 1996;**313**:3–4.
- Rothman KJ, Michels KB. The continuing unethical use of placebo controls. *New England Journal of Medicine* 1994;**331**:394–8.
- Roy DJ. Controlled clinical trials: an ethical imperative. *Journal of Chronic Diseases* 1986a;**39**(3):159–62.
- Roy DJ. Ethics in clinical research and clinical practice. *Clinical and Investigative Medicine* 1986b;**9**:283–9.
- Royall RM. Ethics and statistics in randomized clinical trials, with discussion. *Statistical Science* 1991;**6**:52–88.
- Rubinstein LV, Gail MH. Monitoring rules for stopping accrual to comparative survival studies. *Controlled Clinical Trials* 1982;**3**:325–43.
- Rudicel S, Esdaile J. The randomized clinical trial in orthopaedics: obligation or option. *Journal of Bone and Joint Surgery* 1985;**67**:1284–93.
- Ruse M. At what level of statistical certainty ought a random clinical trial be interrupted? In: The use of human beings in research. Boston: Kluwer, 1988:189–221.
- Russell PS. Commentary on: The rise and fall of the randomized controlled trial in surgery. *Theoretical Surgery* 1989;**4**:169–70.
- Rutstein DD. The ethical design of human experiments. In: Freund PA, editor. Experimentation with human subjects. New York: George Braziller, 1970:383–401.
- Sacks H, Chalmers T, Smith H. Randomised versus historical controls for clinical trials. *American Journal of Medicine* 1982;**72**:233–40.
- Savulescu J, Momeyer RW. Should informed consent be based on rational beliefs? *Journal of Medical Ethics* 1997;**23**(5):282–7.
- Saubrey N, Jensen J, Rasmussen PE, Gjørup T, Guldager H, Riis P. Danish patients’ attitudes to scientific-ethical questions: an interview study focusing on therapeutic trials. *Acta Medica Scandinavica* 1984;**215**:99–104.
- Schafer A. The ethics of randomized clinical trials. *New England Journal of Medicine* 1982;**307**:719–24.
- Schafer A. The randomized clinical trial: for whose benefit? *IRB: A Review of Human Subjects Research* 1985;**7**(2):4–6.
- Schaffner KF. Ethically optimizing clinical trials. In: Kadane JB, editor. Bayesian methods and ethics in a clinical trial design. New York: Wiley, 1996:19–63.
- Schain WS. Barriers to clinical trials part II: knowledge and attitudes of potential participants. *Cancer Supplement* 1994;**74**(9):2666–76.

- Schmoor C, Olschewski M, Schumacher M. Randomized and non-randomized patients in clinical trials: experiences with comprehensive cohort studies. *Statistics in Medicine* 1996;**15**:263–71.
- Schulz KF, Chalmers I, Hayes RJ, Altman DG. Empirical evidence of bias: dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *Journal of the American Medical Association* 1995;**273**:408–12.
- Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutic trials. *Journal of Chronic Diseases* 1967;**20**:637–48.
- Schwartz D, Flamant R, Lellouch J. Clinical trials. Academic Press, London. 1980.
- Scoles L, Silagy C. Are clinical trials in general practice ethical? *Australian Family Physician* 1993;**22**(2):182–3.
- Sedrank N. Issues of statistical design. In: Kadane JB, editor. Bayesian statistics and ethics in a clinical trial design. New York: Wiley, 1996:163–71.
- Segelov E, Tattershall MM, Coates AS. Redressing the balance – the ethics of not entering an eligible patient on a randomized clinical trial. *Annals of Oncology* 1992;**3**:103–5.
- Seibert C, Clark CM. Operational and policy considerations of data monitoring in clinical trials: the Diabetes Control and Complications Trial experience. *Controlled Clinical Trials* 1993;**14**:30–44.
- Senn S. Inherent difficulties with active control equivalence studies. *Statistics in Medicine* 1993a;**12**(24):236–75.
- Senn S. Suspended judgment N of 1 trials. *Controlled Clinical Trials* 1993b;**14**:1–5.
- Senn SJ. Falsificationism and clinical trials. *Statistics in Medicine* 1991a;**10**:1679–92.
- Senn SJ. Controlled clinical trials in single subjects. *British Medical Journal* 1991b;**303**:716–17.
- Sharp SJ, Thompson SG, Altman DG. The relation between treatment benefit and underlying risk in meta-analysis. *British Medical Journal* 1996;**313**:735–9.
- Shaw LW, Chalmers TC. Ethics in co-operative clinical trials. *Annals of the New York Academy of Sciences* 1970;**169**:487–95.
- Shimm DS, Spece RG. Ethical issues and clinical trials. *Drugs* 1983;**46**(4):579–84.
- Shinebourne EA. Ethics of innovative cardiac surgery. *British Heart Journal* 1984;**52**:597–601.
- Shuster JJ, Krischer JP, Boyett JM. Ethical issues in co-operative cancer trials from a statistical viewpoint. 1. A general overview. *American Journal of Pediatric Hematology/Oncology* 1985;**7**:57–63.
- Siebert C, Clark CM. Operational and policy considerations of data monitoring in clinical trials: the Diabetes Control and Complications trial. *Controlled Clinical Trials* 1993;**14**(1):30–44.
- Silva MD, Sorrell JM. Enhancing comprehension of information for informed consent: a review of empirical research. *IRB: Human Subjects Research* 1988;**10**:1–6.
- Silverman WA. Human experimentation: a guided step into the unknown. Oxford: Oxford University Press, 1985.
- Silverman WA, Altman DG. Patients' preferences and randomised trials. *Lancet* 1996;**347**:171–4.
- Sim I, Hlatky MH. Growing pains of meta-analysis. *British Medical Journal* 1996;**313**:702–3.
- Simberkoff MS, Hartigan PM, Hamilton JD, Deykin D, Gail M, Bartlett JG, *et al.* Ethical dilemmas in continuing a zidovudine trial after early termination of similar trials. *Controlled Clinical Trials* 1993;**14**(1):6–18.
- Simel DL, Feussner JR. A randomized controlled trial comparing quantitative informed consent formats. *Journal of Clinical Epidemiology* 1991;**44**(8):771–7.
- Simes RJ, Tattersall MHN, Coates AS, Raghaven D, Solomon HJ, Smartt H. Randomised comparison of procedures for obtaining informed consent in clinical trials of treatment of cancer. *British Medical Journal* 1986;**293**:1065–8.
- Simes SJ. Controlled trials in single subjects. *British Medical Journal* 1991;**303**:716–17.
- Siminoff LA, Fetting JH. Factors affecting treatment decisions for a life threatening illness: the case of medical treatment for breast cancer. *Social Science and Medicine* 1991;**32**(7):813–8.
- Simon R. Adaptive treatment assignment methods and clinical trials. *Biometrics* 1977;**33**:743–9.
- Simon R. Randomized clinical trials and research strategy. *Cancer Treatment Reports* 1982;**66**:1083–7.
- Simon R. Some practical aspects of the interim monitoring of clinical trials. *Statistics in Medicine* 1994;**13**:1401–9.
- Slevin M, Mossman J, Bowling A, *et al.* Volunteers or victims: patients' views of randomised clinical trials. *British Journal of Cancer* 1995;**71**:1270–4.
- Smith JS. Suspended judgment. Remembering the role of Thomas Francis, Jr. in the design of the 1954 Salk Vaccine Trial. *Controlled Clinical Trials* 1992;**13**(3):181–4.
- Smith M, Simon R, Cain D, Ungerleider RS. Children and cancer. A perspective from the cancer therapy evaluation programme, National Cancer Institute. *Cancer* 1993;**71**:3422–8.
- Smithells RW. Iatrogenic hazards and their effects. *Postgraduate Medical Journal* 1975;**15**:39–52.
- Snowdon C, Garcia J, Elbourne D. Understanding randomisation: parental responses to the allocation of alternative treatments in a clinical trial involving their critically ill newborn babies. *Social Science and Medicine* 1997;**45**(9):1337–55.

- Spaight SJ, Nash S, Finison LJ, *et al.* Medical oncologists' participation in cancer clinical trials. In: *Advances in cancer control: epidemiology and research*. New York: Alan R. Liss, 1984:49–61.
- Spicker SF, Alon I, De Vries A, Engelhardt HT. The use of human beings in research, with special reference to clinical trials. Boston: Kluwer, 1988.
- Spiegelhalter DJ. Statistical issues in studies of individual response. *Scandinavian Journal of Gastroenterology* 1988;**147**:40–5.
- Spiegelhalter DJ, Freedman LS, Parmar MK. Applying Bayesian ideas in drug development and clinical trials. *Statistics in Medicine* 1993;**12**(15–16):1501–11, 1513–7.
- Spiegelhalter DJ, Freedman LS, Parmar MKB. Bayesian approaches to randomised trials. *Journal of the Royal Statistical Society* 1994;**157**:357–416.
- Spielberger CD. State-trait anger expression inventory: professional manual review. Odessa, FL: Psychological Assessment Resources, 1988.
- Spiro HM. Doctors, patients and placebos. Yale University Press, London. 1986.
- Spodick DH. The surgical mystique and the double standard. Controlled trial of medical and surgical therapy for cardiac disease. *American Heart Journal* 1973;**85**:579–83.
- Spodick DH. The randomized controlled clinical trial: scientific and ethical bases. *American Journal of Medicine* 1982;**73**:420.
- Spoto M, Krailo MD. Use of unequal allocation in survival trials. *Statistics in Medicine* 1987;**6**:119–26.
- Stamer CF, Lee KL. A data-based approach to assessing clinical interventions in the setting of chronic disease. *Cancer Treatment Reports* 1982;**66**:1083–7.
- Stamler J. Invited remarks on “Terminating a long-term clinical trial”. *Clinical Pharmacology and Therapeutics* 1979;**25**(5):651–4.
- Steinberg A. Ethical considerations in modern human experimentation. *Cancer Investigation* 1991;**9**(1):99–105.
- Stephens RJ, Gibbons D. The impact of clinical trials of the treatment of lung cancer. *Clinical Oncology* 1993;**5**:211–9.
- Stephenson T. Telling parents all relevant details might reduce recruitment of children to trials. *British Medical Journal* 1996;**313**.
- Stewart LA. The role of overviews. In: Williams CJ, editor. *Introducing new treatments for cancer: practical, ethical, and legal problems*. Chichester: Wiley, 1992:383–401.
- Stewart LA, Parmar MKB. Meta-analysis of the literature or of individual patient data: is there a difference? *Lancet* 1993;**341**:418–22.
- Stiller CA. Survival of patients with cancer: those included in clinical trials do better. *British Medical Journal* 1989;**299**:1058–9.
- Stiller CA. Centralized treatment, entry to trials and survival. *British Journal of Cancer* 1994;**70**:352–62.
- Stiller CA, Draper GJ. Treatment centre size, entry to trials, and survival in acute lymphoblastic leukemia. *Archives of Diseases in Childhood* 1989;**64**:219–23.
- Stiller CA, Eatock EM. Survival from acute non-lymphocytic leukaemia 1971–88: a population-based study. *Archives of Diseases in Childhood* 1994;**70**:219–23.
- Stirrat GM, Farrow SC, Farndon J, Dwyer M. The challenge of evaluating surgical procedures. *Annals of the Royal College of Surgeons of England* 1992;**74**(2):80–4.
- Sutherland HJ, Meslin EM, Till JE. What's missing from current clinical trial guidelines? A framework for integrating science, ethics, and the community context. *Journal of Clinical Ethics* 1994;**5**(4):297–303.
- Sutton-Tyrrell K, Snyder JV, Kelsey S, Abramson N. Brain Resuscitation Clinical Trial Study Group. Risk monitoring of randomized trials in emergency medicine. *American Journal of Emergency Medicine* 1991;**9**(2):112–7.
- Takaro T, Hultgren HN, Lipton MJ, Detre KM. The VA cooperative randomized study of surgery for coronary arterial occlusive disease II. Subgroup with significant left main lesions. *Circulation* 1976;**54**(6):107–17.
- Tannock IF, Boyer M. When is a cancer treatment worthwhile? *New England Journal of Medicine* 1992;**323**:989–90.
- Tannsjo T. The morality of clinical research – a case study. *Journal of Medicine and Philosophy* 1994;**19**(1):7–21.
- Tauer CA. The NIH trials of growth hormone for short stature. *IRB: A Review of Human Subjects Research* 1994;**16**:1–9.
- Taves DR. Minimization: a new method of assigning patients to treatment and control groups. *Clinical Pharmacology and Therapeutics* 1974;**15**(5):443–53.
- Taylor KM. The doctor's dilemma: physician participation in randomized clinical trials. *Cancer Treatment Reports* 1985;**69**:1095–100.
- Taylor KM. Integrating conflicting professional roles: physician participation in randomized clinical trials. *Social Science and Medicine* 1992;**35**(2):217–24.
- Taylor KM, Kelner M. Informed consent: the physicians' perspective. *Social Science and Medicine* 1987a;**24**:135–43.
- Taylor KM, Kelner M. Interpreting physician participation in randomized clinical trials: the physician orientation profile. *Journal of Health and Social Behavior* 1987b;**28**:389–400.
- Taylor KM, Margolese RG, Soskolne CL. Physicians' reasons for not entering patients in a randomized control clinical trial of surgery for breast cancer. *New England Journal of Medicine* 1984;**310**:1363–7.
- Taylor KM, Shapiro M, Soskolne CL, Margolese RG. Physician response to informed consent regulations for randomized clinical trials. *Cancer* 1987;**60**:1415–22.

- Thompson SG, Pocock SJ. Can meta-analysis be trusted? *Lancet* 1991;**338**:1127–30.
- Thornton H. Breast cancer trials: a patient's viewpoint. *Lancet* 1992;**339**:44–5.
- Thornton H. Clinical trials – a brave new partnership? *Journal of Medical Ethics* 1994;**20**:19–22.
- Thornton H, Baum M. Ethics of clinical trials – the forbidden fruit phenomena. *Breast* 1996;**5**:1–4.
- Thornton JG, Lilford RJ. Preterm breech babies and randomized trials of rare conditions. *British Journal of Obstetrics and Gynaecology* 1996;**103**:611–13.
- Thornton JG, Lilford RJ, Levine M. Growth Retardation Intervention Trial (GRIT): pilot study. MRC award 1995. Unpublished.
- Tindall B, Forde S, Ross MW, Goldstein D, Barker S, Cooper DA. Effects of two formats of informed consent on knowledge amongst persons with advanced HIV disease in a clinical trial of didanosine. *Patient Education and Counselling* 1994;**24**(3):261–6.
- Tomamichel M, Sessa C, Herzig S, de Jong J, Pagani O, Willems Y, Cavalli F. Informed consent for phase I studies: evaluation of quantity and quality of information provided to patients. *Annals of Oncology* 1995;**6**(4):363–9.
- Toynbee P. No one really wins in this life and death lottery. *The Independent May* 1996:14–15.
- Trochim WM, Cappelleri JC. Cutoff assignment strategies for enhancing randomized clinical trials. *Controlled Clinical Trials* 1992;**13**:190–212.
- Truog RD. Randomised control trials: lessons from ECMO. *Clinical Research* 1992;**40**(3):519–27.
- Tukey JW. Some thoughts on clinical trials, especially problems of multiplicity. *Science* 1977;**198**:697–84.
- Twomey JG. Investigating Pediatric HIV research ethics in the field. *Weston Journal of Nursing Research* 1994;**16**(4):404–13.
- UK Collaborative ECMO Trial Group. Extra-corporeal membrane oxygenation (ECMO): the UK collaborative neonatal ECMO trial. *Lancet* 1996;**345**:805–6.
- Uberla AK. Randomised clinical trials: why not? *Controlled Clinical Trials* 1981;**1**:295–303.
- Urbach P. The value of randomization and control in clinical trials. *Statistics in Medicine* 1993;**12**:1421–41.
- Van der Linden W. Pitfalls in randomized surgical trials. *Surgery* 1980;**87**:258–62.
- Vandekerchove P, O'Donovan, Lilford RJ, Harada E. Treatment of male infertility – from cookery to science. *British Journal of Obstetrics and Gynaecology* 1993;**100**:159–60.
- Veatch RM. A theory of medical ethics. New York: Basic books, 1981.
- Vere DW. Controlled clinical trials – the current ethical debate. Proceedings of the Royal Society of Medicine 74:85–7, 1981.
- Vere DW. Problems in controlled trials – a critical response. *Journal of Medical Ethics* 1983;**9**:85–9.
- Visscher MB. The two sides of the coin in the regulation of experimental medicine. *Annals of the New York Academy of Sciences* 1970;**169**:319–29.
- Vogt TM, Ireland CC, Black D, Camel G, Hughes G. Recruitment of elderly volunteers for a multicentre clinical trial. *Controlled Clinical Trials* 1986;**7**:118–33.
- Wallenstein SL, Heidrich G, Kaiko R, Houde RW. Clinical evaluation of mild analgesics: the measurement of clinical pain. *British Journal of Clinical Pharmacology* 1980;**10**(Suppl 2):319S–27S.
- Ward LC, Fielding JWL, Dunn JA, Kelly KA. The selection of cases for randomized trials: a registry survey of concurrent trial and non-trial patients. *British Journal of Cancer* 1992;**66**:943–50.
- Watson A, Vanderchove P, Lilford RJ, Vai A, Brosens I, Hughes E. A meta-analysis of the therapeutic role of oil soluble contrast media at hysterosalpingogram: a surprising result? *Fertility and Sterility* 1994;**61**:470–7.
- Weijer C, Fuks A. The duty to exclude: excluding people at undue risk from research. *Clinical and Investigative Medicine* 1994;**17**(2):115–22.
- Weinstein MC. Allocation of subjects in medical experiments. *New England Journal of Medicine* 1974;**291**:1278–85.
- Wennberg J. What is outcomes research? In: Gelinjns AC, editor. Medical innovations at the crossroads, vol 1. Modern methods of clinical investigation. Washington, DC: National Academy Press, 1990:33–46.
- Weymuller EA Jr. A consideration of ethical issues in the design of clinical trials. *American Journal of Otolaryngology – Head and Neck Medicine and Surgery* 1996;**17**:2–11.
- White DR, Muss HB, Michielutte R, Cooper MR, Jackson DV, Richards F, et al. Informed consent: patient information forms in chemotherapy trials. *American Journal of Clinical Oncology* 1984;**7**:183–90.
- Whitehead J. Sequential methods based on the boundaries approach for the clinical comparison of survival times. *Statistics in Medicine* 1994;**13**:1357–68.
- Wilcox M, Schroer. The perspectives of patients with vascular disease on participation in clinical trials. *Journal of Medical Ethics* 1994;**12**:112–16.
- Wilhelmsen L. Ethics of clinical trials: the use of placebo. *European Journal of Clinical Pharmacology* 1979;**16**:295–7.
- Wilhelmsen L, Ljungberg S, Wedel H, Werko L. A comparison between participants and nonparticipants in a primary prevention trial. *Journal of Chronic Disease* 1976;**29**:331–9.
- Willan AR. Power function arguments in support of an alternative approach for analyzing management trials. *Controlled Clinical Trials* 1994;**15**:211–19.

- Williams CJ, Zwitter M. Informed consent in European multicentre randomized clinical trials – are patients really informed? *European Journal of Cancer* 1994;**30**(7):907–10.
- Williamson C. Breast cancer: asking patients what they want. *British Medical Journal* 1996;**313**:506–7.
- Williford WO. Comparison of eligible randomised patients with two groups of ineligible patients: can the results of the VA total parenteral nutrition clinical trial be generalised? *Journal of Clinical Epidemiology* 1993;**46**(9):1025–34.
- Working Group on Arrhythmias of the European Society of Cardiology. The early termination of clinical trials: causes, consequences and control. *European Heart Journal* 1994;**15**(6):721–38.
- Wynne A. Is it any good? The evaluation of therapy by participants in a clinical trial. *Social Science and Medicine* 1989;**29**:1289–97.
- Young FE. Ethical and financial considerations in third-party support of investigational cancer therapies. *Cancer* 1993;**72**(9):2854–8.
- Yusuf S, Collins R, Peto R. Why do we need some large simple randomized trials? *Statistics in Medicine* 1984;**3**:409–20.
- Zelen M. Play the winner rule and the controlled clinical trial. *Journal of the American Statistical Society* 1969;**64**:131–46.
- Zelen M. Strategy and alternative randomized designs in cancer clinical trials. *Cancer Treatment Reports* 1982;**66**:1095–100.
- Zelen M. Guidelines for publishing papers on cancer clinical trials: responsibilities of editors and authors. *Journal of Clinical Oncology* 1983;**1**:164–9.
- Zelen MA. A new design for randomised clinical trials. *New England Journal of Medicine* 1979;**300**:1242–5.



Tables

TABLE 1a Effect of participating in clinical trials on mortality

Author	Type of trial	Sample population and method of assessment	Outcome measure	Main results	Comments (see Table 3 for quality of evidence checklist)
(1) Antman (1983)	Randomised trial of adjuvant adriamycin for sarcoma	Trial participants (n = 36) Eligible non-trial controls (n = 48) of which 60% had refused to be randomised and 40% had not been offered randomisation	Disease-free survival and actuarial mortality	Randomised patients did better than non-trial controls according to disease-free survival ($p < 0.07$) and mortality ($p < 0.13$)	A2 B4 C3 D1 E+
(2) Bertelsen (1991)	Two Danish ovarian cancer trials: T1 – to compare two different adjuvant treatments of early ovarian cancer T2 – to compare two chemotherapy treatment of late stages of cancer	Trial participants: T1 – n = 72 T2 – n = 265 Non-trial eligible controls: T1 – n = 52 T2 – n = 96 Data obtained from the DACOVA register (Danish Ovarian Cancer Group) Trial eligibility criteria: Age < 70 years Epithelial ovarian cancer with historical verification of diagnosis Medical contraindication for post-operative treatment Concomitant malignant disease during the last 5 years, except basocellular carcinoma of the skin or carcinoma <i>in situ</i> of the uterine cervix	Mortality – actuarial survival	For patients with early disease (T1), there was no difference in actuarial survival between randomised and non-randomised patients ($p = 0.45$). However, trial patients with late disease (T2) had a significantly higher survival rate than similar non-randomised patients ($p = 0.0002$) This result was not sustained when the comparison was restricted to patients receiving combination chemotherapy (given to all trial participants but only 47% of non-trial patients) Both randomised studies showed no evidence of a survival difference between the treatment regimens	A2 B3 C2. There was no survival advantage for experimental treatments in both trials D3 E+ 23 and 24% of the non-randomised samples for trials 1 and 2, respectively, did not receive any treatment, whereas all trial participants received an active therapy
(3) CASS Working Group (1984)	Randomised trial of coronary artery bypass surgery to compare medical versus surgical treatment	Patients with mild/moderate stable angina pectoris (class 1 or 2 severity), or free of angina with a documented history of myocardial infarction Trial participants (n = 779) Eligible non-trial controls (n = 1309), 57% of whom were treated medically while the remainder were received surgery. All non-trial controls were taken from the same institutions who had refused randomisation Trial exclusion criteria: Prior coronary bypass surgery Progressive or unstable angina Angina more severe than class 2 Congestive heart failure A coexisting illness that would increase the likelihood of death within 5 years Three subgroups were also generated according to the number of diseased vessels, the presence of proximal left anterior descending coronary artery disease and ejection fraction	5 year actuarial survival	There were no significant differences in survival between the trial participants and non-trial controls either overall or according to whether medical or surgical treatment was given (no p value given) There were no significant findings in survival between trial and non-trial patients according to analysis of the three clinical subgroups (no p value given)	A2 B3 C1. Survival of patients assigned to the control arm (medical group) in the trial was compared with that of patients receiving the same type of treatment outside the trial D1. 59% recruitment rate E+ There was a difference in prognosis at the outset. The extent of the disease was less extensive in the non-trial medical control patients than in the medical trial participants. However, for the surgical groups, the disease was more extensive in the non-trial controls. Clinical subgroups were compared for trial and non-trial patients to get round this

continued

TABLE 1a contd Effect of participating in clinical trials on mortality

Author	Type of trial	Sample population and method of assessment	Outcome measure	Main results	Comments (see Table 3 for quality of evidence checklist)
(4) Davis <i>et al.</i> (1985)	Randomised trials for resected non-small cell lung cancer The trial patients were those entered into 1 of 4 adjuvant trials of investigational immunotherapy, chemotherapy, or radiation therapy after surgery	Patients were selected from a register at the Cancer Surveillance System (CSS) Trial participants (n = 78) Non-trial controls (n = 471) were patients with primary lung cancer in CSS population not in trial. Also, a subset of controls were selected who would have been eligible for the trials and who were matched to trial cases according to tumour size, regional lymph node involvement and cell type (n = 152) Trial eligibility criteria: The patient has a surgically resectable non-small cell carcinoma of the lung The patients extent of disease is fully documented at surgery A total resection of the tumour is achieved Material is available for historical review Contraindications of eligibility include: Prior radiotherapy, chemotherapy or immunotherapy Prior history of cancer Active tuberculosis within the last 5 years History of active cardiac disease	Mortality – actuarial survival	Survival rates were better for trial cases at 12 months (93%) and 24 months (82%) than for non-trial controls (72 and 50%, respectively). The overall survival experience of the trial cases was significantly better than that seen in controls ($p < 0.001$). This survival advantage was still observed for the trial cases against the subset of controls which were matched for known prognostic factors, and when the analysis was adjusted for age, sex, and administration of radiation therapy ($p < 0.02$) Survival of the trial patients receiving investigational therapy was not statistically different from those assigned to the placebo or 'standard' therapy	A2 B3 C2 D3 E+ Accuracy of CSS register assessed by reviewing 78 cases with independent records, from which there were 2.4% discrepancies Survival estimates were recorded by the Kaplan–Meier model Multivariate analysis conducted by use of the Cox proportional hazards model
(5) Jha <i>et al.</i> (1996)	Two thrombolytic trials: Trial 1 – Global Utilisation of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) Trial 2 – Late Assessment of Thrombolytic Efficacy (LATE)	GUSTO participants (n = 1304) Eligible but non-trial controls from: Same hospital (n = 12,657) External hospitals (n = 12,299) LATE participants (n = 211) Eligible but non-trial controls: Same hospital (n = 5997) External hospital (n = 12,299) Trial eligibility criteria: hospitalisation for acute myocardial infarction with concomitant bypass grafting or coronary angioplasty Data on concurrent non-trial controls were obtained from the Hospital Medical Records Institute (HMRI) databases	Mortality – survival	GUSTO trial patients had a statistically significant survival advantage over non-trial controls at the same hospital (OR = 1.8) LATE trial patients showed a statistically significant survival advantage over non-trial controls (OR = 2.1) Trial patients had significantly better survival on comparison with non-trial patients at external hospitals (OR = 1.8 for both GUSTO and LATE) All results remained statistically significant after adjustment for age, sex, bypass grafting or coronary angioplasty, and co-morbidity index	A2 B3 C2. There was a non-significant advantage for the experimental treatment in the LATE trial, and a statistically significant advantage for the experimental treatment over four standard treatments in the GUSTO trial D3 E+
(6) Karjalainen and Palva (1989)	A district in Finland where there was a policy to enter patients with multiple myeloma in a clinical trial. Three clinical trials were available between 1979–1985	Patients living in the district before the trials from 1959 acted as part of the control group (n = 85), along with patients who did not live in the district where policy prevailed during the trial period (n = 165) Only some of the patients living in the trial district were actually randomised between 1979 and 1985 (n = 319) Expected survival was obtained from death rates in the general population and actual survival rates were obtained via files of the Central Statistical Office of Finland	Mortality – actuarial relative survival	The 5 year relative survival rate of 38% for residence of the trial district, irrespective of whether they were actually randomised, was significantly higher than the 28% survival for those from non-trial districts. This advantage was only obtained for the period beyond 2 years following diagnosis During the second trial, it was found that the experimental treatment was less effective than the reference treatment which was the main regimen in the reference area	Verification of the diagnosis was missing in 4.8% of the cases in the trial area and in 7% of the cases in the reference area A2/3 B5. See text C2. Experimental treatment was less effective than the standard treatment in one trial, and there was no advantage for maintenance treatment in the second trial. The results of the third trial were not available D3 E+

continued

TABLE 1a contd Effect of participating in clinical trials on mortality

Author	Type of trial	Sample population and method of assessment	Outcome measure	Main results	Comments (see Table 3 for quality of evidence checklist)
(7) Lennox <i>et al.</i> (1979)	MRC clinical trial for children with nephroblastoma	Trial participants (n = 98) Eligible but non-trial patients (n = 172) Trial eligibility criteria: children aged 1–14 years with historically confirmed unilateral nephroblastoma unless they were known to have metastases in the liver or outside the abdominal cavity The non-trial controls were obtained from consultants or from Marie Curie Oxford Survey of childhood cancers	Mortality – 3 year survival	Overall 3 year survival rate for both groups was 58%. Survival rates were significantly higher for children included in an MRC trial (77%) than for those who were eligible but not included (58%), with $p < 0.01$. This result was more pronounced when allowance was made for the distribution of age and tumour stage ($p < 0.001$)	A2 B3 C2. Non-significant survival advantage for the experimental drug vincristine D3 E+
(8) MRC Working Group on Leukaemia in Childhood (1971)	Clinical trials for children with acute leukaemia	Trial participants (n = 220) (treated by physicians associated with the MRC committee) Non-trial controls (not treated by physicians associated with the MRC committee) (n = 691) Non-trial controls were obtained from National Cancer Registration Scheme on children aged 0–14 years during the period running concurrently with trials (1963–1967)	Median survival	Age is a known prognostic factor and so survival was reported as follows: 0–1 year: trial cases 39 weeks controls 14 weeks 2–8 years: trial cases 72 weeks controls 36 weeks 9–14 years: trial cases 74 weeks	Some of the data from the registers were missing as only 11/12 directors supplied information A2 B3 C3. Comparison of physicians, not trials controls 22 weeks D3 E+
(9) Schmoor <i>et al.</i> (1996)	Three multicentre clinical trials conducted by the German Breast Cancer Group (the No. of patients randomised to trial 1 was so small that it was regarded as an observational study) Trial 1 – mastectomy versus lumpectomy + radiation Trials 2 + 3 – different adjuvant therapies in patients previously treated by mastectomy	Trial participants (n = 734) Eligible non-trial controls (n = 1350) Non-trial controls were patients who refused randomisation Eligibility criteria not given	Mortality – 5 year recurrence-free survival	Trial 2 – disease-free survival rates of randomised and non-randomised patients was nearly identical Trial 3 – disease-free survival rates were slightly higher (not significantly) among randomised patients than non-randomised controls Statistical adjustment was made for prognostic factors and the remained no significant difference between groups, though a smaller relative risk was estimated for non-randomised controls than randomised patients indicating a beneficial effect of tamoxifen in trial 2 Trial 2 produced an apparently beneficial effect of tamoxifen ($p = 0.085$, RR = 0.75, confidence interval 0.5–1.04), while trial 3 estimated a benefit from additional radiotherapy (HR = 0.79, confidence interval 0.5–1.3)	Trial 1 left out of the analysis A2 B2 C1. Specific treatments effects of experimental and control arms in trials were compared with those outside the trial using the Cox proportional hazards ratio D1 E+
(10) Stiller and Draper (1989)	Chemotherapy trials for childhood lymphoblastic leukaemia in accordance with MRC protocols	Trial participants (n = 2137) Non-trial controls (n = 1933) All children aged < 15 years who were diagnosed with leukemia during 1971–1982 were recorded from national cancer registration schemes in England, Scotland and Wales. Notifications of children entered in MRC UKALL trials during the same period were received. Non-trial controls were also recorded from the UK Children's Cancer Study Group (CCSG) during 1977–1982	Mortality – 5 year survival, and actuarial survival thereafter up to 1986	Children entered into an MRC trial had a significantly higher actuarial survival rate than those who were not. This result was essentially unchanged when allowance was made for age and white cell count ($p < 0.0001$). When the analysis was limited to children surviving at least 3 months from diagnosis, the effects of trial entry remained highly significant (no p value given). However, the subsequent survival rate for those who had survived 5 years did not differ between trial and non-trial patients	A2 B3 C2. The experimental treatment was significantly less effective in half of the UKALL trials D3 E+
<i>HR, hazard ratio; RR, relative risk</i>					
<i>continued</i>					

TABLE 1a contd Effect of participating in clinical trials on mortality

Author	Type of trial	Sample population and method of assessment	Outcome measure	Main results	Comments (see Table 3 for quality of evidence checklist)
(11) Stiller and Eatock (1994)	National chemotherapy trials for children with acute non-lymphoblastic leukaemia in accordance with MRC protocols	Trial participants (n = 592) Non-trial controls (n = 666) Data obtained from National cancer registry, specialist children's tumour registries, MRC trials, CCSG and death certificates. Confirmation of diagnoses obtained from hospital records, family doctors and clinical trial records	Mortality – 5 year actuarial survival	Entry into a trial was associated with a higher actuarial survival rate in an analysis allowing for age at diagnosis ($p < 0.01$)	A2 B3 C2. There was a slight advantage for the experimental treatments in two trials, and no advantage in a further three trials. Some trial data not available D3 E+ Non-treated children were excluded from all survival analyses
(12) Ward et al. (1992)	British Stomach Cancer Group trial of adjuvant chemotherapy versus placebo in operative cancer	Trial participants (n = 217) Eligible non-trial controls (n = 960) Non-trial controls were obtained from cancer registry survey Trial ineligibility criteria: Unable to attend Not pathologically confirmed adenocarcinoma of the stomach or carcinoma <i>in situ</i> Previous tumour registration for frank malignant condition or previous treatment with chemotherapy or radiotherapy Stage I or non-operative stage 4 Unfit to start chemotherapy within 12 weeks of surgery Diagnosed at initial treatment as an unknown primary site	Mortality – actuarial survival	The trial participants had a higher survival rate than the non-trial sample, though this did not reach statistical significance ($p = 0.24$). However, when the non-trial patients were assessed for eligibility there were only n = 493, and there was no observed survival difference between these two groups	A2 B2 C2. There was no survival advantage with adjuvant therapy D3 E+

TABLE 1b Effect of participating in clinical trials on morbidity

Author	Type of trial	Sample population and method of assessment	Outcome measure	Main results	Comments (see Table 3 for quality of evidence checklist)
(1) Mahon <i>et al.</i> (1996)	n of 1 trials of theophylline versus placebo for irreversible airflow limitation	Trial participants (n = 14) Non-trial controls (n = 12) Patients were randomised to either n of 1 trial or standard practice.	Morbidity – exercise capacity by 6 min walking distance, quality of life measured by respiratory disease questionnaire at baseline and 6 months, and administration of theophylline at 6 months	There were no differences in exercise capacity or quality of life measures, though significantly fewer n of 1 trial patients than non-trial controls were taking theophylline at 6 months	A1 B1 C3 D3 E. The analysis was biased in favour of early stopping.
(2) Reiser and Warner (1985)	Three asthma trials carried out in children: T1. Trial to assess the efficacy of 750 ml spacer for the administration of inhaled corticosteroids. Children inhaled budesonide for 2 months using the Nebuhaler® and for 2 months used the metered-dose inhaler alone. The order of the devices was randomised by trial entry No. in an open crossover design T2. Trial to assess the efficacy of orally administered grass pollen extracts. Oral mixed-grass pollen vaccine versus a matched placebo was allocated in a random, double-blind study for the two groups T3. Trial of placebo versus the active treatment <i>D. pteronyssinus</i> absorbed in tyrosine. Injections were given once a week for 6 weeks and then every 8 weeks for a year	Trial participants: T1. n = 25 children, aged 7–14 years, recruited from paediatric asthma clinic who were thought to have stable, well-controlled asthma at trial entry. They were monitored by diary cards recording daily symptom scores, drug use, and twice daily peak expiratory flow rates (PEFR). Children also attended a clinic monthly for assessment and for more detailed lung function tests T2. n = 47 children with seasonal asthma and rhinitis, poorly controlled on conventional therapies. Progress was monitored by recording daily diary card scores of symptoms and drug usage and 2 x daily PEFR if indicated At the end of the season, patients and parents were asked about the effectiveness of the treatment T3. n = 51 patients with moderate–severe perennial asthma were selected from a paediatric respiratory clinic. Patients completed diary cards of symptoms and drug usage and recorded 2 x daily PEFR. At visits every 2 months the patients and parents were asked if their asthma was better, whether there was no change or any worsening. More detailed lung function tests were also done Informal non-trial controls	Morbidity	T1. Although there was no improvement in tests which reflect peripheral airway calibre, there was a significant improvement in clinical status (diary card symptom scores) and in tests reflecting more proximal airway calibre in both groups. There was a significant period effect when comparing the first 2 months with the last 2 months for either group ($p < 0.02$ in the morning and $p < 0.01$ in the evening) This shows that regardless of the mode of administration of the steroid aerosol, over the first 2 months of the trial there was a significant improvement in symptoms and large-airway calibre T2. There was no significant advantage for the active vaccine over the placebo, though there was observed benefit for most of the children according to the parents' assessments: for the active vaccine, 21 said there was benefit and none said there was no benefit; for the placebo, 20 said there was benefit and six no benefit. This placebo response was claimed by the authors to be much stronger than is usually found T3. More patients and parents in the active group had the impression that the asthma had improved after a year, but all the observations tended to improve in both groups during the course of the year though there was a slight increase in drug scores in the placebo group. Again the authors interpret the improvement of the placebo group as being greater than normal	A3 B5 C3. There was no actual data presented which would indicate that the improvement by trial placebo controls was in any way greater than is normally observed. However, the authors make reference to a published guide on the pharmacology of placebos D3 E+ For studies 2 and 3, there was no indication given as to how the patient's and parents' assessments of the treatment efficacy was carried out
(3) Williford <i>et al.</i> (1993)	RCT of total parenteral nutrition (TPN) in malnourished surgical patients	Trial participants (n = 396) Eligible non-trial controls (n = 199) Non-trial controls refused randomisation and subsequently underwent an operation without receiving TPN	Morbidity – septic and non-septic complication rates	Complication rates were significantly higher for trial patients than for non-trial patients ($p = 0.008$ at 30 days and $p = 0.001$ at 90 days) When adjusted for TPN use the complications rate was no longer statistically significant ($p = 0.650$ at 30 days and $p = 0.598$ at 90 days)	A2 B3 C3 D1. Recruitment rate to trial 66% E+

TABLE 2a Effect of participating in clinical trials on mortality according to quality of evidence

Author	Outcome measures	Type of trial(s)	Nature of non-trial control	Prognostic variables taken into account	Finding before adjustment for non-trial and trial group	Finding with an adjustment for non-trial control and trial group	Trial control compared with non-trial control	Summary of quality of evidence (see Table 3)
(1) Antman (1983)	Disease-free and actuarial survival	Clinical trial of adjuvant adriamycin for sarcoma	Non-randomised concurrent controls who declined trial entry and non-trial	There was a difference in prognostic variables between the trial groups, but no adjustment was made	Favourable trend for disease-free and actuarial survival ($p < 0.07$ and $p < 0.13$, respectively)	–	No data available	A2 B4 C3 D1 E+
(2) Bertelsen (1991)	Actuarial survival	Two ovarian cancer trials of adjuvant or chemotherapeutic treatments	Non-randomised concurrent controls who were not offered trial entry	Statistical adjustment for known prognostic differences	Survival experience was significantly higher in the trial group than among non-trial controls ($p = 0.0005$)	No significant difference	No significant treatment effect for either trials	A2 B3 C2 D3 E+ 23 and 24% of the non-randomised samples for trials 1 and 2, respectively, did not receive any treatment, whereas all trial participants received an active therapy
(3) CASS Working Group (1984)	5 year actuarial survival	Clinical trial of coronary artery bypass surgery versus medical therapy	Non-randomised concurrent controls who declined trial entry	Statistical adjustment for known prognostic differences	Favourable trend for trial group (p value not given)	No significant difference	No significance was found between the trial control arm and non-trial patients receiving the same therapy	A2 B3 C1. Survival of patients assigned to the control arm (medical group) in the trial was compared with that of patients receiving the same type of treatment outside the trial D1. 59% recruitment rate E+ There was a difference in prognosis at the outset. The extent of the disease was less extensive in the non-trial medical control patients than in the medical trial participants. However, for the surgical groups, the disease was more extensive in the non-trial controls. Clinical subgroups were compared for trial and non-trial patients to get round this

continued

TABLE 2a contd Effect of participating in clinical trials on mortality according to quality of evidence

Author	Outcome measures	Type of trial(s)	Nature of non-trial control	Prognostic variables taken into account	Finding before adjustment for non-trial and trial group	Finding with an adjustment for non-trial control and trial group	Trial control compared with non-trial control	Summary of quality of evidence (see Table 3)
(4) Davis et al. (1985)	Actuarial survival	Four trials in lung cancer comparing postoperative immuno-therapy, chemotherapy or radiation therapy	Non-randomised concurrent controls who were not offered trial entry	Statistical adjustment for known prognostic differences	Survival experience was significantly higher in the trial group than among non-trial controls ($p < 0.001$)	Significant difference was maintained ($p < 0.02$)	No significant treatment effect in any of the trials	A2 B3 C2 D3 E+ Accuracy of CSS register assessed by reviewing 78 cases with independent records, from which there were 2.4% discrepancies Survival estimates were recorded by the Kaplan–Meier model Multivariate analysis conducted by use of the Cox proportional hazards model
(5) Jha et al. (1996)	Actuarial survival	Two thrombotic trials for myocardial infarction (GUSTO and LATE).	Non-randomised concurrent controls who were not offered trial entry	Statistical adjustment for known prognostic differences	Survival experience was significantly higher among trial cases than among non-trial cases (p value not given)	Significant difference was maintained (OR = 1.8 and 2.1 for GUSTO and LATE, respectively)	There was a non-significant advantage for the experimental treatment in the LATE trial, and a statistically significant advantage for the experimental treatment over four standard treatments in the GUSTO trial	A2 B3 C2 D3 E+
(6) Karjalainen and Palva (1989)	Comparison of actuarial survival by district of residence	Three clinical trials for multiple myeloma	Non-randomised concurrent controls who were not offered trial entry (because they lived in different districts)	Adjustment not possible because data on individual patients was not available	Survival in trial district was significantly higher than in non-trial district ($p < 0.001$)		The experimental treatment was less effective than the standard treatment in one trial, and there was no advantage for maintenance treatment in the second trial. The results of the third trial were not available	Verification of the diagnosis was missing in 4.8% of the cases in the trial area and in 7% of the cases in the reference area A2/3 B5. See text C2 for 1/3 trials and C3 for 2/3 trials D3 E+
(7) Lennox et al. (1979)	3 year survival	Trial of chemotherapy for children with nephroblastoma	Non-randomised concurrent controls who were not offered trial entry	Statistical adjustment for known prognostic differences	Survival experience was significantly higher in the trial group than among non-trial controls ($p < 0.01$)	Significant difference was more pronounced ($p < 0.001$)	There was a non-significant survival advantage for experimental drug	A2 B3 C2 D3 E+

continued

TABLE 2a contd Effect of participating in clinical trials on mortality according to quality of evidence

Author	Outcome measures	Type of trial(s)	Nature of non-trial control	Prognostic variables taken into account	Finding before adjustment for non-trial and trial group	Finding with an adjustment for non-trial control and trial group	Trial control compared with non-trial control	Summary of quality of evidence (see Table 3)
(8) MRC Working Group on Leukaemia in Childhood (1971)	Median survival Comparison between patients treated by physicians associated with the MRC trials and those not	MRC clinical trials for children with acute leukaemia (No. of trials not given) different physicians	Non-randomised concurrent controls who were not offered trial entry because they attended	Statistical adjustment for known prognostic differences	Survival experience was significantly higher in trial group than among non-trial controls (p value not given)	Significant difference was maintained	Comparison by physician not by trial	Some of the data from the registers were missing as only 11/12 directors supplied information A2 B3 C3 D3 E+
(9) Schmoor et al. (1996)	5 year recurrence-free survival	Two multicentre clinical trials of different adjuvant therapies for breast cancer	Non-randomised concurrent controls who declined trial entry	Trial and non-trial groups were matched for known prognostic variables	Favourable trend in one of the trials with virtually no difference between groups in the other	–	No significant difference was found between the trial control arm and non-trial patients receiving the same therapy	Trial I left out of the analysis A2 B2 C1. Specific treatment effects of experimental and control arms in trials were compared with those outside the trial using the Cox proportional hazards ratio D1 E+
(10) Stiller and Draper (1989)	5 year actuarial survival	Chemotherapy trials for childhood lymphoblastic leukaemia	Non-randomised concurrent controls who were not offered trial entry	Statistical adjustment for known prognostic differences	Survival experience was significantly higher in trial group than among non-trial controls (p value not given)	Significant difference was maintained (p < 0.0001)	The experimental treatment was significantly less effective in half of the UKALL trials	A2 B3 C2 D3 E+
(11) Stiller and Eatock (1994)	5 year actuarial survival	Chemotherapy trials for children with acute non-lymphoblastic leukaemia	Non-randomised concurrent controls who were not offered trial entry	Statistical adjustment for known prognostic differences	Survival experience was significantly higher among trial cases than among non-trial cases (p value not given)	Significant difference was maintained (p < 0.01)	There was a slight advantage for the experimental treatments in two trials, and no advantage in a further three trials. Some trial data were not available	A2 B3 C2 D3 E+ Non-treated children were excluded from all survival analyses
(12) Ward et al. (1992)	Actuarial survival	Stomach cancer trial of adjuvant chemotherapy versus placebo	Non-randomised concurrent controls who were not offered trial entry	Trial and non-trial groups were matched for known prognostic variables	Favourable trend (p = 0.24)		There was no survival advantage with adjuvant therapy	A2 B2 C2 D3 E+

* This analysis was conducted by Stiller (1987) in a previous review.

TABLE 2b Effect of participating in clinical trials on morbidity according to quality of evidence

Author	Outcome measures	Type of trial(s)	Nature of non-trial control	Prognostic variables taken into account	Finding before adjustment for non-trial and trial group	Finding with an adjustment for non-trial control and trial group	Trial control compared with non-trial control	Summary of quality of evidence (see Table 3)
(1) Mahon <i>et al.</i> (1996)	Morbidity – exercise capacity, quality of life (measured by respiratory disease questionnaire) at baseline and 6 months, and theophylline requirements at 6 months	n of 1 trials of theophylline versus placebo for irreversible airflow limitation	Randomised concurrent controls.	This was a randomised trial of n of 1 trials, i.e. trial and non-trial groups generated by randomisation	Significantly higher proportion of non-trial controls was taking theophylline at 6 months than n of 1 trial cases (p value not given)	Favourable trend for exercise capacity and quality of life measures (p value not given)	–	No data available, i.e. the trial was itself the intervention. A1 B1 C3 D3 E. The analysis was biased in favour of early stopping
(2) Reiser and Warner (1985)	Morbidity – patient-assessed clinical status in all trials	Three childhood asthma trials of different inhalers	Non-randomised historical controls	No comment on prognostic variables between trial and non-trial groups	A significant improvement in symptoms was experienced among trial cases in one of the trials (p value not given) with non-significant improvement in the remainder	–	There was an improvement in symptoms for trial control cases but not for non-trial controls	A3 B5 C3. There was no actual data presented which would indicate that the improvement by trial placebo controls was in any way greater than is normally observed. However, the authors make reference to a published guide on the pharmacology of placebos D3 E+ For studies 2 and 3, there was no indication given as to how the patient's and parents' assessments of the treatment efficacy was carried out
(3) Williford <i>et al.</i> (1993)	Morbidity – septic and non-septic complication rates	RCT of TPN in malnourished surgical patients	Non-randomised concurrent controls who declined trial entry and who did not receive TPN	Statistical adjustment for known prognostic differences	Complication rate was significantly higher among trial cases than among non-trial controls (p = 0.008 at 30 days and p = 0.001 at 90 days)	No significant difference	No data available	A2 B3 C3 D1. Recruitment rate to trial 66% E+

TABLE 3 Quality of evidence checklist for physical effects

Key	Type of evidence
A	Sampling: (1) RCT of trial versus no trial (2) non-randomised concurrent cohort study (3) non-randomised historical cohort study
B	Prognostic variables: (1) randomised study, i.e. A1 (2) trial participants and non-trial controls matched for known prognostic variables (3) trial participants and non-trial controls not matched for prognostic variables but statistical adjustment was made (4) recorded imbalance between trial participants and non-trial controls with no statistical adjustment (5) no data on prognostic variables
C	Comparison of trial controls and non-trial controls: (1) formal comparison of trial controls and non-trial controls carried out (2) no formal comparison but result of trial given [*] (3) no data on outcome of trial controls
D	Patients refusing randomisation: (1) refusers followed up (2) recruitment rates given but refusers not followed up (3) recruitment rates not given
E	Was the statistical method used to analyse the results appropriate (acceptable, positive; flawed, negative)?
[*] If the data were not given in the study, then the original trial publication was consulted.	

TABLE 4a Categorisation of studies for Table 4b

1. Prognostic variables similar/ matched/adjusted	a. No prior effective treatment included in trial protocol	Trial result: i. experimental treatment significantly better than placebo ii. null result/experimental treatment significantly worse than placebo	Where proportion of patients receiving treatment of interest and/or regimen (package of care) between trial and non-trial patients might affect outcome: α. Both similar β. Treatments balanced but regimen different χ. Regimens the same but treatment imbalance δ. Both different
2. Serious prognostic imbalance between trial and non-trial patients	b. Effective treatment prior to trial which was included in the trial protocol	Trial result: i. experimental significantly better than standard ii. null result/ experimental treatment significantly worse than standard	

TABLE 4b Data sets for Figure 3

Trial/ data set	Design Category (see Table 4a) outside trial which was included in trial protocol	Effective treatment already exists	Protocol ensures similar regimens/ follow-up for similar trial and non-trial patients	Differences in trial and non-trial patients prognoses: 1 – no difference/ fully adjusted 2 – small differences/ partially adjusted 3 – no adjustment for large differences	Results of trial treatments and/or non-randomised treatments	Was there a more adjusted result without sufficient data for the graph?	Quality of data acquisition for graph: 1 – good 2 – okay 3 – bad	Overall quality assessment (within category): 1 – good 2 – okay 3 – bad
(1) Schmoor <i>et al.</i> (1996) Trial 2 – Sc(i)	I biiγ	Yes	Treatment balance among trial and non-trial patients differed but the regimens were the same (both trials)	Trial and non-trial patients had similar prognoses for both trials (1)	Nearly significant difference between trial treatments	Yes	3 – measured	2
Trial 3 – Sc(ii)	I biiα	Yes		As above	Non-significant difference between trial treatments	Yes	3 – measured	2
(2) CASS Working Party (1984) Medical arm Surgical arm	2	Yes	Similar treatments and regimens but not identical	Some important differences between trial and non-trial patients within treatment arms (3)	No difference between trial treatments	No	3 – measured	2
Treatment arms combined – C	I biiα	Yes	Treatment balance among trial and non-trial patients differed and regimens were slightly different	Not adjusted but no big difference overall (1)	No difference between trial treatments	No	3 – measured	2
(3) Davis <i>et al.</i> (1985) – D	I aiiβ	Surgery effective but not adjuvants	No	'Fully' adjusted for recorded differences (1)	No difference between trial treatments	No	1	1
(4) Bertelsen (1991) III/IV patients with cisplatinum + others – B	I biiβ	Yes	Treatment the same but possibly protocols different	No differences (2)	Small difference between treatments in the trial	No	3 – measured	2
III/IV trial versus non-trial	2	Yes	No (including exclusions)	No adjustment for recorded differences (3)	As above	No	N/A	N/A
I/II trial versus non-trial	2	Yes	Slightly different	No adjustment for recorded differences (3)	As above	No	N/A	N/A
(5) Lennox <i>et al.</i> (1979) Stage I/II age 1–3 L(i)	I biiδ	Yes	No	Adjusted for age and stage 2	There was a non- significant survival advantage for experimental arm	Could have adjusted for a hospital effect which could have due to the protocols used	1	1–2
Stage I/II age 4–14 L(ii)	I biiδ	Yes	No	Adjusted for age and stage 2	As above	As above	1	1–2
Stage III all ages L(iii)	I biiδ	Yes	No	Adjusted for age and stage 2	As above	As above	1	1–2
(6) MRC Working Group on Leukaemia in Childhood (1971) Not trial versus non-trial comparison but expert versus non-expert – M	I biiδ	Yes	No	Adjusted for age (2/3)	Difference in effectiveness of treatments is probable but not investigated within a trial	No	3	3

continued

TABLE 4b contd Data sets for Figure 3

Trial/ data set	Design Category (see Table 4a) which was included in trial protocol	Effective treatment already exists	Protocol ensures similar regimens/ follow-up for similar trial and non-trial patients	Differences in trial and non-trial patients prognoses: 1 – no difference/ fully adjusted 2 – small differences/ partially adjusted 3 – no adjustment for large differences	Results of trial treatments and/or non-randomised treatments	Was there a more adjusted result without sufficient data for the graph?	Quality of data acquisition for graph: 1 – good 2 – okay 3 – bad	Overall quality assessment (within category): 1 – good 2 – okay 3 – bad
(7) Stiller and Draper (1989) Year group (i–iv) by hospital category (A–C) with 12 comparisons Year group: (i) 1971–1973 (ii) 1974–1976 (iii) 1977–1979 (iv) 1980–1984 Hospital type: A > 6 patients treated per year on average I < B > 6 patients treated per year on average C < I patient treated per year on average	Ibiiδ	Yes	No, though for patients in group A their treatments and regimens were probably more similar than for those in B and C	No adjustment for recorded differences (3)	The experimental treatment was significantly less effective in half of the UKALL trials	Yes (adjusted for age)	2 – data from 3 tables but some guessing and assume complete 5 year follow-up	3
(8) Stiller and Eatock (1994) Years 1975–1983 – S94(i) Years 1984–1988 – S94(ii)	Ibiiδ Ibiiδ	Yes Yes	Treatments partially adjust- ed by stratifying period No No	No adjustment for recorded differences (3) No adjustment for recorded differences (3)	There was a slight advantage for the experimental treat- ments in two trials, and no advantage in a further three trials. Some trial data were not available	Yes (3 month survival but no data for age adjustment) Yes (3 month survival but no data for age adjustment)	3 – measured from graph and assume complete 5 year follow-up	3 3
(9) Ward (1992) – W	Iaiiβ	No	Adjuvants not widely used outside trial	No adjustment for small differences (2)	No significant difference between trial treatments	None reported	1	2
(10) Karjalainen and Palva (1989) – K	Ibiiδ	Yes	No	Yes – 'self'-historical control (3)	The experimental treatment was less effective than the standard treatment in one trial, and there was no advantage for maintenance treatment in the second trial. The results of the third trial were not available	–	1	3
(11) Antman (1983)	2	Insufficient data	Insufficient data	Yes (3)	Insufficient data	None reported	Insufficient data	3
(12) Reiser and Warner (1985) Excluded as there were insufficient data for a graph	–	–	–	–	–	–	–	–

continued

TABLE 4b contd Data sets for Figure 3

Trial/ data set	Design Category (see Table 4a) outside trial which was included in trial protocol	Effective treatment already exists	Protocol ensures similar regimens/ follow-up for similar trial and non-trial patients	Differences in trial and non-trial patients prognoses: 1 – no difference/ fully adjusted 2 – small differences/ partially adjusted 3 – no adjustment for large differences	Results of trial treatments and/or non- randomised treatments	Was there a more adjusted result without sufficient data for the graph?	Quality of data acquisition for graph: 1 – good 2 – okay 3 – bad	Overall quality assessment (within category): 1 – good 2 – okay 3 – bad
(13) Jha (1996) Trial 1 GUSTO – J(i)	Ibiδ	Yes	No (difference in revascularisation controlled for)	Adjusted for important differences (1)	Yes	There was a statisti- cally significant advan- tage for the experi- mental treatment in the GUSTO trial	No	I
Trial 2 LATE – J(ii)	Ibiiδ	Yes	No (difference in revascularisation controlled for)	Adjusted for important differences (1)	Yes	There was a non- significant advantage for the experimental treatment in the LATE trial	No	I
(14) Mahon (1996) Excluded as n of 1 trial	–	–	–	–	–	–	–	–

TABLE 4c Data for Figure 3

Prior treat- ment	Trial result	Regimen/ non- regimen treatment	Data quality	Authors	Initials	HR credible interval		HR median	In trial		Not in trial	
						Upper	Lower		Okay	At risk	Okay	At risk
a	ii	b	1	Davis 85	D	0.68	0.19	0.36	'RR' (presumably HR) from Cox regression in paper			
a	ii	b	2	Ward 92	WV	1.05	0.65	0.83	119	217	238	493
b	ii	a	2	Schmoor 96	Sc(ii)	1.10	0.48	0.73	143	191	86	128
b	ii	a	2	CASS 84	C	1.51	0.63	0.98	714	752	887	935
b	ii	b	2	Bertelson 91	B	1.77	0.66	1.05	132	264	19	37
b	ii	c	2	Schmoor 96	Sc(i)	1.34	0.74	0.99	308	440	155	222
b	i	d	1	Jha 96	J(i)	0.71	0.45	0.56	Reported OR for GUSTO patients versus others in GUSTO hospitals with myocardial infarction			
b	i	d	3	Stiller 94	S94(i)	0.95	0.62	0.77	54	244	41	291
b	i	d	3	Stiller 94	S94(ii)	1.25	0.67	0.92	51	125	60	158
b	ii	d	1	Jha 96	J(ii)	0.83	0.28	0.48	Reported OR for LATE patients versus others in LATE hospitals with myocardial infarction			
b	ii	d	1.5	Lennox 79	L(i)	1.75	0.33	0.79	37	46	39	52
b	ii	d	1.5	Lennox 79	L(ii)	0.81	0.10	0.31	19	23	16	32
b	ii	d	1.5	Lennox 79	L(iii)	0.71	0.14	0.33	19	29	5	20
b	ii	d	3	MRC 71	MRC	0.61	0.36	0.47	73	146	104	454
b	ii	d	3	Stiller 89	S89(iA)	0.72	0.44	0.56	215	422	43	144
b	ii	d	3	Stiller 89	S89(iB)	0.74	0.33	0.51	31	59	69	246
b	ii	d	3	Stiller 89	S89(iC)	0.93	0.25	0.52	7	16	40	201
b	ii	d	3	Stiller 89	S89(iiA)	1.17	0.74	0.92	172	331	132	269
b	ii	d	3	Stiller 89	S89(iiB)	1.05	0.56	0.77	104	208	50	124
b	ii	d	3	Stiller 89	S89(iiC)	1.07	0.41	0.66	29	55	29	77
b	ii	d	3	Stiller 89	S89(iiiA)	1.01	0.61	0.78	217	374	108	215
b	ii	d	3	Stiller 89	S89(iiiB)	0.91	0.45	0.63	119	199	43	97
b	ii	d	3	Stiller 89	S89(iiiC)	0.78	0.26	0.45	36	59	14	43
b	ii	d	3	Stiller 89	S89(ivA)	0.91	0.59	0.74	393	546	312	488
b	ii	d	3	Stiller 89	S89(ivB)	1.15	0.59	0.82	152	214	149	226
b	ii	d	3	Stiller 89	S89(ivC)	1.07	0.27	0.55	24	35	24	49
b	ii	d	3	Karjalainen 89	K	0.89	0.52	0.68	153	405	45	164 trial period
									227	948	128	461 no-trial period
									Trial area		No-trial area	

TABLE 5 Psychological effects of trial participation

Author	Purpose and type of study	Outcome measurement	Main results	Comments (see Table 6 – quality of evidence checklist)
(1) Cassileth <i>et al.</i> (1986)	<p>Study to compare the psychological outcome of participants in two clinical trials</p> <p>Two chemotherapy trials of adjuvant therapy versus observation for early breast cancer</p> <p>Women with stage 2 breast cancer (n = 68)</p>	<p>Four psychological measures of anxiety were used:</p> <p>(1) state anxiety (2) trait anxiety (3) SCL-90 total score (4) SCL-90 anxiety score</p> <p>Patients were asked to complete the state-trait inventory and the SCL-90 immediately before randomisation and then at 3, 6 and 12 months following</p>	<p>(1) Between trial protocols. There was no effect on anxiety levels by clinical trial protocol (no trend given)</p> <p>(2) Within trial protocols. There was a statistically significant difference in anxiety according to treatment allocation within the trials: patients in the observation group displayed higher anxiety levels at each time of assessment than those in the adjuvant therapy group ($p < 0.05$). However, when the prerandomisation score was omitted from the analysis, the result was no longer statistically significant</p>	<p>A– B2 C2 D– E+ F+. Mostly closed-ended G–. 26% of patients entered on to the breast protocols also consented to participate in the psychosocial study, of which 60% completed all the tests H+ I+. Low power</p>
(2) Mann (1977)	<p>Study to examine the psychological effect of a screening programme and clinical trial for hypertension</p> <p>Trial participants: patients in MRC placebo-controlled trial for mild-moderate hypertension (n = 235)</p> <p>Non-trial controls: two groups were selected at random from participants who took part in a screening programme but who did not enter the trial Control group 1 (n = 233) Control group 2 (n = 231)</p>	<p>Outcome measurement:</p> <p>(1) Self-administered questionnaire – Goldberg General Health Questionnaire completed at: T1 – screening T2 – after trial entry T3 – 3 months after entry T4 – 1 year after entry</p> <p>(2) Goldberg Standard Psychiatric Interview to those judged from (1) to be likely psychiatric cases at: T3 – 3 months T4 – 1 year after trial entry</p>	<p>Outcome measure (1): T1–T2 – there were no significant differences between trial entrants and controls T2–T3 – there was a greater number of improved psychological scores among trial than control group patients ($p < 0.05$) T3–T4 – significant difference was sustained 1 year after trial entry. Furthermore, the prevalence of psychological disturbance was significantly lower in the trial participants than in the controls after 1 year ($p < 0.05$), though there was no significant difference in the number of new cases</p> <p>Outcome measure (2): T3 – trial participants had a significantly lower prevalence ($p < 0.05$) than normal controls. The incidence of new cases however did not differ in the three groups T4 – the trend was the same, though it was not statistically significant</p>	<p>A+ B2 C2 D+ E+ F+. Authors claim that the questionnaire was previously validated and piloted. The questionnaire was not a diagnostic measure of psychiatric morbidity, so 85% of all respondents giving a positive score were interviewed by a psychiatrist G–. Response rate varied over time, though overall, 1 year after entry, 62% of those initially involved responded H– I+</p>
(3) Robiner <i>et al.</i> (1993)	<p>Study to assess the psychological effect of participating in a clinical trial</p> <p>Placebo-controlled trial of zidovudine in asymptomatic HIV-seropositive persons Trial participants (n = 46) ineligible concurrent non-trial controls (n = 27)</p>	<p>Standardised psychological measures, inc. BDI, Scale 2 (Depression) of the Minnesota Multiphasic Personality Inventory, Beck Hopelessness Scale, Self Evaluation Questionnaire (state anxiety), and Stress Reaction and Well Being scales of the Multidimensional Personality Questionnaire</p> <p>All outcome measures were administered at: T1 – trial entry T2 – 2 months T3 – 6 months T4 – after trial modification</p>	<p>T1 – trial participants were somewhat more distressed than non-trial controls on 80% of measures, but this was not statistically significant T1–T2 – trial participants reported more anxiety symptoms (2 weeks; $p < 0.05$) and had higher mean scores than non-trial controls on all 10 measures ($p < 0.002$). Also, more trial participants than non-trial controls reported BDI levels of depression ($p < 0.05$), but the groups' mean scores were not different. More trial participants than non-trial controls met GAD criteria ($p = 0.03$) T2–T3 – there were no longer differences between trial participants and non-trial controls T3–T4 – trial participants were less depressed and distressed than non-trial controls ($p < 0.002$)</p> <p>Both groups had statistically significant overall improvement in terms of depression ($p < 0.01$) and anxiety ($p < 0.01$). That said, non-trial controls differed in their relative patterns of distress over a 6 month period: there was an initial decrease in distress at 2 months but an increase by 6 months whereas, for trial participants, there was a consistent decrease in distress from entry to 6 months</p> <p>There was no difference in distress based on whether trial participants thought they knew their group assignment or thought they were taking a placebo</p>	<p>A+ B2 C2 D– E+ F+ G+. Psychological assessments were completed by 78% of trial participants but only 38% of non-trial controls H+ I+</p> <p>Larger sample size of trial participants increased likelihood of finding their reduced distress</p>

TABLE 6 Quality of evidence checklist for psychological effects

Key	Type of evidence
A	External validity, i.e. how representative is the sample of the target population (acceptable +, flawed -)?
B	Sampling: (1) all patients offered trial entry or random sample (2) not stated or grab sampling
C	Study design: (1) comparative study – RCT (2) comparative study – concurrent cohort (3) comparative study – historical cohort
D	Recruitment rates to trials should be given and refusers followed-up (acceptable +, flawed -)
E	Repeated measured before and after trial entry (acceptable +, flawed -)
F	Outcome measure: interobserver reliability should be carried out where appropriate for questionnaires and/or interviews and psychometric validity should be given for scales (acceptable +, flawed -)
G	Response rate to outcome measurement should be 70% or more (acceptable +, flawed -)
H	Questionnaire should be supplied in study or available from authors (acceptable +, flawed -)
I	The statistical method used to analyse data must be appropriate (acceptable +, flawed -)

TABLE 7a Methods of obtaining informed consent for real trials

Author	Study design and sample (n = study participants)	Outcome measures	Main results	Comments (see Table 8 for quality of evidence checklist)																												
(1) Aaronson et al. (1996)	<p>Patients were randomised to one of two informed consent procedures:</p> <p>(1) standard informed consent procedure based on oral and written information</p> <p>(2) standard informed consent plus a supplementary, telephone-based interview with an oncology nurse</p> <p>Subpopulation (n = 180) offered entry to Phase 2 or three trials at the Netherlands Cancer Institute</p>	<p>Anxiety</p> <p>Anxiety was measured by the state version of the Spielberger State-Trait Anxiety Inventory (STAI) presented 1 week after completion of the consent process</p> <p>Understanding</p> <p>Recall was assessed by interview (a series of semi-structured questions with follow-up probes) conducted 1 week after completion of the consent process</p> <p>Recruitment rates</p> <p>Actual participation</p>	<p>Anxiety</p> <p>There was no association between consent format and anxiety, though the control group had slightly higher measured anxiety scores</p> <p>Understanding</p> <p>Patients undergoing the second interview were significantly ($p < 0.01$) better informed</p> <p>Respondents with correct answers</p> <table border="1"> <thead> <tr> <th></th> <th>Second interview:</th> <th>Control:</th> <th>p:</th> </tr> </thead> <tbody> <tr> <td>(a) Concept of the clinical trial</td> <td>97%</td> <td>86%</td> <td>< 0.01</td> </tr> <tr> <td>(b) Trial objective</td> <td>87%</td> <td>71%</td> <td>< 0.01</td> </tr> <tr> <td>(c) Concept of randomisation</td> <td>75%</td> <td>54%</td> <td>< 0.01</td> </tr> <tr> <td>(d) Right to withdraw</td> <td>87%</td> <td>65%</td> <td>< 0.01</td> </tr> <tr> <td>(e) Alternative treatments</td> <td>86%</td> <td>67%</td> <td>< 0.005</td> </tr> <tr> <td>(f) Side-effects (average % recalled)</td> <td>78%</td> <td>61%</td> <td>< 0.001</td> </tr> </tbody> </table> <p>Recruitment</p> <p>Patients in the second interview group were more likely to decline participation though this did not reach statistical significance ($p = 0.17$)</p> <p>Interactions</p> <p>Patients scoring high on overall understanding within the two groups were significantly less anxious ($p = 0.001$). Younger and better educated patients exhibited less anxiety than older and less educated patients</p> <p>See also Table 10 – audit</p>		Second interview:	Control:	p :	(a) Concept of the clinical trial	97%	86%	< 0.01	(b) Trial objective	87%	71%	< 0.01	(c) Concept of randomisation	75%	54%	< 0.01	(d) Right to withdraw	87%	65%	< 0.01	(e) Alternative treatments	86%	67%	< 0.005	(f) Side-effects (average % recalled)	78%	61%	< 0.001	<p>A2</p> <p>B1</p> <p>C+</p> <p>D+. 63% of patients asked to enter the trials were referred to this study, for which there was a response rate of 82%</p> <p>E-</p> <p>F+</p> <p>Interview was pilot tested</p>
	Second interview:	Control:	p :																													
(a) Concept of the clinical trial	97%	86%	< 0.01																													
(b) Trial objective	87%	71%	< 0.01																													
(c) Concept of randomisation	75%	54%	< 0.01																													
(d) Right to withdraw	87%	65%	< 0.01																													
(e) Alternative treatments	86%	67%	< 0.005																													
(f) Side-effects (average % recalled)	78%	61%	< 0.001																													
(2) Davis et al. (1990)	<p>Patients were randomised to one of two consent procedures:</p> <p>(1) oral and written information (National Cancer Institute's booklet) (n = 203)</p> <p>(2) control – oral information only (n = 194)</p> <p>Eligible and participating patients in cancer clinical trials at four centres (n = 187 and 210, respectively)</p>	<p>Anxiety</p> <p>Anxiety was assessed by questionnaire (details not given)</p> <p>Understanding</p> <p>Understanding was assessed by questionnaire (details not given)</p> <p>Recruitment rates</p> <p>Self-reported participation and data on actual participation in trials taken from medical records</p>	<p>Anxiety</p> <p>Respondents receiving the National Cancer Institute's booklet were significantly more likely to feel somewhat or very relieved by receiving the consent information (p value not given)</p> <p>Understanding</p> <p>The experimental group was significantly more likely to feel that they had understood their clinical trial and were less likely to feel 'confused'.</p> <table border="1"> <thead> <tr> <th></th> <th>Control:</th> <th>Booklet:</th> <th>p:</th> </tr> </thead> <tbody> <tr> <td>(a) Voluntary nature</td> <td>83%</td> <td>92%</td> <td>< 0.03</td> </tr> <tr> <td>(b) Side-effects</td> <td>86%</td> <td>92%</td> <td>0.06</td> </tr> <tr> <td>(c) Concept of randomisation</td> <td>49%</td> <td>40%</td> <td>0.05</td> </tr> </tbody> </table> <p>Recruitment</p> <p>There was no statistically significant difference between the groups in terms of clinical trial participation (no trend given)</p> <p>See also Table 10 – audit</p>		Control:	Booklet:	p :	(a) Voluntary nature	83%	92%	< 0.03	(b) Side-effects	86%	92%	0.06	(c) Concept of randomisation	49%	40%	0.05	<p>A1</p> <p>B1</p> <p>C-. Anxiety was not measured by a psychometric scale</p> <p>D-. Response rate not given though 78% of those receiving the National Cancer Institute's booklet actually read it.</p> <p>E-</p> <p>F. Insufficient information</p>												
	Control:	Booklet:	p :																													
(a) Voluntary nature	83%	92%	< 0.03																													
(b) Side-effects	86%	92%	0.06																													
(c) Concept of randomisation	49%	40%	0.05																													
(3) Levene et al. (1996)	<p>The same parents were offered entry for their new-born babies into two trials requiring different informed consent procedures:</p> <p>(1) trial A – consent obtained 2 h after eligibility established (n = 42)</p> <p>(2) trial B – consent obtained 7–14 days after eligibility established at birth (n = 37)</p> <p>Parents of babies eligible for two separate but concurrent clinical trials; one of blood volume support and one of erythropoietin (n = 79)</p>	<p>Recruitment</p> <p>Actual participation</p>	<p>When approached for consent early, the parents were more willing for their baby to undergo randomisation than when they were approached later ($p = 0.013$)</p> <p>Consent rates</p> <p>(a) Early consent: 71%</p> <p>(b) Late consent: 43%</p>	<p>A1</p> <p>B2</p> <p>C. Not applicable</p> <p>D. Not applicable</p> <p>E-</p> <p>F+</p>																												

continued

TABLE 7a contd Methods of obtaining informed consent for real trials

Author	Study design and sample (n = study participants)	Outcome measures	Main results	Comments (see Table 8 for quality of evidence checklist)
(4) McLean (1980)	The first 22 respondents were allocated to the first interview format and then the remainder (n = 104) to an alternative interview: (1) written and verbal information with no mention of randomisation (2) written and verbal information including an explanation of randomisation Clinically depressed patients offered entry to a clinical trial of four treatments (n = 126)	Recruitment Willingness to participate (recruitment) was rated by the interviewing clinician according to four categories: (1) free consent with no questions (2) consent after mild questioning (3) consent after persuasion (4) refusal	There was no statistically significant difference between interviews in terms of willingness to participate according to category, with no refusals in either group Interview 1: Interview 2: (1) consent with no questioning 81% 86% (2) consent after mild questioning 17% 14% (3) consent after persuasion 2% 0% (4) refusal 0% 0%	A2 B3 C- D+. 100% response rate E- F. Not applicable
(5) Myers et al. (1987)	Patients were randomised to one of two consent scenarios: (1) information about gastrointestinal side-effects (n = 399) (2) no information about side-effects (n = 156) Participants in a placebo-controlled trial for unstable angina (n = 555)	Experience of side-effects Minor gastrointestinal side-effects experienced by the patients was assessed by a questionnaire, while major complications were diagnosed by the study physicians	There were no statistically significant differences between the two group in the occurrence of major side-effects as documented by the study physicians However, there was a statistically significant difference between reporting of minor gastrointestinal side-effects by the patients ($p < 0.001$) Reporting rates Group 1: 44% Group 2: 16% These minor side-effects were not confirmed independently by study nurse or physician	A1 B2 C+. 100% response rate D. Insufficient information E+. Consent information given but no questionnaire F. Post hoc statistical analysis
(6) Simes et al. (1986)	Respondents randomised to one of two consent methods: (1) individual approach (2) total disclosure Subpopulation (n = 57) of eligible cancer patients for any one of 16 trials	Anxiety Anxiety assessed by questionnaire completed before receiving treatment and again 3–4 weeks later with responses recorded on a five-point scale Understanding Understanding assessed by questionnaire to assess recall of diagnosis, treatment, possible side-effects, and research aspects Recruitment Actual participation	Anxiety Patients in total disclosure group were also more anxious initially ($p = 0.02$) but later showed that this significant effect was transient Understanding Patients in the total disclosure group were more knowledgeable about their illness and treatment ($p = 0.0001$), and also about research aspects of the trial ($p = 0.03$). In particular, the concept of randomisation was understood better by the total disclosure group ($p = 0.004$) Recruitment Patients in total disclosure group were less amenable to receiving randomised treatment ($p = 0.01$) See also Table 10 – audit	A2 B1 C-. Anxiety was not measured by a psychometric scale D+. 87% response rate E+. Questionnaire not supplied but available from authors and consent information given. 54% of topics were in fact mentioned to the individual approach group as compared with 86% of topics for the total disclosure group F+ Questionnaire pilot tested
(7) Tindall et al. (1994)	Respondents were randomly allocated to receive one of two consent formats: (1) written only (n = 52) (2) written and oral (n = 61) AIDS patients in to a dose-control trial of didanosine (n = 113)	Understanding Understanding assessed by an eight-item instrument presented prior to and subsequent to receiving consent information	No statistically significant difference between groups in pre-consent or post-consent knowledge scores between the two groups ($p = 0.222$) There was a statistically significant increase in scores for both groups when baseline scores were compared with those obtained after the provision of information ($p = 0.0003$), and a weak interaction between time and format, indicating that those provided with written and verbal information increased their knowledge score more over time ($p = 0.079$) Mean knowledge scores Baseline: After information: (a) written only 4.4 4.8 (b) written and oral 4.0 5.0 See also Table 10 – audit, and Table 12a – views of patients	A2 B1 C- D-. Response rate not given E+ F-

TABLE 7b Methods of obtaining informed consent in hypothetical trial scenarios

Author	Study design and sample (n = study participants)	Outcome measures	Main results	Comments (see Table 8 for quality of evidence checklist)
(1) Dal-re (1991)	<p>Students were assigned to one of two consent forms:</p> <p>(1) standard + minimal information on side-effects</p> <p>(2) Standard + detailed information on side-effects</p> <p>Student volunteers in a hypothetical Phase I trial of isoniazide</p>	<p>Recruitment rates</p> <p>Anonymous indication on consent document</p>	<p>There was a significant difference between the two consent groups according to consent rates ($p < 0.05$)</p> <p>Consent rates: (1) form 1: 11% (2) form 2: 4%</p> <p>Among the women, only students of medicine agreed to participate, with 8 and 12% of women consenting in group 1 and group 2, respectively</p>	<p>A1 B2 C. Not applicable D-. Response rate not given E+ F+</p>
(2) Epstein and Lasagna (1969)	<p>Respondents were randomised to one of three informational forms:</p> <p>(1) short (2) medium (3) long</p> <p>The forms differed only in the amount of detail about the risks and benefits of aspirin, in addition to baseline information</p> <p>Hospital employees with no medical qualification (n = 66) offered entry to a hypothetical placebo-controlled trial of acetyl-hydroxybenzoate (fictitious name for aspirin)</p>	<p>Anxiety</p> <p>Anxiety was assessed by structured questionnaire</p> <p>Understanding</p> <p>Recall of information was assessed by structured questionnaire</p> <p>Recruitment rates</p> <p>Willingness to participate was assessed by structured questionnaire</p>	<p>Anxiety</p> <p>Respondents who thought the information was frightening or not useful: (a) short: 0% (b) medium: 23% (c) long: 41% (no statistical analysis given)</p> <p>Understanding</p> <p>Statistically significant differences were found between short and long forms in favour of shorter forms ($p < 0.001$)</p> <p>Mean understanding scores: (a) short: 67% (b) medium: 45% (c) long: 35%</p> <p>Recruitment</p> <p>Consent rates: (a) short form: 86% (b) medium form: 64% (c) long form: 55%</p> <p>Interactions</p> <p>Higher scores for understanding were significantly associated with greater willingness to participate. See also Table 12b – views of the public</p>	<p>A1 B1 C-. Anxiety was not measured by a psychometric scale D+. 91% response rate E+ F-. Should not have used multiple t test though this probably made little difference to the result</p> <p>Oral explanations of the research had already been given to the respondents</p>
(3) Fetting et al. (1990)	<p>Patients were randomised in the proportion 3:1, to one of two versions of a clinical vignette:</p> <p>(1) descriptive (2) numerical</p> <p>The vignettes differed only on how results of standard therapy were described in terms of disease-free survival (DFS)</p> <p>Female patients (n = 282) offered entry to a hypothetical clinical trial of chemotherapy for cancer</p>	<p>Understanding</p> <p>Understanding was assessed by patients' estimate of 10 year DFS with standard treatment</p> <p>Recruitment rates</p> <p>Willingness to participate in the trial rather than to choose their own treatment was assessed by structured interview</p>	<p>Understanding</p> <p>The mean estimate of percentage chance of living 10 years DFS with standard therapy was significantly higher (and accurate) in the numerical group than in the descriptive group ($p = 0.04$)</p> <p>Mean estimate of percentage chance of 10 year DFS: (a) descriptive group: 55% (b) numerical group: 61%</p> <p>Recruitment</p> <p>A statistically significant difference was found between the two groups in terms of consent rate ($p = 0.01$)</p> <p>Consent rates: (1) descriptive vignette: 52% (2) numerical vignette: 35%</p> <p>Interaction</p> <p>Patients in the descriptive group giving pessimistic or conservative estimates of DFS were significantly more likely to consent to trial entry ($p = 0.005$)</p> <p>Consent rate of descriptive group according to DFS estimate: (1) pessimistic estimate: 59% (2) conservative estimate: 59% (3) optimistic estimate: 35%</p>	<p>A1 B1 C- D+. 79% response rate E+. Questionnaire and vignettes available from authors F+</p>

continued

TABLE 7b contd Methods of obtaining informed consent in hypothetical trial scenarios

Author	Study design and sample (n = study participants)	Outcome measures	Main results	Comments (see Table 8 for quality of evidence checklist)
(4) Gallo et al. (1995)	<p>Participants were randomised to one of four consent scenarios:</p> <p>(1) pre-randomisation consent with refusers getting standard treatment</p> <p>(2) pre-randomisation consent with refusers choosing their treatment</p> <p>(3) consent to experimental interview treatment with refusers getting standard treatment (no knowledge of randomisation)</p> <p>(4) consent to standard treatment with refusers getting experimental treatment (no knowledge of randomisation)</p> <p>Quantitative information about disease severity given to respondents in the form of three levels of 5 years expected survival (20, 50 or 80%)</p> <p>General public offered entry to a hypothetical trial to evaluate the Zelen consent design (n = 2035)</p>	<p>Understanding Understanding was assessed by interview which covered perceptions of severity of disease and of relative efficacy of standard and experimental treatment</p> <p>Recruitment rates Willingness to participate was assessed by structured</p>	<p>Understanding 38.2% of respondents correctly understood individual equipoise 51.7% of respondents thought that the new treatment was better than the standard one, despite being told that equipoise applied Misunderstanding rates were independent of the consent procedures (data not given)</p> <p>Recruitment Consent rates for each consent scenario: (1) consent scenario 1: 83.8% (2) consent scenario 2: 80.1% (3) consent scenario 3: 87.9% (4) consent scenario 4: 50.8% (no statistical analysis given)</p> <p>Interaction The consent rate was greatest when the patients perceived the efficacy of the experimental treatment to be greater than that of the standard treatment and least when the patients perceived the efficacy of the experimental treatment to be less than that of the standard treatment</p> <p>Consent rate amongst those who understood that equipoise applied: (1) consent scenario 1: 81.1% (2) consent scenario 2: 81.5% (3) consent scenario 3: 86.8% (4) consent scenario 4: 41.6% (no statistical analysis given)</p>	<p>AI BI C- D-. Response rate not given E- F+</p>
(5) Llewellyn-Thomas et al. (1995)	<p>Patients were randomised to one of three consent formats:</p> <p>(1) neutrally framed probabilistic information</p> <p>(2) positively framed probabilistic information</p> <p>(3) negatively framed probabilistic information</p> <p>Cancer patients with resectable adenocarcinoma offered entry to a hypothetical clinical trial of different chemotherapy treatments (n = 90)</p>	<p>Recruitment Willingness to undergo randomisation rather than to choose their treatment was assessed by interview</p>	<p>There was no statistically significant difference between groups in terms of consent rate</p> <p>Consent rates: (1) neutral: 76% (2) positive: 60% (3) negative: 66%</p>	<p>AI BI C- D+. 36% of the eligible population was approached, of which 94% agreed to participate in the study E+ F+</p>
(6) Simel and Feussner (1991)	<p>Patients randomised to receive one of two consent forms:</p> <p>(1) randomised trial of usual treatment versus new medication that 'may work 2x as fast as usual treatment' (n = 52)</p> <p>(2) trial of new treatment that 'may work 1/2x as fast as the usual treatment' (n = 48)</p> <p>Adult ambulatory patients in a hypothetical clinical trial of standard versus new medication for an unspecified disease (n = 100)</p>	<p>Recruitment Willingness to participate was assessed by a tape-recorded interview with opportunity to ask questions</p>	<p>Patients randomised to form 1 were significantly more likely to consent than those randomised to form 2 ($p < 0.01$)</p> <p>Consent rate: (1) form 1: 67% (2) form 2: 42%</p> <p>The respondents who cited quantitative information on their informed consent form as a reason for either consenting or declining trial entry (62%) were no more likely to agree to participate than those who did not cite quantitative information as a basis for their decision</p> <p>See also Table 12b – views of patients</p>	<p>AI BI C+. Independent attorney reviewed random sample of taped interviews, and there was agreement over citation of quantitative information D- E+</p>

continued

TABLE 7b contd Methods of obtaining informed consent in hypothetical trial scenarios

Author	Study design and sample (n = study participants)	Outcome measures	Main results	Comments (see Table 8 for quality of evidence checklist)
(7) White et al. (1984)	<p>Respondents were randomised to one of three model consent forms:</p> <p>(1) long – explained randomisation and rationale for trial</p> <p>(2) medium – described the study as 'research' and did not mention randomisation</p> <p>(3) short – indicated that treatment was selected by physician</p> <p>All forms contained identical information about side-effects and drugs</p> <p>Breast cancer patients in a hypothetical randomised controlled trial (n = 75)</p>	<p>Understanding</p> <p>Attitudes and understanding were assessed by structured questionnaire</p>	<p>There was no significant difference between form length and patient perception of helpfulness in understanding therapy. The trend was in favour of better understanding in the longer form</p> <p>Percentage of respondents who were aware that treatment allocation was by chance:</p> <p>(a) short: 76%</p> <p>(b) medium: 84%</p> <p>(c) long: 96%</p> <p>Percentage of respondents who were unaware that the best chemotherapy regimen was unknown:</p> <p>(1) short: 84%</p> <p>(2) medium: 54%</p> <p>(3) long: 64%</p> <p>See also Table 12b – views of patients</p>	<p>A1</p> <p>B1</p> <p>C+</p> <p>D+. 99% response rate</p> <p>E+</p> <p>F+</p>

TABLE 8 Quality of evidence checklist for comparative studies of informed consent

Code	Dimension of methodology
A	Sampling hierarchy: (1) all patients offered entry in a trial or random sample of all patients (2) not stated or convenience sampling
B	Controls: (1) comparative study: RCT (2) comparative study: concurrent cohort (3) comparative study: historical cohort
C	Outcome measurement: interobserver reliability should be assessed where appropriate for questionnaires and/or interviews (particularly where open-ended questionnaire are used) (acceptable +, flawed –)
D	Response rate to outcome measure must be given, and is acceptable at 70% or above (acceptable +, flawed –)
E	Actual information given at consent, and questionnaire should be supplied in study (acceptable +, flawed –)
F	The statistical method used to analyse data must be appropriate (acceptable +, flawed –)

TABLE 9 Quality of evidence checklist for audit

Code	Dimension of methodology
A	External validity of study, i.e. how clearly defined is the target population to which the sample results may in theory be generalised (acceptable +, flawed –)?
B	Sampling: how representative is the sample of the target population? (1) Entire population approached or random selection of eligible patients (2) Quota sampling, i.e. deliberate selection from specific groups (3) Grab sampling
C	Controls: (1) RCT (2) non-randomised concurrent cohort (3) descriptive study
D	Outcome measurement: Interobserver reliability should be assessed where appropriate for questionnaires and/or interviews (particularly where open-ended questionnaire are used) (acceptable +, flawed –)
E	Response rate: outcome measure must be given and be acceptable at 70% or above (acceptable +, flawed –)
F	Original consent information and questionnaire should be supplied in study or available from authors (acceptable +, flawed –)
G	The statistical method used to analyse data must be appropriate (acceptable +, flawed –)

TABLE 10 Audit of the quality of communication

Author	Population assessed and sample size (n = No. of patients in survey)	Outcome measurement and purpose of study	Main results	Comments (see Table 9 for quality of evidence checklist)																								
(1) Aaronson et al. (1996)	Eligible cancer patients for Phase 2 or 3 trials at the Netherlands Cancer Institute (n = 30)	<p>Patients were randomised to one of two informed consent procedures:</p> <p>(1) standard informed consent procedure based on verbal and written information from physician</p> <p>(2) standard informed consent plus a supplementary, telephone-based contact with an oncology nurse</p> <p>Knowledge and understanding was assessed during an interview (a series of semi-structured questions with follow-up probes based on recall of information) 1 week after completion of the consent process</p> <p>Study to assess the effect of different consent procedures on comprehension of patients offered entry to a clinical trial</p>	<p>Overall No. of respondents who had knowledge of the following:[*]</p> <p>(1) the clinical trial context of the treatment (in general): 92%</p> <p>(2) the objectives of the clinical trial: 79%</p> <p>(3) the use of randomisation in allocating treatment: 65%</p> <p>(4) the availability of alternative treatments: 77%</p> <p>(5) the voluntary nature of participation: 89%</p> <p>(6) the right to withdraw from the clinical trial: 77%</p> <p>On average, group 2 was aware of 77.5% of the potential side-effects as compared with 60.7% for group 1 ($p < 0.01$)</p> <p>See also Table 7a – methods of informed consent</p>	<p>A–</p> <p>B3</p> <p>C1</p> <p>D+</p> <p>E+. 100% response rate (73 and 76% of patients from groups 1 and 2 were interviewed, respectively)</p> <p>F–</p> <p>G+</p> <p>Interview was pilot tested</p> <p>Recruitment rates to trials not given</p>																								
(2) Bergler et al. (1980)	Participants in a controlled trial of hydrochlorothiazide versus propranolol (n = 39)	<p>Interview with multiple-choice quiz to assess knowledge of trial at 2 h and 3 months following enrolment</p> <p>Study to assess comprehension of participants in a clinical trial</p>	<p>Percentage of patients answering correctly at:</p> <table border="1"> <thead> <tr> <th></th> <th>2 h:</th> <th>3 months:</th> </tr> </thead> <tbody> <tr> <td>(1) Action of hydrochlorothiazide</td> <td>92%</td> <td>82%</td> </tr> <tr> <td>(2) Action of propranolol</td> <td>77%</td> <td>38%</td> </tr> <tr> <td>(3) Side-effects</td> <td>28%</td> <td>4%</td> </tr> <tr> <td>(4) Duration of trial</td> <td>64%</td> <td>65%</td> </tr> <tr> <td>(5) Freedom to withdraw</td> <td>77%</td> <td>61%</td> </tr> <tr> <td>(6) Expect to receive best possible treatment</td> <td>95%</td> <td>100%</td> </tr> <tr> <td>(7) Meaning of double blind</td> <td>64%</td> <td>46%</td> </tr> </tbody> </table>		2 h:	3 months:	(1) Action of hydrochlorothiazide	92%	82%	(2) Action of propranolol	77%	38%	(3) Side-effects	28%	4%	(4) Duration of trial	64%	65%	(5) Freedom to withdraw	77%	61%	(6) Expect to receive best possible treatment	95%	100%	(7) Meaning of double blind	64%	46%	<p>A–</p> <p>B3</p> <p>C3</p> <p>D+</p> <p>E+. 100 and 64% response rate at 2 h and 3 months after enrolment</p> <p>F+</p> <p>G+</p> <p>Recruitment rate to trial not given</p>
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(3) Daughterty et al. (1995)	Participating patients in eight different Phase I cancer trials (n = 27)	<p>Structured interview: open- and closed-ended questions to determine whether respondents thought that they had understood the material and had been told about certain aspects of the trial</p> <p>Study to assess comprehension of participants in a Phase I clinical trial</p>	<p>93% reported that they understood all or most of the information about the trials in which they had decided to participate, though only 33% were able to state the actual scientific purpose of the Phase I trial</p> <p>The patients able to state the purpose of Phase I trials were significantly more educated ($p = 0.01$)</p> <p>See also Table 12a – views of patients, and Table 13 – views of healthcare professionals</p>	<p>A–</p> <p>B3</p> <p>C3</p> <p>D+. Most questions closed-ended</p> <p>E+. 90% response rate</p> <p>F+. Questionnaire supplied but not original consent information</p> <p>Recruitment rates to trials not given</p>																								
(4) Davis et al. (1990)	Eligible patients for a cancer clinical trial (n = 397)	<p>Patients were randomly allocated to receive experimental consent procedure (National Cancer Institute booklet) or to control procedure (not receive booklet until after understanding test 2 weeks later). Method for assessing comprehension not given</p> <p>Study to assess the effect of different consent procedures on comprehension of patients offered entry to a clinical trial</p>	<p>Correct responses:</p> <p>(1) Right to withdraw at any time 87%</p> <p>(2) Right to withdraw before the trial is over 54%</p> <p>(3) Standard treatments may be as good as experimental treatments 53%</p> <p>(4) The treatments may cause side-effects 89%</p> <p>(5) Randomisation means that treatment will be chosen by chance 45%</p> <p>See also Table 7a – methods of informed consent</p>	<p>A–</p> <p>B3</p> <p>C1</p> <p>D– Insufficient information</p> <p>E– Response rate not given</p> <p>F–</p> <p>G. Insufficient information</p> <p>Recruitment rate to trial not given</p>																								

* Level of understanding for all respondents was calculated from the raw data given in the study.

TABLE 10 contd Audit of the quality of communication

Author	Population assessed and sample size (n = No. of patients in survey)	Outcome measurement and purpose of study	Main results	Comments (see Table 9 for quality of evidence checklist)
(5) DCCT Research Group (1989)	Patients eligible for the Diabetes Control and Complications Trial (n = 278) Recruitment rate to trial = 79%	Self-administered multiple-choice questionnaire presented immediately prior to randomisation and 1 year after entry Study to assess the knowledge of participants in a clinical trial	80% of respondents obtained a perfect overall score Knowledge pre- and post-randomisation respectively: (1) 97 and 85% understood the scientific background ($p < 0.05$) (2) 96 and 95% knew the purpose of the study (3) 100 and 99% understood random assignment (4) 98 and 88% knew standard treatment risks ($p < 0.05$) (5) 94 and 85% knew experimental treatment risks ($p < 0.05$)	A- B3 C3 D+ E+. 100% for first test and 79% for test 1 year later F+. Questionnaire supplied but not original consent information G+
(6) DeLuca et al. (1995)	Patients eligible for participation in one of 12 randomised cardiovascular trials (n = 247) Recruitment rate to trial = 70%	Questionnaire using 30 variables, one of which assessed level of understanding of the study on a five-point scale Study to assess comprehension of patients offered entry to a clinical trial	Level of understanding after patients received verbal and written information: ^a (1) 5% had low understanding – level 1 (2) 3% had understanding – level 2 (3) 11% had moderate understanding – level 3 (4) 23% had understanding – level 4 (5) 58% had complete understanding – level 5 32% of potential participants reported not reading the consent form, despite being given the opportunity See also Table 12a – views of patients	A- B3 C3 D- E-. Response rate not given F- G+ Errors in how p value was reported and some strange percentages in some tables
(7) Gallet et al. (1994)	Multicentre Randomised trial Mexiletine and Placebo Antiarrhythmic Coronary Trial (IMPACT) Patients with a recent myocardial infarction (n = 77)	Questionnaire administered 5–21 months after consent had been secured. Comprehension assessed by recall Study to assess comprehension of participants in a clinical trial	Global quantity of information recalled was estimated as being 60% 40% of respondents correctly recalled the aim of the study and the concept of a placebo 55 and 43% correctly recalled the nature of the active treatment, and of randomisation, respectively 46% correctly recalled possible side-effects Right to withdraw and the nature of a double-blind study were understood by 81 and 62%, respectively	A- B3 C3 D- E+ response rate 84% F- G+ Recruitment rates to trial not given
(8) Harth and Thong (1995)	Parents of children participating in a randomised, placebo-controlled trial of ketotifen, an oral asthma drug (n = 62)	Structured questionnaire was presented 6–9 months after the children had been entered into the trial Study to assess comprehension of parents and their participating children in a clinical trial	While most parents (98.8%) were clear about the aim of determining drug efficacy, only a small percentage (12.9%) were aware that the trial was designed to assess safety as well. 45.2% of respondents knew that they had the unconditional right to withdraw their children from the trial See also Table 12a – views of patients	A- B3 C3 D-. Insufficient data E+. Of the 88% of families that were available after the trial, 95% agreed to participate in the survey F- G+ Recruitment rate to trial not given
(9) Harrison et al. (1995)	Eligible volunteers for a placebo-controlled Phase 2 trial of two HIV vaccines: (1) injection drug users (IDUs) (n = 39) (2) others (n = 32) Recruitment rate to trial = 100%	17-item true/false questionnaire was presented after disclosure of information but before the signing of the consent form Study to assess comprehension of patients offered entry to a Phase 2 HIV vaccine trial	Accurate responses: IDUs: Others: (1) Trial vaccines have been used in people before 85% 91% (2) The vaccines cannot cause HIV and AIDS 100% 100% (3) Not everyone in the trial will get a vaccine 74% 84% (4) People who participate in the trial might get HIV anyway 85% 94% (5) The vaccines might cause side-effects including aches and a fever 92% 84%	A- B2 C3 D- E+. 96% response rate F- G+
(10) Hassar and Weinstein (1976)	Participants in a double-blind clinical trial of an anti-inflammatory drug (n = 49) Recruitment rate to trial = 37%	Interview and questionnaire presented at the end of the trial (16 weeks) to elicit trial participants' understanding of the information sheet given at consent Study to assess comprehension of participants in a clinical trial	88% of trial participants were aware that their physician did not know which medication they had been allocated 65% did not remember being told that there was a risk of peptic ulceration 65% of respondents thought correctly that the experimental drug was not safer than other drugs for arthritis All participants knew that their physician would not be upset if they refused trial entry See also Table 12a – views of patients	A- B3 C3 D- E+. 94% response rate F+ G+

continued

TABLE 10 contd Audit of the quality of communication

Author	Population assessed and sample size (n = No. of patients in survey)	Outcome measurement and purpose of study	Main results	Comments (see Table 9 for quality of evidence checklist)
(11) Howard et al. (1981)	Beta-blocker Heart Attack Trial (BHAT) Participants from 11 geographical areas (n = 64) Recruitment rate to trial = 53%	In-depth home interviews in person or over the telephone to assess recalled information Study to assess comprehension of participants in a clinical trial as well as patients	91% of respondents were clearly aware that the BHAT study was a research enterprise, while 83% recognised that some participants took the experimental drug and others took a placebo. 67% of respondents gave a completely accurate description of the purpose of the trial, and 86% expressed an awareness of the possibility of side-effects. Only 42% of the respondents knew that the allocation of treatment was based on chance, while 77% clearly understood that the assignments were concealed from physicians	A+ B1 C3 D- E+. 98% response rate F- G+ Possibility that information about side-effects acquired from other sources other than the consent process
(12) Jensen et al. (1993)	Eligible women for three Danish breast cancer co-operative group trials dealing with adjuvant treatment of primary breast cancer (n = 34)	Structured interview with 36 questions which was tape-recorded. Recalled information was measured on a four-point scale: good, reasonable, questionable and bad Study to assess comprehension of patients offered entry in a clinical trial	Patients were generally able to remember the given information 3 months after it had been received. Patients' memory was rated 'good' for the randomisation aspect of the project, the available treatment alternatives, and the side-effects in 73, 65 and 76% of the patients, respectively See also Table 12a – views of patients	A+ B3 C3 D+. Interview conducted and cross-rated by two researchers who had not participated in the consent procedure E-. Response rate not given F- G+ Recruitment rates to trials not given
(13) Lynoe et al. (1991)	Patients who had participated in a multi-centre gynaecological clinical trial for acute inflammation of the Fallopian tube (n = 43)	Postal 10 closed-ended item questionnaire assessing recall, 18 months after trial completion Study to assess comprehension of participants in a clinical trial	98% of respondents were aware that they had participated in a research project 11% stated that they had not been aware that a second laparoscopy was performed only for research reasons 40% reported that had no information about the possibility of withdrawing from the study whenever they wanted 42% of respondents reported having weighed the pros and cons before consenting 56% reported not having weighed the pros and cons before consenting Women who weighed the pros and cons before consenting were significantly older ($p < 0.05$) See also Table 12a – views of patients	A- B3 C3 D-. There was a possibility that respondents were 'fed' answers E+. Response rate 81% F- G+ Recruitment rate to trial not given
(14) Marini et al. (1976)	Participating convicted violent men in a placebo-controlled trial of lithium carbonate (n = 44)	Open-ended and closed-ended questionnaire presented at end of trial (5 months after consent) Study to assess comprehension of participants in a clinical trial	97% of respondents knew that lithium was the drug being tested 82% of respondents knew that a placebo was also a treatment option in the trial 71% of respondents knew that they were part of an experiment 47% of respondents indicated the importance of aggressive behaviour in the experiment 65% of respondents gave at least one correct side-effect, while only 19% could give three or more	A- B3 C3 D- E+. 76% response rate F+. Consent information given but questionnaire not supplied G. Not applicable Recruitment rate to trial not given

continued

TABLE 10 contd Audit of the quality of communication

Author	Population assessed and sample size (n = No. of patients in survey)	Outcome measurement and purpose of study	Main results	Comments (see Table 9 for quality of evidence checklist)
(15) Maslin (1994)	There were three sample groups: (1) healthy volunteers not in a trial, i.e. a hypothetical decision scenario (2) healthy volunteers participating in a tamoxifen prevention trial (3) breast cancer patients in a clodronate trial and in a chemotherapy versus primary conservative trial (n = 213)	Two self-completed postal questionnaires: (1) participant satisfaction with informed consent process – 21 closed-ended questions with room for comment (2) patient/participant opinion on the informed consent process – 16 closed-ended questions with room for comment Respondents were asked whether they had been given the appropriate information Study to compare the comprehension of participants in a clinical trial with that of healthy volunteers	Healthy volunteers in a clinical trial were found to be better informed than corresponding cancer patients: (1) they were given more information: 86 versus 60% ($p < 0.005$) (2) better indication of their time commitment: 81 versus 62% ($p < 0.025$) (3) better informed about possible side-effects: 75 versus 57% ($p < 0.025$) (4) more aware of their rights to withdraw from the trial: 84 versus 46% ($p < 0.005$)	A– B1. Random sample of three different patient groups C2 D– E+ 62%, 73% and 76% response rate F+ G+ Recruitment rates to trial not given Authors' comments: (1) many of the asymptomatic patients were self-referred and were, as a result, strongly motivated and wanted to be monitored (2) many of the asymptomatic patients may have been familiar with the trial due to general press coverage
(16) Miller et al. (1994)	Random selection (25%) of participating patients in a double-blind, controlled trial of ibuprofen versus ketoprofen for over-the-counter analgesic use (n = 168)	Telephone interview using a questionnaire for open-ended recall, cued recognition and perception of their participation Study to assess comprehension of participants in a clinical trial	(1) Recall and recognition tasks: > 98% of respondents recalled participating in the trial 73% were able to accurately state the purpose of the trial 29% could not recall the study medications, 17% could correctly recognise both study drugs from a list while 18% could not recognise either drug No respondent could correctly recall all eight indications for administration of the medication 52% were unable to recall any of the 12 possible side-effects, while only 5% were able to recognise six or more when given a list (2) Perception of understanding: 98% of respondents thought that they had understood the information given	A+ B1 C3 D– E+. 84% response rate F+ G+ Recruitment rate to trial not given
(17) Oddens et al. (1992)	Random selection (32%) of cardiovascular patients (n = 81) eligible for one of two trials: (1) comparison of two doses of acetylsalicylic acid (2) atenolol versus placebo	Telephone interview using a structured questionnaire	88% of respondents knew that their trial was scientific research 92% of respondents were aware that the decision to participate was voluntary nature 63% of respondents knew that they could withdraw if they so wished 79% of those offered entry in trial one knew that their doctor did not know the allocated dose	A+ B1 C3 D– E+. 17% could not participate in the telephone survey. Of those that could participate, there was a response rate of 98% F+ G+
(18) Olver et al. (1995)	Cancer patients (n = 100) who had signed a consent form for one of 18 different chemotherapy trials	Interview with a nurse using a structured questionnaire, presented 6–43 days after trial entry	60% respondents claimed to understand the consent form fully 40% of respondents thought that the main purpose of the informed consent procedure was to explain the trial 52% of respondents could name all the drugs in their chemotherapy regimen 37% of the respondents could remember at least half the number of side-effects, and only 4% could remember all of them Only 80% of respondents reported having read the consent form	A+ B3 C3 D–. Insufficient information E+. 95% response rate F– G. Not applicable BMDP software was used to analyse the data

continued

TABLE 10 contd Audit of the quality of communication

Author	Population assessed and sample size (n = No. of patients in survey)	Outcome measurement and purpose of study	Main results	Comments (see Table 9 for quality of evidence checklist)
(19) Penman et al. (1984)	Participating patients from three cancer centres in 65 different Phase 2 or 3 investigative chemotherapy trials, of which 47% were randomised studies (n = 121)	Structured interview with computer coding of quantitative recall responses Patients asked whether they believed that they had been informed about the five major points conveyed in obtaining consent and whether each point was covered by physician at interview and/or consent form Study to assess comprehension of participants in a clinical trial	The point best recognised was the possibility of treatment-related side-effects, which virtually all patients acknowledged Actual recall of specific side-effects was poor. The average consent form cited 11 potential side-effects, and patients recalled correctly an average of three. 69% of respondents could list no more than three > 70% of respondents were aware of having been informed of the research nature of their treatment 69% claimed that the informed consent form played no role in their decision-making See also Table 12a – views of patients, and Table 13 – views of healthcare professionals	A– B3 C3 D–. Insufficient information E–. Response rate not given F– G. Not applicable Recruitment rates to trials not given
(20) Postlewaite et al. (1995)	Participating children with chronic renal failure and their parents in a failed trial of growth hormone Parents (n = 30) Children (n = 14)	Semi-structured interview shortly after recruitment to assess recall of information Participants' knowledge was compared with information on a checklist. Also, respondents were asked to indicate the ease with which they made their decision on a three-point scale Study to assess comprehension of participants in a clinical trial	Parental understanding: 80% of parents had good or very good understanding of the treatment trial Among 20% whose understanding was poor, ignorance and uncertainty were mainly about side-effects and expectations of outcome rather than details of treatment, and 50% of this group did not speak English as a first language Children's understanding: 36% of children were unable to understand or recall in any detail the information given about the trial No correlation was found between age and understanding No significant association between the level of children's and level of parent's understanding about the trial There was no association between the ease of parental decision-making and the level of understanding about the trial	A– B3 C3 D– E–. Response rate not given F–. Information checklist supplied but not interview questions G–. Use a correlation coefficient to look for a group difference Recruitment rates to trial not given
(21) Rodebuis et al. (1984)	Patients eligible for a Phase I trial of a new antitumor agent, SOAz (n = 10) Recruitment rate to trial = 85%	Semi-structured interview conducted by trained observer to assess recalled information Study to assess comprehension of patients offered entry to a Phase I clinical trial	80% of those interviewed were adequately informed. They recalled relevant aspects of the Phase I study though 50% of these patients did not achieve complete understanding See also Table 12a – views of patients	A+ B3 C3 D– E+. Only 21% of patients approached were interviewed but all were willing to participate F– G. Not applicable
(22) Simes et al. (1986)	Cancer patients eligible for any one of 16 trials (n = 55) Recruitment rates to trials = 88%	Respondents randomly allocated to one of two consent types: (1) individual approach (2) total disclosure Questionnaire completed before receiving treatment and again 3–4 weeks later with responses recorded on a five-point scale Two measures of patients' knowledge were calculated by recall of: (1) diagnosis, treatment, and possible side-effects (2) research aspects Study to assess the effect of different consent procedures on comprehension of patients offered entry to a clinical trial	Level of understanding for all respondents* 68% of respondents were knowledgeable about treatment and side-effects 66% of respondents were knowledgeable about research aspects of their treatment Only 24% of respondents understood that their treatment would be allocated at random See also Table 7a – methods of informed consent	A– B3 C1 D–. Insufficient information E+. 96% response rate F+. Questionnaire not supplied but available from authors and consent information given Questionnaire pilot tested Recruitment rate to trial not given

* Level of understanding for all respondents was calculated from the raw data given in the study.

TABLE 10 contd Audit of the quality of communication

Author	Population assessed and sample size (n = No. of patients in survey)	Outcome measurement and purpose of study	Main results	Comments (see Table 9 for quality of evidence checklist)
(23) Tomamichel <i>et al.</i> (1995)	Eligible patients for Phase I oncology study (n = 44 for second interview)	Informed consent procedure was three tiered: (1) initial introduction (2) detailed conversation (3) clarification if needed and signing of consent form The second session was taped, transcribed and analysed quantitatively along three dimensions of informed consent (information – 12 items, emotion – 5 items, and interactive dimension – 11 items), and consisted of calculating the No. of patients to whom the essential items of information had been conveyed Study to assess the quantity and quality of information actually given to patients in a Phase I clinical trial	Quantitative analysis: information concerning the characteristics of a Phase I drug (investigational drug used on only a few humans) was given to 78% of patients, information concerning patients' right to refuse or to withdraw was given to 34% of patients, details of side-effects were given to 81% of patients, and 91% of patients were informed that there was a lack of known treatments of proven efficacy	A– B3 C3 D+ 73% were quantitatively analysed Interobserver variability of the scoring was studied in the first six consultations by comparing the evaluations of two psychiatrists and three psychologists E. 39% of interviews were taped and (selected by logistical considerations) but actual response rate not given F+ G+ Recruitment rate to trial not given
(24) Tindall <i>et al.</i> (1994)	Eligible AIDS patients for a dose-controlled trial of didanosine (n = 113)	Respondents received either written only consent format or written and verbal according to random assignment An eight-item instrument assessed knowledge of ddl prior to and subsequent to receiving information. Respondents were asked whether they thought that they had understood the information provided Study to assess the effect of different consent procedures on comprehension of patients offered entry in a clinical trial	44% of subjects stated that they did not understand all of information provided, despite having signed the consent form No significant difference in pre-consent knowledge scores for both groups, or post-consent-knowledge scores There was a significant increase in knowledge after consent for both groups ($p = 0.0003$) See also Table 7a – methods of informed consent, and Table 12a – views of patients	A– B3 C1 D– E–. Response rate not given F+ G– Recruitment rate to trial not given

TABLE 11 Quality of evidence checklist for attitude studies

Code	Dimension of methodology
A	External validity of study, i.e. how clearly defined was the target population which the sample results may in theory be generalised (acceptable +, flawed –)?
B	Sampling: how representative is the sample of the target population? (1) Entire population (consenters and refusers) approached or random selection of eligible patients (2) 'Quota' sampling, i.e. deliberate selection from specific groups (3) Grab sampling
C	Response rate must be given and acceptable at 70% or above (acceptable +, flawed –)
D	Interobserver reliability should be assessed where appropriate for questionnaires and/or interviews (particularly where open-ended questionnaire are used) (acceptable +, flawed –)
E	Questionnaire should be supplied in study or available from authors (acceptable +, flawed –)
F	The statistical method used to analyse data must be appropriate (acceptable +, flawed –)

TABLE 12a Views of the patients and public in real trial scenarios*

Author	Purpose of study and sample population (n = No. of respondents to survey)	Method of assessment	Main results	Comments (see quality of evidence checklist – Table 11)
(1) Barofsky and Sugarbaker (1979)	<p>Study to identify the motivations of patients to participate in trials</p> <p>Consenting and refusing patients in sarcoma clinical trials (n = 76):</p> <p>(A) extremity soft-tissue sarcoma – trial of amputation versus limb-sparing surgery plus radiation (patients offered randomisation)</p> <p>(B) head-neck-trunk soft-tissue sarcoma – trial of limited surgery + radiation + adriamycin versus limited surgery + radiation + adriamycin + parvum immunotherapy (patients offered randomisation)</p> <p>(C) primary osteogenic sarcoma – trial to receive versus not receive immunotherapy with BCG (patients offered randomisation)</p> <p>USA</p>	Standardised semi-structured interview, sometimes conducted over the telephone	<p>54% of the participants reported that they consented and complied with the treatment protocol for reasons of self-interest</p> <p>Patients who received an amputation justified it almost exclusively in terms of self-interest, whereas patients who received limb sparing therapy justified participating in the trial with a broader range of answers</p> <p>Ratings of quality of medical care were mostly excellent or good and did not vary between consenters and refusers</p>	<p>Descriptive study</p> <p>A+</p> <p>B2</p> <p>C+. 100% response rate</p> <p>D-</p> <p>E+</p> <p>F+</p>
(2) Bevan et al. (1993)	<p>Study to assess patients attitudes to participation in clinical trials</p> <p>Group A – patients (n = 66) in previous or current clinical trials under care of the authors whose interests including hypertension, clinical pharmacology, and general medicine</p> <p>Group B – patients who had declined participation in trials (n = 12)</p> <p>Group C – patients who had not been offered trial entry (n = 119)</p> <p>Scotland</p>	Structured interview	<p>(1) Motivation: In group A, 62% stated that their motivation for participation was to help others, and 39% to improve their own treatment Reasons given by group B for not participating included unwillingness to change treatment (25%) and objections from family members (25%)</p> <p>(2) Informed consent: In group A, 83% felt that they had adequate time to consider their participation 60% of respondents would have liked written information to retain for reference 54% of consenting patients were happy with every aspect of the trial</p> <p>See also Table 12b – views of the public</p>	<p>Descriptive study</p> <p>A+</p> <p>B2</p> <p>C+. 99% response rate</p> <p>D-</p> <p>E-</p> <p>F+</p>
(3) Daughterty et al. (1995) [†]	<p>Pilot study to examine issues related to participation and the perceptions of patients towards their trial</p> <p>Participating patients in eight different Phase I cancer trials (n = 27)</p> <p>USA</p>	Structured interview: using open- and closed-ended questions from a standardised survey form	<p>Although 85% of respondents chose to participate in their trial explicitly for the chance of personal gain, only 22% actually expected to receive therapeutic benefit. However, 70% of patients said that they believed that they would receive psychological benefit by participating</p> <p>Few patients actually estimated the quantitative chance of therapeutic benefit (no data supplied)</p> <p>See also Table 10 – audit, and Table 13 – views of healthcare professionals</p>	<p>Descriptive study</p> <p>A-</p> <p>B3</p> <p>C+. 90% response rate</p> <p>D+. Most questions closed-ended</p> <p>E+</p> <p>F+</p>

* Tables 12a and 12b list all articles pertaining to the attitudes of patients and the public to real and hypothetical clinical trials. Table 12c extracts the articles from the first two tables which relate specifically to the patient's reported motivations behind participating in trials.

[†] This paper examines attitudes to Phase I trials.

continued

TABLE 12a contd Views of the patients and public in real trial scenarios*

Author	Purpose of study and sample population (n = No. of respondents to survey)	Method of assessment	Main results	Comments (see quality of evidence checklist – Table 11)
(4) DeLuca et al. (1995)	Study to determine variables contributing to patient participation in RCTs Patients eligible for participation in one of 12 randomised cardiovascular trials (n = 248) USA	Questionnaire designed by the authors using 30 variables, along a five-point scale	32% of respondents reported not reading the consent form, with no difference between consenters and refusers 97% of those approached initially by the doctor consented whereas 66% of those initially approached by the nurse consented 79% of those who felt that their participation would contribute to medical knowledge actually consented 88% of those who believed that they would receive better medical treatment also consented See also Table 10 – audit	Descriptive study A–. Insufficient information B3 C–. Response rate not given D– E– F+ Errors in how p value was reported and some strange percentages in some tables
(5) Harth and Thong (1990)	Study to assess motivational characteristics of parents who volunteer their children for clinical trials Parents of participating children (n = 68) in a randomised, placebo-controlled trial of a drug to treat asthma and to a control group of parents whose children were eligible but who refused (n = 42) Australia	Questionnaire administered at interview consisting of structured and open-ended questions	100% of those that consented expressed a wish to contribute to medical research 99% wanted the research to benefit other children 90% consented in order to benefit their own child 95% of refusers did not volunteer for fear of side-effects 52% expressed a dislike of modern medicines	Descriptive study A– B2 C+. Of the 88% of families that were available after the trial, 95% agreed to participate in the survey D– E– F–
(6) Harth and Thong (1995)	Study to examine the attitudes and knowledge of parents after having given informed consent for their children to enter a trial Parents of children participating in a randomised, placebo-controlled trial of ketotifen, an oral asthma drug (n = 62) Australia	Structured questionnaire was presented 6–9 months after the children had been entered into the trial	15% of parents considered the information provided at consent to be unnecessary because of their faith in their physician's advice 40% saw the legal requirement of a signature on the informed consent form as a device for protecting physicians from litigation while 19% saw it as a protective mechanism for research participants 79% of parents thought that there were no or low risks to enrolment in clinical trials at their hospital See also Table 10 – audit	Non-randomised cohort study A+ B2 C+. Response rate of 94 and 70% of consenters and refusers, respectively D–. Insufficient information E– F+
(7) Hassar and Weinstein (1976)	Study to examine the motivations and understanding of participants in a clinical trial Participants in a clinical trial of an anti-inflammatory drug (n = 49). Recruitment rate to the trial = 37% USA	Interview and questionnaire presented at the end of the trial to elicit patients motivations for entering the trial	(1) Perceived motivations of investigators by patients participating in the trial: 94% of respondents thought that the investigator had undertaken the study to help the patient's medical condition 88% of respondents thought that the investigator wanted to help other patients 24% thought that the investigator wanted to help the university involved with the trial (2) Motivations of patients: 13% of those that refused trial entry did so for logistic reasons, while 3% were concerned about toxicity 50% of trial participants stated that they had wanted to contribute to the welfare of other patients, while the remainder felt that they would be the major beneficiaries (3) Quality of care in the trial: All trial participants thought that the quality of their care had not suffered during the trial period See also Table 10 – audit	Descriptive study A– B3 C+. 94% response rate D– E+ F+
* Tables 12a and 12b list all articles pertaining to the attitudes of patients and the public to real and hypothetical clinical trials. Table 12c extracts the articles from the first two tables which relate specifically to the patient's reported motivations behind participating in trials.				

continued

TABLE 12a contd Views of the patients and public in real trial scenarios*

Author	Purpose of study and sample population (n = No. of respondents to survey)	Method of assessment	Main results	Comments (see quality of evidence checklist – Table 11)
(8) Henzlova et al. (1994)	Study to assess experiences of patients in a clinical trial Participating patients in treatment (n = 1162) or prevention (n = 2360) Studies of Left Ventricular Dysfunction (SOLVD) USA	10-item self-administered close-out questionnaire	(1) Motivation: 32% of respondents participated out of altruistic reasons, contribute to medical science or help others 16% of respondents, on the other hand, participated through selfish reasons, to live longer or to get free care and medication (2) Satisfaction with participation: 97% of respondents were satisfied with participation in the trial 87% would be willing to participate in another trial (3) Benefits and disadvantages: 62% of respondents thought that they would benefit psychologically (statistically more significant in prevention trial) 56% perceived a physical benefit (statistically more significant in treatment trial) 37% expressed logistic problems associated with participation	Descriptive study A+ B3 C+. 74% response rate (33% of whom had participated in the treatment trial and 67% in the prevention trial) D+ E+ F+ There were some missing data, not more than 22% of participants for all questions
(9) Henshaw et al. (1993)	Study to assess whether women who undergo pregnancy terminations are willing to enter a clinical trial Women approached for a patient centred, partially randomised trial of medical abortion versus vacuum aspiration (n = 348). There were three sample groups: (1) women preferring medical abortion (n = 73 offered trial entry) (2) women preferring vacuum aspiration (surgery) (n = 95 offered trial entry) (3) women willing to be allocated to treatment at random (n = 195 offered trial entry) UK	The acceptability of the operation was assessed by a self-administered questionnaire and by a semantic differential rating technique	There were no significant differences in acceptability of the procedure among women allocated according to their preference. However, there was a significant difference between treatment groups who had been randomised according to whether or not they would opt for a different procedure in the future. 2 and 22% of women randomised to vacuum aspiration and to medical abortion, respectively, would opt for a different procedure in future ($p < 0.001$). This result was confirmed by the semantic differential ratings	Descriptive study A+ B3 C+. 100% response rate D+ E-. Questionnaire not supplied F+
(10) Jensen et al. (1993)	Study to evaluate the information strategy used in the consent procedure for clinical trial entry, and what motivates patients to enrol Breast cancer patients in one of three Danish breast cancer co-operative group trials dealing with adjuvant treatment of primary breast cancer (n = 34) Denmark	Structured interview. Tape-recorded 36 questions	53% of respondents had consented to enter an RCT 50 and 44% of respondents were motivated to participate in their trial by the desire to support science and the hope of receiving better treatment, respectively 15% of respondents had a negative attitude towards the trial but the rest stated that they would consider participating in future studies 76% of respondents emphasised that the concrete knowledge about the disease and treatment made it easier to cope and reduced uncertainty. However, 6% claimed that the information, particularly about the trial, had increased their anxiety. The rest reported no change in anxiety levels or did not know See also Table 10 – audit	Descriptive study A+ B3 C+. 94% response rate D+. Interview conducted and cross-rated by two researchers who had not participated in the information procedure E- F+

* Tables 12a and 12b list all articles pertaining to the attitudes of patients and the public to real and hypothetical clinical trials. Table 12c extracts the articles from the first two tables which relate specifically to the patient's reported motivations behind participating in trials.

continued

TABLE 12a contd Views of the patients and public in real trial scenarios*

Author	Purpose of study and sample population (n = No. of respondents to survey)	Method of assessment	Main results	Comments (see quality of evidence checklist – Table 11)
(11) Lynoe et al. (1991)	Study to determine whether the participants in a clinical trial had perceived adequate information about the trial according to the guidelines of the Helsinki Declaration Patients who had participated in a multicentre gynaecological clinical trial for acute inflammation of the Fallopian tube (n = 43) Sweden	Postal questionnaire, 18 months after trial completion	56% of respondents stated that their motive for agreeing to participate had been altruistic in the sense that the study might benefit future patients However, 35% of respondents had seen the study as offering the chance to receive better medical care 9% had agreed to participate simply because their doctors had asked them to See also Table 10 – audit	Descriptive study A– B3 C+. Response rate 81% D–. There was a possibility that respondents were 'fed' answers E+ F+
(12) Marsden et al. (unpublished)	Study to test the feasibility of conducting a randomised trial of hormone replacement therapy (HRT) use in women with a history of breast cancer Consenters (n = 100) and refusers (n = 144) in a pilot trial of HRT versus no HRT in menopausal women with a diagnosis of early breast cancer Recruitment rate to the pilot trial = 38.3% UK	The views of participants in the pilot trial were solicited by three focus groups, orchestrated by an independent researcher. Of the 14 women involved, eight and six had been assigned to the control and HRT groups, respectively (see qualitative studies) A postal questionnaire was sent to the population of refusers	(1) Between consenters and refusers: There was no statistically significant difference between consenters and refusers with respect to concerns about uncertainty or sharing treatment decisions However, refusers were significantly more worried about being used as 'guinea-pigs' ($p < 0.001$), and thought that the research may do more harm than good ($p = 0.007$), and were more nervous about trial entry ($p < 0.001$) (2) Within refusers: 4% of refusers had no treatment preference (equiposed) but still refused randomisation Perceived side-effects with HRT was the most commonly cited reason for refusal (no frequency given) (3) Within consenters 50% in the control group wished to commence HRT at the end of the study, while 76% of women taking HRT wished to continue with it See also Table 13 – attitudes of healthcare professionals	A. Insufficient information B1 C–. 89.4% D–. Insufficient information E– F+
(13) Mattson et al. (1985)	Study to obtain patients' perceptions of advantages and disadvantages to trial participation and their motivations for enrolment Participants in two multicentre clinical trials sponsored by the National Heart, Lung and Blood Institute: Trial 1 – the Aspirin Myocardial Infarction Study (AMIS) (n = 380 were obtained through random selection (10%) of patients) Trial 2 – the BHAT (n = 594 in subsample A and n = 608 in subsample B obtained through random selection (50%) of patients) USA	Trial 1 – AMIS using structured interview with open-ended questions Trial 2 – BHAT using one of two questionnaires with closed-ended questions inviting answers on a five-point scale presented to subsample A and subsample B on a random basis	The results fall into three broad categories: (1) Motivation for participation: 74 and 76% of respondents from AMIS and BHAT, respectively, were motivated to participate in the trial because they believed that they would benefit in some way from participation, while 65% from AMIS participated at least partly for altruistic reasons 82% of respondents in BHAT (subsample A) perceived the beneficiary of participation as the scientists, while 59% thought that it was the patient (2) Perceived advantages to participation: 84% of AMIS participants thought that they had benefited in some way from their participation. The most frequently cited benefit was the receipt of additional clinical attention from specialists, by 44 and 72% of patients in AMIS and BHAT, respectively, while personal awareness and reassurance from being in the trial were cited by 38 and 54% of these patients, respectively (3) Perceived disadvantages to participation: 10 and 11% of respondents from AMIS and BHAT (subsample B), respectively, thought the major disadvantages to participation involved getting transport to the hospital Attitude to future participation: 87 and 78% from AMIS and BHAT, respectively, said they would either definitely or probably participate in a future study, while 13 and 21% would not or were uncertain	Descriptive study A– B1. Consenters only C+. 95% response rate in AMIS, 80% in BHAT D–. Insufficient information E– F+
* Tables 12a and 12b list all articles pertaining to the attitudes of patients and the public to real and hypothetical clinical trials. Table 12c extracts the articles from the first two tables which relate specifically to the patient's reported motivations behind participating in trials.				

continued

TABLE 12a contd Views of the patients and public in real trial scenarios*

Author	Purpose of study and sample population (n = No. of respondents to survey)	Method of assessment	Main results	Comments (see quality of evidence checklist – Table 11)
(14) Penman et al. (1984)	Study to examine perceptions of the informed consent procedure and of trial participation Participating patients from 65 different Phase 2 or 3 investigational chemotherapy trials, 47% of which were randomised studies (n = 144) USA	Structured interview with computer coding of quantitative responses	78% of respondents expected a considerable benefit from the trial, though only 43% had no doubt that they would benefit 93% of respondents reported 'to fight my illness' as a reason for participating, while 47% reported 'to be part of research' as a reason for participating, though never as a primary reason 91% perceived the physician as strongly wanting them to accept randomisation, though 80% felt that they had nevertheless made their own decision 6% said that the consent form played no role in their decision-making process See also Table 10 – audit, and Table 13 – views of healthcare professionals	Descriptive study A– B3 C–. Response rate not given D–. Insufficient information E– F. Not applicable
(15) Rodebuis et al. (1984)	Study to evaluate patient's motivation and the informed consent process in a Phase I study Patients eligible for a Phase I trial of a new anti-tumour agent, SOAz (n = 10) Holland	Semi-structured interview conducted by trained observer	50% of patients stated that 'the hope of improvement in their diseases was the main motive for taking part in the study', while 20% did not formulate an explicit motivation but indicated that they were taking the advice of their physician 20% of patients believed that the active treatment offered was effective, while 20% of patients believed that it was not effective, and the remainder were uncertain See also Table 10 – audit	Descriptive study A+ B3 C–. Only 21% of patients approached were interviewed but all were willing to participate D– E– F. Not applicable
(16) Ross et al. (1993)	Study to assess patients' reasons for trial participation HIV patients participating in a zidovudine trial (n = 32) USA/Australia	Questionnaire: (A) responses rated on a seven-point bipolar analogue scale: (1) the degree of influence a variety of sources had on their decision to enter the trial (2) how important participation in the trial was for themselves, the gay community, medical science and medical researchers (B) using a subjective expected utility model of decision-making participants were asked to rate: (1) what weight they had given the reasons provided (2) the chance of that risk or benefit happening to them	Benefits were seen in all cases to be substantially larger than risks Making a contribution to research was the most highly rated benefit, followed by showing concern for one's health and dealing with the illness Medical researchers were rated as being most important beneficiaries, followed by medical science, the gay community, and, finally, oneself	Descriptive study A+ B3 C–. Response rate not given D–. Insufficient information E– F–. Could have used non-parametric correlations instead of group comparisons
(17) Tindall et al. (1994)‡	Study to determine patient's perceptions of the purpose of informed consent AIDS and ARC (AIDS-related complex) patients offered entry to a dose-controlled trial of didanosine (n = 113) USA/Australia	Two questionnaires presented 1 week prior to trial enrolment and repeated one week later: (1) looked at past experience of zidovudine, most frequent sources of information, and perceptions of informed consent (2) assessment of knowledge	88% of respondents believed that their specialist medical practitioner always acted in their best interest 79% thought that people should be allowed the choice between participating in a clinical trial of unproved medications and of receiving it outside the trial mechanism 96% believed that informed consent was necessary See also Table 7a – methods of informed consent, and Table 10 – audit	Descriptive study A– B3 C–. Response rate not given D– E+ F–

* Tables 12a and 12b list all articles pertaining to the attitudes of patients and the public to real and hypothetical clinical trials. Table 12c extracts the articles from the first two tables which relate specifically to the patient's reported motivations behind participating in trials.

‡ This paper also reported attitudes of patients to their own understanding of the consent process. For further discussion, refer to the audit of quality of communication (Table 9).

continued

TABLE 12a contd Views of the patients and public in real trial scenarios*

Author	Purpose of study and sample population (n = No. of respondents to survey)	Method of assessment	Main results	Comments (see quality of evidence checklist – Table 11)
(18) Vogt et al. (1986)	Pilot study to assess factors influencing the recruitment of older adults (> 60 years) to clinical trials Multicentre clinical treatment trial of systolic hypertension (SHEP) (n = 551 at initial screening, and n = 422 at first clinic visit) USA	Interview after initial screening	Of the participants, 53% of respondents at initial screening intimated that they were motivated to participate by the hope of an improvement in personal health, 34% cited an improvement to the health of others, 31% cited a contribution to science and 24% cited free medical care (reasons not mutually exclusive) 32 and 27% of respondents at first clinic visit refused trial entry on the basis of physician or family advice, or because of logistic problems respectively	Descriptive study A– B3 C–. Response rate not given D–. Insufficient information E– F–
(19) Wilcox and Schroer (1994)	Study to assess the patients' attitudes to trial participation and what motivates them to enrol Participants in one of two trials: (1) Asymptomatic Carotid Atherosclerosis Study (ACAS) sponsored by the National Institutes of Health (n = 15) (2) Clopidogrel versus Aspirin in Patients at Risk for Ischemic Events (CAPRIE) trial sponsored worldwide by a pharmaceutical company (n = 25) USA	Interview conducted by nurse using a questionnaire of six questions: closed- and open-ended yielding quantifiable answers	(1) Motivation: 30.2% of participants reported improved health as a factor in the decision to participate, and only 11.3% reported altruism as a factor 90% of respondents reported that their physician was influential when they were deciding whether to participate (2) Benefits and disadvantages: 22.5% of respondents saw the main advantage to participation as being the necessary close medical follow-up, 20% thought it was improved health, 15% thought increased medical monitoring, and 12.5% altruistic factors 52.5% of respondents saw no disadvantage to being in the study, while 12.5% viewed the inconvenience of more frequent visits to the centre as a disadvantage (3) Quality of care in the trial: 87.5% of respondents would enter the same study again 57.5% of respondents would be interested to participate in studies in the future, while the remainder were uncertain and none would automatically refuse	Descriptive study A– B3 C–. No response rate given D– E+ F+ Questionnaire was piloted (the questionnaire was revised so that the word 'study' was used instead of 'clinical trial' from the pilot study of n = 10)

* Tables 12a and 12b list all articles pertaining to the attitudes of patients and the public to real and hypothetical clinical trials. Table 12c extracts the articles from the first two tables which relate specifically to the patient's reported motivations behind participating in trials.

TABLE 12b Views of patients and public in hypothetical trial scenarios

Author	Purpose of study and sample population (n = No. of respondents to survey)	Method of assessment	Main results	Comments (see quality of evidence checklist – Table 11)
(1) Autret et al. (1993)	Study to obtain parental opinions about clinical trials Couples in which the wife had been hospitalised for delivery in Tours (n = 582) France	Self-administered questionnaire	73% of respondents said they knew that drug trials were carried out in humans 31% of parents said that they would agree to take part in a drug trial for themselves, whereas 64% would refuse 21% of respondents said that they would agree to their child taking part in a study, whereas 74% said that they would refuse (replies were identical among 79% of couples, of which 12% would give parental consent) 67 and 53% of respondents said that the reason for consenting was to benefit other children and to contribute to medical science, respectively, whereas 44% said that they would consent to benefit their own child 19% of those who would refuse stated that they disagreed with trials in principle, while 75 and 49% were averse to risk of side-effects and unproven efficacy respectively The idea of randomisation was responsible for 4% of refusals	Descriptive study A+ B1 C–. 59% response rate D– E– F+

continued

TABLE 12b contd Views of patients and public in hypothetical trial scenarios

Author	Purpose of study and sample population (n = No. of respondents to survey)	Method of assessment	Main results	Comments (see quality of evidence checklist – Table 11)
(2) Bevan et al. (1993)	<p>Study to assess patients' attitudes to participation in clinical trials</p> <p>Group A – patients (n = 66) in previous or current clinical trials under care of the authors whose interests including hypertension, clinical pharmacology and general medicine</p> <p>Group B – patients who had declined participation in trials (n = 12)</p> <p>Group C – patients who had not been offered trial entry (n = 119)</p> <p>USA</p>	Structured interview	<p>67% in group C who had not been offered trial entry would or might participate in future trials, of which 57% would do so to help others and 47% to improve their own treatment</p> <p>See also Table 12a – views of patients</p>	<p>Descriptive study</p> <p>A–</p> <p>B2</p> <p>C+. 99% response rate</p> <p>D–</p> <p>E+</p> <p>F+</p>
(3) Cassileth et al. (1982)	<p>Study to obtain opinions on the purpose and ethicality of clinical research or trials</p> <p>Cancer patients (n = 104), cardiology patients (n = 84), and general public (n = 107) in hypothetical trial scenario, though some respondents had participated in trials before (n = 38)</p> <p>USA</p>	Self-reported questionnaire: 10 multichoice and one open-ended questions	<p>71% thought that patients should serve as research participants for altruistic reasons</p> <p>However, > 50% indicated that they were 'self-motivated and would participate in the trial simply to get the best medical care'</p> <p>30% thought it unlikely that doctors would enter patients in trials when personal equipoise was disturbed</p> <p>Those participants who had actually participated in trials thought that any patient should be allowed to enter trials, whereas those who had not done so thought that clinical trial participation should be restricted by patients' medical status</p>	<p>Descriptive study</p> <p>A–</p> <p>B2</p> <p>C–. Response rate not given</p> <p>D+</p> <p>E+</p> <p>F+</p> <p>Questionnaire pretested for study</p>
(4) Corbett et al. (1995)	<p>Study to ascertain views on clinical trials, and on how the concept of randomisation should be described</p> <p>Members of general public (n = 50), medical secretaries (n = 25) and medical students (n = 25) in one of three hypothetical decision scenarios:</p> <p>Scenario 1 – trial of therapy for a non-life-threatening condition (migraine headache) (n = 99)</p> <p>Scenarios 2 and 3 – trials of life-saving therapy (n = 97)</p> <p>UK</p>	<p>Three parts of interview:</p> <p>Part 1 – verbal versus written consent. One of three medical RCT scenarios were described to the respondent. The respondent had to choose one of three consent formats</p> <p>Part 2 – wording to explain randomisation. Respondents were asked to assess the quality of descriptions of the concept of randomisation on a 100 mm visual-analogue scale</p> <p>Part 3 – expected effects of being offered entry in a trial</p>	<p>Part 1:</p> <p>Written information was preferred over verbal information in 91% of replies, but opinion was evenly split between those favouring presentation of material before or after consultation</p> <p>86% of respondents favoured signing a consent form</p> <p>Part 2:</p> <p>Of the seven statements explaining randomisation, a significant difference was found in favour of explanations that were less explicit about the play of chance ($p = 0.0004$)</p> <p>Part 3:</p> <p>55% of those questioned thought that they would find being invited to enter a clinical trial upsetting. However, 33% thought that participating in an RCT would affect their recovery, 63.6% thought that it would be for the worse ('make me more likely to give up'), and 36.4% thought that it would affect them for the better ('make me try harder'). There was no significant difference between groups for any of these comparisons</p>	<p>Descriptive study</p> <p>A–</p> <p>B2</p> <p>C–. Response rate not given</p> <p>D–</p> <p>E–. Only part of questionnaire supplied in paper</p> <p>F+</p> <p>Questionnaire assessed for readability by Microsoft Word 6.0, and scored 11.6 on Gunning Fog Index</p>

continued

TABLE 12b contd Views of patients and public in hypothetical trial scenarios

Author	Purpose of study and sample population (n = No. of respondents to survey)	Method of assessment	Main results	Comments (see quality of evidence checklist – Table 11)
(5) Epstein and Lasagna (1969)	Study to assess the effect of different informational forms on comprehension and recruitment A mock experimental scenario involving a trial of acetylsalicylic acid (fictitious name for aspirin) versus placebo Hospital employees with no medical qualification were approached (n = 66) USA	One of three different informational forms (short, medium and long) were given at random to the respondents, supplementing oral information given by the physician. Their level of comprehension (recall) was assessed by a questionnaire subsequent to reading the forms	There was a difference of opinion concerning the desirability of providing detailed information of aspirin to the general public according to the form of the protocol which the subject had read. Those subjects reading the short form unanimously believed that such information was useful and should be provided. Among those in the medium-form group, 23% felt that the information was either frightening or not useful, and 41% in the long-form group felt similarly See also Table 7b – methods of informed consent	Descriptive study A– B1 C+. 91% response rate D– E+ F–. Should not have used multiple t test though this probably made little difference to the result Oral explanations of the research had already been given to the respondents
(6) Flanery et al. (1978)	Study to assess the attitudes of the public to and understanding of clinical trials. A mock clinical trial of a new versus standard post-operative drug to relieve pain (1) Freshman medical students (n = 57) (2) Undergraduate mathematics students (n = 67) USA	Multiple-choice 11-item questionnaire administered after reading the consent form	(1) Benefit: 88 and 73% of respondents thought that the researchers and other patients, respectively, would benefit from the clinical trial, while 49% thought that they themselves would benefit (2) Motivation to participate: 80 and 63% of those that would be willing to consent, thought that other patients and they themselves would benefit, respectively (3) Willingness to participate: 41% of respondents said that they would be willing to sign the consent form	A+ B2 C–. Response rate not given D+ E+ F+
(7) Gerard et al. (1995)	Study to assess the attitudes of psychiatric patients both in the general population and in hospitals to clinical trials Four psychiatric subsamples: (1) subjects taking psychotropic medication prescribed by specialists (n = 154) (2) subjects taking psychotropic medication prescribed by generalists (n = 202) (3) subjects who had not been prescribed medication for at least 6 months prior to responding to the questionnaire (n = 253) (4) hospitalised patients (n = 103) France	Postal 14-item questionnaire	A large majority of respondents (50–74%, depending on subgroup) recognised the need for biomedical studies 27–42% of respondents did not know whether they had actually participated in a clinical trial before, though approximately 50 and 70% of subgroups 1–3 and hospitalised patients, respectively, would be willing to participate in a future clinical trial, even if it were placebo-controlled (approximately 50% in all subgroups). The most influential factor in motivating respondents to participate would be the severity of their illness (approximately 80% in all subgroups), while remunerating subjects was the least motivating factor	Descriptive study A– B2 C+. Response rate for subsamples 1–3 was > 80% C–. Response rate for hospitalised patients was 48% D–. Interchange wording – clinical 'research' and clinical 'trial' E+ F+
(8) Johnson et al. (1991)	Study to evaluate the level of collective equipoise that people think is ethical, i.e. the condition necessary for a trial to be offered to patients Members of general public hypothetically assuming the role of an ethics committee member (n = 93) UK	Subjects asked to indicate the level of collective doubt (equipoise) between two treatment modalities that would make a trial ethical. This level of doubt was presented on a series of cards showing varying numbers of experts favouring one or other treatment arm. A set of scenarios was presented in random order	Degree of tolerated inequality of numbers favouring treatment A or B was greatest when the condition was less serious (headache analgesics) than when it was fatal (cancer or AIDS treatment). The median level of equipoise was 67% (67:33) with an interquartile range of 60%. 97% would regard a trial as substantively unethical if equipoise was disturbed above 80:20 A high level of collective equipoise was demanded if the issues are highly emotive, e.g. if a trial involves infants, collective equipoise must be high (close to 50:50)	Descriptive study A– B3 C+. 82% of those recruited actually took part in study D– E+ F+. Low power to detect subgroup differences

continued

TABLE 12b contd Views of patients and public in hypothetical trial scenarios

Author	Purpose of study and sample population (n = No. of respondents to survey)	Method of assessment	Main results	Comments (see quality of evidence checklist – Table 11)
(9) Kemp et al. (1974)	<p>Primarily a study to find out what people thought about participating in RCTs</p> <p>General public in three different scenarios for clinical trials which reflected progressively more serious clinical conditions:</p> <p>Trial 1 – new versus existing treatment for major illness (n = 1022)</p> <p>Trial 2 – new versus existing treatment for potentially curable early stage cancer (n = 1022)</p> <p>Trial 3 – treatments for cancer of the bone at an early stage (removal of limb + radiation versus bone graft + radiation) (men, n = 501); treatments for breast cancer at an early stage (mastectomy + radiation versus lumpectomy + radiation) (women, n = 521)</p> <p>UK</p>	<p>Interview survey using questionnaire in three hypothetical trial situations</p> <p>Respondents asked to choose from following options:</p> <p>A – not to be told about trial and to leave everything up to the doctor</p> <p>B – to be told about the trial and then select the option to be randomised to one of two trial arms</p> <p>C – to be told about trial and then select a treatment option without wishing to be randomised</p>	<p>32–35% of respondents would not enter a trial</p> <p>12% of respondents faced with trials 1 and 2 chose option A, preferring to remain ignorant of the trial and of their possible participation. > 50% in trials 1 and 2 chose option B, preferring to be informed about the trial and to accept randomisation</p> <p>However, as the clinical condition became increasingly grave in trial 3, so more respondents (> 50%) preferred to choose their own treatment and to refuse randomisation (option C)</p> <p>Of the respondents prepared to participate (those choosing options A or B), 10% in trial 1 and 5% in trial 3 gave altruistic reasons for their willingness</p>	<p>Descriptive study</p> <p>A+</p> <p>BI</p> <p>C–. Response rate not given</p> <p>D–</p> <p>E–. Questionnaire not supplied</p> <p>F–</p> <p>Two pilot studies were conducted</p> <p>Hypothetical situation involving choice of treatment outside trial context was presented before interview to introduce the concept of alternative treatments</p>
(10) Llewellyn-Thomas et al. (1991)	<p>Study to examine the relationship between willingness to participate and patients' desire to take control of personal decisions. Also to examine the relationship between willingness to participate and the trade-offs expressed during a decision-analytic task</p> <p>Non-eligible colorectal cancer patients in hypothetical decision scenario using a protocol of a chemotherapy trial for colonic adenocarcinoma (n = 60)</p> <p>Canada</p>	<p>Each respondent was given three tasks:</p> <p>(1) To measure the desire to take control of personal decisions using a validated questionnaire</p> <p>(2) Assessment of patient preferences regarding risks and benefits, to measure trade-offs respondent was willing to make between specific risks and benefits</p> <p>(3) Randomisation task to assess willingness to participate in a trial in which a series of scenarios was presented</p>	<p>(1) Decision-making questionnaire* 53% of respondents scored high for preferred patient participation in decision-making. Such people were significantly more likely to refuse to enter the trial and select their own treatment</p> <p>(2) Trade-off task: refusers tended to want greater increment in treatment benefit, and tended to be less willing to experience short term toxicity for possible gain in long term survival</p> <p>(3) Randomisation task: 42% of respondents would consent to trial entry. 63% of refusers reported aversion to randomisation as primary reason for non-participation</p>	<p>Descriptive study</p> <p>A–</p> <p>BI</p> <p>C–. Response rate not given</p> <p>D+</p> <p>E+</p> <p>F+</p>
(11) Mettlin et al. (1985)	<p>Study to assess willingness to enter a cancer prevention trial</p> <p>Random sample of persons seen at detection–prevention centre in New York in a hypothetical cancer prevention trial (n = 576)</p> <p>USA</p>	<p>Postal questionnaire</p>	<p>77% expressed an interest to participate in a trial which involved making changes in dietary habits</p> <p>73% expressed a willingness to participate in a trial which involved taking medication</p> <p>A respondent's willingness to enter a prevention trial was significantly associated with greater awareness of the possible link between cancer risk and dietary habits</p>	<p>Descriptive study</p> <p>A+</p> <p>BI</p> <p>C–. 65% response rate</p> <p>D+</p> <p>E–</p> <p>F+</p> <p>Data on non-respondents indicated that they were statistically significantly older, better educated, more likely to be married, white and non-smokers</p>

* Decision participation preference was analysed by the authors in terms of its influence on patient's decision to enter the trial. Decision participation preference reported here is the combined percentages for consenters and refusers abstracted by the reviewer, given the raw data in the study.

continued

TABLE 12b contd Views of patients and public in hypothetical trial scenarios

Author	Purpose of study and sample population (n = No. of respondents to survey)	Method of assessment	Main results	Comments (see quality of evidence checklist – Table 11)
(12) Millon-Underwood (1993)	Study to assess impact of minority attitudes on participation in cancer prevention and treatment trials Cancer patients and public from a population of African Americans in a hypothetical scenario using investigational cancer prevention, diagnostic, and treatment programmes and/or trials (n = 220 randomly selected from 325 who agreed to be interviewed) USA	Three-part instrument including 21 forced-choice items, four items requiring sentence completion and/or explanation of response, and seven items on personal characteristics	28% of the respondents perceived the motivation of trial participants to be 'personally seeking hope of cure and control over their cancer' 22% of respondents believed that 'trial participants were willing to sacrifice themselves for the advancement of scientific knowledge', and 22% to 'help future generations' 51% of respondents reported that 'cancer patients should have the opportunity to participate because they should have a choice and they have nothing to lose by participating' Conversely, 13% did not approve of cancer patients participating because 'they should be treated fairly, and not be exposed to dangerous experiments' 71% of those expressing a specific positive attitude to participation responded that 'all cancer patients regardless of medical status should be given the opportunity to participate', 7% thought that 'only those cancer patients doing well should participate', while 10% thought that 'only those cancer patients doing poorly should participate' 26% of respondents believed that physicians commonly entered patients when equipoise does not apply	Descriptive study A+ B1 C+. 81% response rate D+ E- F+ The instrument was reviewed by panel of four experts, including two nurses, a psychologist, and a statistician using the Martuza formula to yield a content validity index 1 indicating total agreement, and a cultural sensitivity index of 1
(13) Alderson et al. (1994)	Study to obtain attitudes to various aspects of a clinical trial Hypothetical trials of: (1) tamoxifen versus placebo (2) mastectomy versus lumpectomy (3) radiotherapy versus chemotherapy Patients treated for primary breast cancer (n = 50) Doctors, nurses and radiographers (n = 40) Women undergoing breast screening (n = 93) UK	Screened women received a postal questionnaire while the remainder underwent an interview	(1) Informed consent: 68 and 69% of treated and screened women respectively thought that they would want to know about the uncertainty associated with treatments in trials 68% of treated women thought that the decision to participate should be shared by the physician and patient or made by the patient only 73 and 48% of treated and screened women, respectively, would want to know if they had been assigned to the control group (2) Risks/benefits: 85% of treated patients thought that breast cancer trials save lives/reduce morbidity, increase knowledge and reduce uncertainty 39 and 41% of treated patients thought that breast cancer trials can exploit people, and increase anxiety, respectively (3) Motivation: 92 and 80% of treated and screened women, respectively, gave altruistic reasons why they would enter a trial 43 and 40% of treated and screened women, respectively, expressed self-interested motivations 58 and 56% of treated and screened women, respectively, reported an aversion to the process of randomisation as a possible reason why they might not enrol in a trial See also Table 13 – views of healthcare professionals	Descriptive study A- B2 C+. 100% response rate for interview C-. 58% response rate to postal questionnaire D-. Insufficient information E- F-. Insufficient information
(14) Saurbrey et al. (1984)	Study to elicit views of Danish patients to clinical trials Patients attending a department of internal medicine in Denmark (n = 114) were presented with all four mock clinical trials of increasing severity: (1) placebo-controlled trial of a new treatment for irritable bowel syndrome (2) trial to compare two antihypertensive drugs on moderately increased blood pressure (3) trial to compare two or three treatment periods of 1 or 3 months for deep thrombophlebitis (4) surgical versus X ray versus drugs for lung cancer Denmark	Structured interviews	98% of respondents thought that patient–doctor cooperation on new therapeutic methods is necessary 87% thought that their participation should be dependent solely on free volition 75% of respondents were of the opinion that patients who are unable to grant consent could be included in a trial Full information for consent was required by 80, 83, 85 and 83% for the four mock trials, respectively 85 and 73% of respondents would accept participation in trials 1 and 4, respectively, solely on the basis of their doctor's 'guarantee'	Descriptive study A- B2 C-. 69% response rate D-. No inter-rater reliability, particularly important since the authors reported having deliberately made no attempt to conceal their attitudes when interviewing the patients E- F+

continued

TABLE 12b contd Views of patients and public in hypothetical trial scenarios

Author	Purpose of study and sample population (n = No. of respondents to survey)	Method of assessment	Main results	Comments (see quality of evidence checklist – Table 11)
(15) Simel and Feussner (1991)	Study to compare the effect of two different consent forms providing different quantitative information on willingness to participate in trials. Adult ambulatory patients in a clinical trial deceptively presented involving usual treatment versus new medication for an unspecified disease (n = 100) USA	Random allocation of adult ambulatory patients to receive consent forms in one of two ways: (1) randomised trial of usual treatment versus new medication that 'may work 2x as fast as usual treatment' (n = 52) (2) trial of new treatment that 'may work 1/2x as fast as the usual treatment' (n = 48) Tape-recorded interview with opportunity to ask questions	The respondents who cited the quantitative information on their informed consent form as a reason for either consenting or declining trial entry (62%) were no more likely to agree to participate than those who did not cite quantitative information as a basis for their decision See also Table 7b – methods of informed consent	RCT A+ BI C–. Response rate not given D+. Independent attorney reviewed random sample of taped interviews, and there was agreement over citation of quantitative information E– F+
(16) Slevin et al. (1995)	Study to elicit patients' views on clinical trials Cancer patients attending one of eight oncology clinics were presented with a mock trial (n = 75) UK	Self-administered closed-ended questionnaire	(1) Motivation: 36 and 11% of respondents thought that the most important aspect of the trial was specialist monitoring and access to new treatments, respectively 21% of respondents thought that the most important aspect of the trial was contributing to research knowledge and benefiting humanity (2) Participation: 90% of respondents expressed an interest in participating in future trials or were uncertain (3) Treatment choice: Only 9% of respondents would prefer to choose their own treatment	Descriptive study A– BI C–. Response rate not given D+ E– F– Questionnaire was pilot tested
(17) White et al. (1984)	Study to examine the effect of different length of consent form on patient attitudes Breast cancer patients in a mock RCT (n = 75) USA	Three model consent forms allocated at random: (1) long – explained randomisation and rationale for trial (2) medium – described the study as 'research' and did not mention randomisation (3) short – indicated that treatment was selected by physician All forms contained identical information about side-effects and drugs	There was no significant difference between form length and whether or not to consent to therapy Patients receiving the long form were no more likely to feel that the form was too long than were the others (88% receiving long and short forms, 96% receiving medium form) After comparing all three forms, 68% of the respondents preferred the long form 62% of respondents agreed that patients have decision-making rights 28% of respondents showed a willingness to question medical advice See also Table 8b – methods of informed consent	RCT A+ BI C+. 99% response rate D+ E+ F+ No evidence of bias of form preference by form first read

TABLE 12c Studies taken from Tables 12a and 12b relating specifically to patients' motivation behind participating in trials*

Author	Number of respondents citing altruistic motivations for participation	Number of respondents citing self-interested motivations for participating in trials
(1) Autret <i>et al.</i> (1993) ^H	67% parents thought that they would consent to their children's participation in order to help other children	44% of parents said that they would consent to their children's participation to benefit their own children
(2) Barofsky and Sugarbaker (1979) ^R	–	54% of the participants reported that they consented and complied with the treatment protocol for reasons of self-interest
(3) Bevan <i>et al.</i> (1993) ^R	62% of trial participants stated that they consented in part to help others	39% of trial participants consented in part to improve their own treatment
(4) Bevan <i>et al.</i> (1993) ^H	57% of those who would be willing to participate in future hypothetical trials would do so to help others	47% of those who would be willing to participate in future hypothetical trials would be motivated by the possibility of improving their own treatment
(5) Cassileth <i>et al.</i> (1992) ^H	71% thought that patients should serve as research subjects for altruistic reasons	> 50% indicated that they were self-motivated and would participate in the trial simply to get the best medical care
(6) Daugherty <i>et al.</i> (1995) ^R	–	85% of respondents chose to participate in their trial explicitly for the chance of personal gain
(7) Flanery <i>et al.</i> (1978) ^H	80% of those that would consent, thought that other patients would benefit from the clinical trial	63% of those that would consent, thought that they themselves would benefit from the clinical trial
(8) Gerard <i>et al.</i> (1995) ^H	–	The most influential factor in motivating respondents to participate would be the severity of their illness (approximately 80% in all subgroups), while remunerating subjects was the least motivating factor
(9) Harth and Thong (1990) ^R	99% of those that consented expressed a wish to contribute to research to benefit other children	90% of those that consent did so to benefit their own children
(10) Hassar and Weinstein (1976) ^R	50% of respondents wanted to contribute to the welfare of other patients	50% felt that they would be the major beneficiaries
(11) Henzlova <i>et al.</i> (1994) ^R	32% of respondents participated out of altruistic motivations	16% of respondents participated to live longer or to get free care and medication
(12) Jensen <i>et al.</i> (1993) ^R	50% of respondents were motivated to participate in a trial by the desire to support science	44% of respondents were motivated to participate in a trial by the hope of receiving better treatment
(13) Kemp <i>et al.</i> (1974) ^H	10% in trial 1 and 5% in trial 3 gave altruistic reasons for their willingness to participate	–
(14) Lynoe <i>et al.</i> (1991) ^R	56% of respondents stated that their motive for agreeing to participate had been altruistic in the sense that the study might benefit future patients	35% of respondents had seen the study as offering the chance to receive better medical care
(15) Mattson <i>et al.</i> (1985) ^R	65% of respondents from AMIS participated at least partly for altruistic reasons	74 and 76% of respondents from AMIS and BHAT, respectively, were motivated to participate in the trial because they believed that they would benefit in some way from participation
(16) Millon-Underwood <i>et al.</i> (1993) ^H	22% of respondents believed that 'trial participants were willing to sacrifice themselves for the advancement of scientific knowledge', 22% 'to help future generations' (the authors did not indicate whether these were different respondents, but we have taken them to be for purposes of synthesis)	28% of the respondents perceived trial participants as personally seeking hope of cure and control over their cancer
(17) Alderson <i>et al.</i> (1994) ^H	92 and 80% of treated and screened women gave altruistic reasons for enrolment	43 and 40% of treated and screened women, respectively, expressed self-interested reasons for possible enrolment
(18) Penman <i>et al.</i> (1984) ^R	47% reported 'to be part of research' as a reason for participating, though this was never a primary reason	93% of respondents reported 'to fight my illness' as a reason for participating
(19) Rodebhuys <i>et al.</i> (1984) ^R	–	50% of patients stated that 'the hope of improvement in their diseases was the main motive for taking part in the study'
(20) Slevin <i>et al.</i> (1995) ^H	21% of respondents thought that the most important aspect of the trial was contributing to knowledge and benefiting humanity	36 and 11% of respondents thought that the most important aspect of the trial was specialist monitoring and access to new treatments, respectively
(21) Vogt <i>et al.</i> (1986) ^R	33% cited an improvement to the health of others and a contribution to science	53% of respondents intimated that they were motivated to participate by the hope of an improvement in personal health, and 24% cited free medical care
(22) Wilcox and Schroer (1994) ^R	11% reported altruism as a factor in their decision to participate	30.2% of participants reported improved health as a factor in the decision to participate

* Not all motivations cited in this table are of a primary nature, so the altruistic and self-interested motivations are not necessarily mutually exclusive.

H, hypothetical trial scenario; R, real trial scenario.

TABLE 13 Views of health professionals on clinical trials

Author	Purpose of study and method of assessment	Type of trial and sample population (n = No. of respondents to survey)	Main results	Comments (see quality of evidence checklist – Table 11)
(1) Benson <i>et al.</i> (1991)	Study to assess oncologists reluctance to accrue patients into clinical trial Questionnaire of 50 items presented in four sections: (1) nine closed- and open-ended questions to determine self-appraised level of participation in trials (2) 11 true/false statements eliciting opinions on informed consent (3) 24 closed-ended questions inquiring whether a particular statement, concerning the effect on the patient of offering participation in trials, is true for nearly all, some or none of their eligible patients (4) Respondents were asked to indicate whether any of above issues had been major reasons for not entering patients into trials	Trials conducted through the Illinois Cancer Centre, USA (n = 244 physician members of the research centre)	(1) Trial entry: 82% of respondents thought that it was always or sometimes true that 'they dislike entering patients when there is a chance that they will receive a placebo', while 55% were willing to select a specific treatment for their patient from the trial protocol thereby eschewing the randomisation process (2) Physician-patient relationship: 55% of physicians identified uneasiness in discussing treatment options as of concern to them (3) Effect of trial participation: 78% of respondents thought that 'patients would probably receive better care in a trial' (4) Informed consent: 77% of respondents 'usually encourage patients who are eligible to enter RCTs' 98% believed that it is always or sometimes true that written informed consent before entry into RCT is necessary, while 83% of responding physicians thought that it is always or sometimes true that 'the consent procedure gives more information than patients actually desire', and as a result 57% preferred 'to adapt consent for each individual patient than to have a standardised procedure'	Descriptive study A+ B1 C-. Response rate 58% D+ E- F+ (a) Questionnaire was pilot tested, (b) 3% of respondents were retired and their data were not used, and (c) the percentage of university affiliated doctors was lower in non-respondents than in respondents, $p < 0.0001$)
(2) Blum <i>et al.</i> (1987)	Study to assess attitudes of different professional groups to clinical trials Questionnaire given to participants and non-participants at the Lugano conference	Members of academia (n = 18) Government officials (n = 7) Drug industry representatives (n = 23) from the following countries: Belgium (n = 1) Denmark (n = 1) France (n = 1) Germany (n = 10) Britain (n = 4) Italy (n = 1) Sweden (n = 3) Switzerland (n = 19) USA (n = 7) Participants at conference asked for a 'matched pair' or colleague who was not there (n = 47)	(1) The RCT design: 94% of respondents thought that the controlled clinical trial (CCT) was the best way to advance medicine, while 59% saw no valid alternatives to the RCT 95% thought that practising in the face of uncertainty is worse than conducting CCTs (2) Doctor-patient relationship: 30% of respondents thought that the CCT violated the doctor-patient relationship, while 69% thought that the individual usually sacrifices some personal interest in favour of societal benefits 45% thought that there was public hostility against CCTs (3) Informed consent: 39% thought that the legal requirement of informed consent should be changed to allow for special circumstances 86% saw informed consent as problematic since the patient rarely understands the implications 31% thought that informed consent must always be based on a written form 60% thought the placebo is an obstacle to patient consent whether or not there is a standard treatment in existence (4) Placebos: 78% were in favour of placebo use in toxicity trials (5) Research and practice: 82% of respondents thought that research findings filter too slowly into practice There was no overall significant difference between participants and non-participants at the conference	Descriptive study A- B2 C+. 98% response rate D+ E+ F+
(3) Dal-re (1990)	Study to determine the perspective of clinical trials committee members on informed consent 48 closed-ended item questionnaire	Members of 16 clinical trials committees in 11 different hospitals and the clinical trials evaluation team of the Spanish Ministry of Health (n = 104)	97% of respondents thought that informed consent must be obtained prior to including patients in RCTs In special circumstances, 68% of respondents thought that the investigator could administer drugs in a trial without having obtained informed consent 96% agreed that a minimum information sheet was necessary, and 76% responded that the patient should be provided with a copy 90% thought that the necessary minimum information should be invitation to participate, the purpose of trial, approval from clinical trials committee, risks/benefits, voluntary nature of participation, and refusal did not imply loss of usual medical care 68% felt that informed consent must always be obtained in writing, while 13% stated that informed consent should always be obtained verbally in the presence of a witness, and that only in some cases should written consent be obtained 89% thought that the period between being given the information sheet and the elicitation of consent/refusal should be at least 'some' hours	Descriptive study A- B1 C+. Response rate 81% of hospital committee members and 100% of evaluation team D- E+ F+

continued

TABLE 13 contd Views of health professionals on clinical trials

Author	Purpose of study and method of assessment	Type of trial and sample population (n = No. of respondents to survey)	Main results	Comments (see quality of evidence checklist – Table 11)
(4) Dal-re (1992)	Study to assess physician's attitudes to the informed consent procedure for clinical trials Questionnaire using mostly closed-response items	Spanish physicians who had participated in clinical trials with investigational drugs (n = 302)	91% of investigators found it necessary that a patient's information sheet be prepared for each clinical trial At least 83% of investigators considered that seven items of information should always be included, i.e. an invitation to participate, the aim of the study, a description of the predictable benefits and risks, a declaration that participation is voluntary, and a statement that refusal to participate does not imply loss of normal medical care and that the trial has been approved by a clinical trials committee Only 29 and 53% considered that the patient should always be informed about clinical trial design and data confidentiality, respectively	Descriptive study A+ B3 C-. 49% response rate D+ E+ F+
(5) Dal-re (1993)	Study to assess attitudes to the informed consent procedure for, and sponsorship of, clinical trials Postal questionnaire with closed-ended responses	Spanish hospital medical staff with any speciality (n = 827)	(1) Informed consent: 96% of respondents thought that consent must be obtained before entry in a trial, and 65% thought that this must always be obtained in writing 90% thought that 'minimum information' should be given to all patients before entry in a clinical trial. Of these, 40% thought that consent should be obtained within a few days of being informed, while 25% thought that it should be obtained within a few minutes of being informed > 85% of those in favour of minimum information thought that it should include the aim of the trial, the benefits and known risks associated with the treatments, and the voluntary nature of participation. 72% thought that the existence alternative treatments should be disclosed, while 64% thought that the possibility of unforeseen risks should be mentioned (2) Sponsorship: 78% of respondents were in favour of clinical audits when a trial is sponsored by a drugs company 85% thought that patients should be insured against the possibility of harm due to trial participation	A- B3 C-. 48% response rate D+ E+ F+
(6) Daughterty et al. (1995)	Study to examine issues related to participation and the perceptions of patients and their physicians towards their trial Postal standardised survey	Participating oncologists (n = 18) in eight different Phase I cancer trials conducted in the USA	(1) Expected benefit: Psychological benefits were regarded as most probable in their Phase I trial (median 65%), although there was some expectation of a survival advantage not more than 2 months for the trial participants (median 10%) (2) Risk of toxicity: Some toxic effect was expected from the Phase I studies (median 50%), though this was not considered life-threatening or fatal in many cases (median: 10 and 5% respectively) See also Table 10 – audit and Table 12a – patient views	Descriptive study A- B3 C+. 90% response rate D+. Most questions closed-ended E+ F+
(7) Kodish et al. (1992)	Study to examine views of investigators and institutional review board chairpersons on ethical propriety and practice of Phase I research 24-item postal questionnaire	Phase I oncology research in the USA Investigators (n = 53) Chairpersons (n = 32)	(1) General: 55% of investigators and 75% of IRB chairpersons believed that Phase I trials present an ethical difficulty (p = 0.06). Of these, 100 and 87% of chairpersons and investigators, respectively, cited toxicity as a specific ethical concern. Undertreatment, raising false hopes, and allocation of resources were other reported concerns (2) Informed consent: Of the above, 100% of IRB chairpersons and 90% of investigators reported informed consent as a specific ethical concern. However, 40% of investigators and 16% of chairpersons considered the quality of informed consent obtained for Phase I trials to be superior to other research protocols (p = 0.037). Conversely, 6% of investigators and chairpersons thought that Phase I consent was generally inferior in quality to other protocols (3) Benefit of participation: Although few thought that patients usually benefited medically (7 and 6% of chairpersons and investigators, respectively), 75% of investigators and 37% of chairpersons thought that patients usually benefited psychologically from participation in such trials	Descriptive study A+ B1. Random sampling for investigators stratified by institution B3. Grab sampling for chairpersons C-. Response rate 68% in both groups D- E+ F+

continued

TABLE 13 contd Views of health professionals on clinical trials

Author	Purpose of study and method of assessment	Type of trial and sample population (n = No. of respondents to survey)	Main results	Comments (see quality of evidence checklist – Table 11)
(8) Langley et al. (1987)	Study to assess physicians' willingness to participate in clinical trials At interview, respondents were asked to complete a two-part questionnaire	Clinical oncology trials at two major cancer treatment centres in metropolitan Toronto, Canada Clinicians (n = 52) Nurses (n = 26) Family physicians (n = 23)	(1) Frequency of participation: 29% of respondents participate in all trials available, 71% participate in some of the trials available, and none did not participate in any trial (2) No. of eligible patients entered: 14% responded that they entered all their eligible patients, 82% entered most of their eligible patients, while 4% only entered a few of their eligible patients 88% of oncologists regarded the need for scientific information as their primary reason for entering patients; however, family physicians and nurses cited this reason with less frequency ($p < 0.001$) The opportunity to improve regular patient care was cited by 10% of oncologists and 67% of family physicians as their primary reason	Descriptive study A– B2 C–. Response rate not given D– E+ F+
(9) Lilford (1994)	Study to formally assess physicians' clinical uncertainty before offering patients entry into a hypothetical trial Interview of specialists presented in foetal medicine using four scenarios, for each of which the decision between immediate and delayed delivery was difficult. Respondents were asked to state the perceived relative risk of permanent morbidity for each scenario. Responses were recorded on an analogue dial connected to a microcomputer (one showed no expected difference between immediate and delayed delivery, 0.5 suggested that the chance of morbidity would be halved by immediate delivery, while two indicated that it would be doubled)	Trial of early versus delayed delivery for pre-term foetuses that are failing to thrive in the uterus Specialists in foeto-maternal medicine, UK (n = 10)	For each scenario, the mean result considered to be most likely was close to 1, with a wide scatter in the individual results, e.g. from a 75% decrease to a 25% increase in the risk to a foetus delivered early in the practice scenario, i.e. the scenarios caused collective uncertainty	Descriptive study Results show that, although there is collective uncertainty, some clinicians are in two minds when others have strong expectations of either benefit or harm A– B3 C–. Response rate not given D+ E+ F+
(10) Mammel and Kaplan (1995)	Study to determine attitudes of IRBs to consent for adolescent minors and to changes in federal regulations IRBs were sent a self-administered questionnaire on parental consent for minors undergoing research	12 hypothetical scenarios were presented of which two were drug trials: (1) AIDS experimental drug trial for over 16 year olds (2) Treatment of urinary tract infection trial in emancipated minors University hospital IRBs (n = 51) Children's hospital IRB (n = 15) Private community hospital IRBs (n = 15) Other institutions (n = 102) USA	69% of respondent IRBs required parental consent for all research on minors 58% and 60% of respondents required parental consent for the first and second scenario respectively. The remainder thought that parental consent could be waived 85% of respondents thought that research carrying minimal risk should be open to minors without parental consent There was a statistically significant trend of IRBs reviewing more adolescent protocols showing a greater willingness to waive parental consent for general research categories ($p < 0.05$)	Descriptive study A+ B2 C–. 39% responded while 30% of questionnaires were fully scorable D+ E– F–

continued

TABLE 13 contd Views of health professionals on clinical trials

Author	Purpose of study and method of assessment	Type of trial and sample population (n = No. of respondents to survey)	Main results	Comments (see quality of evidence checklist – Table 11)
(11) Marsden <i>et al.</i> (unpublished)	Study to assess the feasibility of conducting a randomised trial of hormone replacement therapy (HRT) use in women with a history of breast cancer Postal questionnaire	Pilot trial of HRT versus no HRT in women with diagnosis of early breast cancer Breast cancer surgeons, UK (n = 124)	50.8% of surgeons thought that HRT could cause recurrence of cancer, while 28.2% were uncertain 73.4% felt that an RCT of HRT would be ethical, but difficult to do Of those who felt that a trial would be unethical, many thought that more observational data in breast cancer survivors was needed, and/or the treatment arm (HRT) was definitely harmful See also Table 12a – attitudes of patients	A+ B1 C–. 50% response rate D–. Insufficient information E– F+
(12) Alderson <i>et al.</i> (1994)	Study to obtain attitudes to various aspects of the clinical trial Healthcare professionals underwent an interview	Hypothetical trials of: (1) tamoxifen versus placebo (2) mastectomy versus lumpectomy (3) radiotherapy versus chemotherapy Patients treated for primary breast cancer (n = 50) Doctors, nurses and radiographers (n = 40) Women undergoing breast screening (n = 93) UK	(1) Informed consent: 83% of professionals thought that medical uncertainty should be explained to treated patients prior to enrolment 67% of professionals thought that the decision to participate should be shared or left to the patient 45% of professionals thought that patients should be told if they had been assigned to a control group (2) Willingness to participate: 53, 20 and 23% stated that they would be willing to participate in trials 1, 2 and 3, respectively 39% expressed an aversion to the process of randomisation as a possible reason for non-enrolment (3) Risks/benefits: 59 and 85% of professionals thought that breast cancer trials save lives/reduce morbidity of patients in general, and increase knowledge/reduce uncertainty, respectively 52 and 68% thought that breast cancer trials can exploit people, and increase anxiety, respectively (4) Equipoise: 25% of professionals thought that equipoise is possible for doctors, 18% thought that some patients could achieve it, while 13% thought that the breast cancer team as a whole could agree on equipoise See also Table 12b – views of the public	Descriptive study A– B2 C+. 100% response rate for interview C–. 58% response rate to postal questionnaire D–. Insufficient information E– F–. Insufficient information
(13) Penman <i>et al.</i> (1984)	Study to examine patients' and physicians' perceptions of the informed consent procedure Structured interview with computer coding of quantitative responses	Physicians (n = 68) from three cancer centres, USA, conducting trials of chemotherapy by 65 different Phase 2 or 3 investigative chemotherapy protocols, 47% of which were randomised studies	(1) Informed consent: Physicians believed that during their discussions over trial entry 33% of their patients were too inhibited to talk about the more serious aspects of the procedure, and 33% of patients were viewed as being completely passive in the decision-making process. They thought that 49% of patients had not actively raised questions, and 20% had asked few or none. 41% of patients had not appeared 'eager to know the details of the proposed treatment', even when both trial arms were active therapies. Also, physicians concluded that 49% of patients showed little or no anxiety, while substantial anxiety was seen in 16% of patients during the consent discussion though this was mostly dispelled by the end of the conversation (94%) (2) Benefits of participation: Virtually all physicians believed that their patients would benefit from particular investigational treatments offered in the placebo-controlled trials. They felt the treatment would be of considerable benefit for 69% of patients, and for the rest, they thought that the benefit would at least outweigh the potential risks and side-effects See also Table 10 – audit and Table 12a – views of patients	Descriptive study A– B3 C–. Response rate not given D–. Insufficient information E– F. Not applicable
(14) Richardson <i>et al.</i> (1986)	Study to evaluate the participation of community medical oncologists in clinical trials Postal questionnaire containing 35 items	Oncology clinical research trials Physicians from three counties in the USA (n = 59)	Perceived benefits associated with protocol use including increase in time spent per patient, offering a slightly increased chance of recovery, and providing slightly better overall medical care The extent to which physicians believed that the use of RCTs would provide the best treatment outcome for the patient was correlated with the participation ($r = 0.32$)	Descriptive study A– B3 C–. Response rate 56% D– E+ F–

continued

TABLE 13 contd Views of health professionals on clinical trials

Author	Purpose of study and method of assessment	Type of trial and sample population (n = No. of respondents to survey)	Main results	Comments (see quality of evidence checklist – Table 11)
(15) Spaight et al. (1984)	Study to assess oncologists' reluctance to participate in cancer clinical trials Structured interviews conducted by two cancer control staff members	Oncology clinical trials Practising Maine medical oncologists (n = 19) and haematologists (n = 4) treating cancer patients USA	(1) Randomisation: 77% of respondents strongly disagreed with the idea that randomisation lessens patient's trust in their physician, and 68% thought that randomisation is the only available method for obtaining objective data on treatment efficacy (2) Informed consent: 4% of respondents thought that truly informed consent is unobtainable, while 26% thought that patient's are unable to comprehend the information about the trial. In particular, 73% thought that the randomisation procedure is impossible to explain adequately to patients (3) Willingness to participate: 35% of respondents would not enrol eligible patients due to protocol indications of toxicity and side-effects	Descriptive study A+ B1 C–. Response rate not given D– E– F+ Instrument was pilot tested with two medical oncologists
(16) Taylor (1992)	Study to evaluate the conflicting professional roles as seen by physicians Self-administered postal questionnaire (Physician Orientation Profile) consisting of 15 demographic questions, 45 binary option questions and six open-ended questions and telephone structured interview	Canadian collaborative Ocular Melanoma Study (COMS) involving physicians (n = 101) in trials to compare surgical removal of the eye with radiation in the treatment of medium-size eye cancers	72% of physicians believed that their core task was to care for the individual patient, as opposed to adding to scientific knowledge. However, radiation therapists viewed this as their core task significantly more often than the ophthalmologists ($p < 0.05$) 55% of physicians thought that the patient/families had the final responsibility with regard to medical decision-making. Respondents planned to approach 81% of all eligible patients, and assumed that 68% of approached would agree to participate	Descriptive study A+ B1 C+. 95% response rate D– E+ F+. Used 'instead of'
(17) Taylor et al. (1984)	Study to examine factors influencing low accrual rate in oncology trials Postal questionnaire with closed-ended and open-ended items	National Surgical Adjuvant Project for Breast and Bowel Cancers, B-06 multi-centre trial with three treatment arms: segmental mastectomy without radiation, segmental mastectomy with radiation, and total mastectomy Principal investigators at member institutions, Canada (n = 94)	(1) Participation: 65% of respondents stated that they had entered some or all of their eligible patients in trials 73% of those physicians who did not enrol all eligible patients made some reference to their relationship with their patients as a reason for their lack of enthusiasm In addition to other reasons for non-enrolment, 38% of respondents cited trouble with informed consent, and 23% expressed difficulty in discussing uncertainty (2) Informed consent: Obtaining informed consent was noted as problematic by 25% of respondents	Descriptive study A+ B1 C+. 97% response rate D+. Follow-up telephone interview conducted for 87% of respondents transcribed verbatim and analysed using a grounded theory by Glaser and Strauss E– F– Questionnaire was pilot tested on surgical oncologists
(18) Taylor and Kelner (1987a)	Study to interpret physician participation in clinical trials Questionnaire and interview to obtain a single score along the continuum pure experimenter–pure therapist (Physician Orientation Profile) using six variables: (1) allegiance to present versus future patients (2) interpretation of medical uncertainty as personal uncertainty versus clinical controversy (3) viewing patients as research subjects versus clinical cases	Sample from 57 institutions in five countries: USA (49%) Canada (26%) UK (12%) France (6%) Poland (3%) Other (4%) Sample represented three specialties: surgeons (n = 188) medical oncologists (n = 224) radiation therapists (n = 72)	(1) Score on continuum: 15% of respondents regarded themselves as 'pure therapists' while 7% saw themselves as 'pure experimenters'. Scores did not vary significantly with age, medical speciality or by country of practice It is shown that physicians' choices on the six variables reflect a significant division among doctors with regard to their overall view of the current practice of medicine (2) Participation in trials: 31% of respondents placed all eligible patients in clinical trials, while 38% had never participated in trials 36% of respondents intimated that they would be prepared to enter patients in a trial even when personal equipoise did not obtain (3) Informed consent: 87% of respondents said that they would enter more patients in clinical trials if written informed consent was not required. Furthermore, 73% thought that it would be possible to design a	Descriptive study A+ B2 C+. 87% response rate D–. No psychometric testing but test–retest reliability gained via interview and 80% of interviews were taped and 20% were videotaped. To reduce observer bias, data from a particular physician was tabulated and coded by independent researcher E– F+

continued

TABLE 13 contd Views of health professionals on clinical trials

Author	Purpose of study and method of assessment	Type of trial and sample population (n = No. of respondents to survey)	Main results	Comments (see quality of evidence checklist – Table 11)
<i>continued</i>				
	(4) priority of published data versus personal clinical experience (5) the view of scientific research as an outgrowth versus as a part of individual patient care (6) willingness to share information or discomfort with professional accountability versus colleagues	No. of trials in which participated: none: 38% 1–3: 41% 3+: 21%	more individualised approach to patient consent regulations 57% of respondents thought that of the eligible patients approached to participate consent was achieved more than 50% of the time	Questionnaire was pilot tested It could be argued that the profile is not a continuum at all, and that one can have many 'experimenter' instincts as well as many 'therapist' instincts
(19) Taylor and Kelner (1987b)	Study to assess the physicians' perspective on informed consent Self-administered questionnaire, followed by structured interview which expanded on the questionnaire	Medical oncologists were taken from eight countries: USA (40%) Canada (25%) England (7%) Scotland (3%) Australia (4%) France (9%) Sweden (4%) Italy (8%) The sample represented three medical specialities: medical oncologists (n = 90) surgeons (n = 51) radiotherapists (n = 29)	41% of respondents said that it was always difficult to assess the patients' desire for information, while only 7% believed that the current regulations simplified the task. 15% of responding physicians thought that their patients were always aware that they were subjects in an experiment when they signed the consent form before trial entry and 47% thought that their patients were never so aware. 34% thought that if the requirement for written informed consent were abandoned, they would enter more patients since informed consent procedure is often seen as an intrusion into the doctor–patient relationship (95%). 22% of respondents reported never obtaining informed consent before placing eligible patients in a trial	Descriptive study A– B2 C+. 100% response rate D+ E+ F–
(20) Taylor et al. (1987)	Study to evaluate physicians' responses to the regulation of obtaining written informed consent Self-administered questionnaire and follow-up interview	Breast cancer specialists from eight countries: USA (40%) Canada (25%) France (9%) Italy (8%) England (7%) Sweden (4%) Australia (4%) Scotland (3%) Sample approached: medical oncologists (n = 90) surgeons (n = 65) radiotherapists (n = 29) (there were 170 respondents)	53% of respondents stated that the obtaining of informed consent always highlights their dual role as investigator and primary care-giver 55% of respondents said that the duality of their role always makes them feel uncomfortable. 65% of respondents said that obtaining informed consent sometimes makes entering patients in RCTs difficult 70% felt that it was not always necessary to for patients to give informed consent prior to entry in an RCT 41% said that it is always difficult for physicians to assess accurately a patient's desire for information 90% said that they feel having to obtain written informed consent is an intrusion into the privacy of the doctor–patient relationship 81% of respondents felt that telling patients that physicians do not know whether treatment A is better than treatment B sometimes has a negative effect on patients	Descriptive study A+ B2 C+. 100% response rate D+ E– F+ Questionnaire was pilot tested
(21) Williams and Zwitter (1994)	Study to examine the standard of informed consent used by investigators in European RCTs Five-item closed-ended questionnaire	Participants of 12 multi-centre RCTs published in the <i>European Journal of Cancer</i> (n = 60) UK/Slovenia	12% of clinicians did not inform their patients about the trial prior to randomisation, while 38% of clinicians did not always tell their patients that they had been assigned to treatment randomly 32% of clinicians used written consent, 21% used written consent without obligatory signing, 42% used verbal consent, and in 5% no consent was sought 58% gave full information on all aspects of the trial, and 42% gave information on the proposed treatment arm only (27% revealing inclusion in an RCT) Level of consent was higher in trials of supportive care than in trials testing curative or palliative anti-tumour therapies Clinicians in northern Europe were more likely to obtain full consent than those from southern Europe	Descriptive study A+ B3 C–. 68% response rate D+ E+ F+

TABLE 14 The number of ethics articles obtained by electronic searches

Database	Time to present	Total yield	No. of hits
BIDS	January 1994 –	253	12
MEDLINE	January 1991 –	245	108
PsycLIT	January 1984 –	117	5

TABLE 15 The number of articles obtained by electronic searches

Database	Time to present	Total yield	No. of hits	Overlap
BIDS	January 1994 –	253	12	9 with MEDLINE + PsycLIT
MEDLINE	January 1991 –	245	27	4 with PsycLIT
PsycLIT	January 1984 –	117	19	4 with MEDLINE

TABLE 16 In-house search algorithms

<p>(1) BIDS</p> <p>1 Ethics + clinical trials</p> <p>2 Participation + clinical trials</p> <p>3 Knowledge + clinical trials</p>	<p>(3) PsycLIT</p> <p>1 (clin\$ adj trial\$).tw.</p> <p>2 exp informed consent</p> <p>3 1 and 2</p> <p>4 consent\$.tw.</p> <p>5 1 and 4</p> <p>6 3 or 5</p> <p>7 exp anxiety</p> <p>8 1 and 7</p> <p>9 anxi\$.tw.</p> <p>10 1 and 9</p> <p>11 8 or 10</p> <p>12 exp participation</p> <p>13 1 and 12</p> <p>14 participat\$.tw.</p> <p>15 1 and 14</p> <p>16 13 or 15</p> <p>17 recruit\$.tw.</p> <p>18 1 and 17</p> <p>19 know\$.tw.</p> <p>20 1 and 19</p> <p>21 understand\$.tw.</p> <p>22 1 and 21</p> <p>23 6 or 11 or 16 or 18 or 20 or 22</p> <p>24 limit 24 to English</p> <p>25 limit 25 to abstracts</p>
<p>(2) MEDLINE*</p> <p>1 exp ethics</p> <p>2 exp informed consent</p> <p>3 1 or 2</p> <p>4 exp clinical trials</p> <p>5 (clin\$ adj trial\$).tw.</p> <p>6 clinical trial phase i.pt.</p> <p>7 clinical trial phase ii.pt.</p> <p>8 clinical trial phase iii.pt.</p> <p>9 clinical trial phase iv.pt.</p> <p>10 clinical trial.pt.</p> <p>11 randomized controlled trial.pt.</p> <p>12 6 or 7 or 8 or 9 or 10 or 11</p> <p>13 4 or 5 or 12</p> <p>14 3 and 13</p> <p>15 limit 14 to English language</p> <p>16 limit 15 to abstracts</p>	
<p>*Search terms included Phase 1 and 2 trials for future work.</p>	

Appendix I

Electronic search strategies

The electronic searching was carried out on three bibliographic databases: MEDLINE, PsycLIT and BIDS – both Science and Social

Science Citation Indices (SCI and SSCI) (*Tables 14 and 15*). We used in-house algorithms in each case (*Table 16*).

Appendix 2

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Appendix 3

Bayesian and frequentist statistics in clinical trials

The Bayesian and frequentist statistical approaches differ essentially in their concept of probability. A Bayesian considers that probability is a measure of degree of personal (subjective) belief while, for a strict frequentist, probability is the (objective) relative frequency as sample size becomes infinite.

The Bayesian approach requires a model that relates (usually unobservable) parameters of particular interest (such as true risk of stroke) to observable data (such as how many patients of a particular age, sex, and treatment regimen actually suffered a stroke, and how many did not). Bayes's theorem shows how a 'coherent' (broadly, a rational) person will alter his/her beliefs about a parameter, given the data, the model and that person's prior beliefs.

Problems exist with both approaches: for Bayesians there are no objective probabilities, different individuals may have very different beliefs (which may also be incompatible with the data), and people do not always behave coherently. On the other hand, frequentists can only make probability statements about observable quantities that may be repeatedly observed – which is severely limiting (or requires a certain amount of 'imagination' when interpreting analyses!). In particular, for making decisions it is often desirable to have probability statements about the key parameters. Frequentists find themselves limited to making statements about how probable the data are, given assumed values of the key parameters.

There is an obvious association of these statistical approaches with differing philosophical approaches to science and knowledge. The frequentist stance seems to correspond more closely with Popper's rejection of induction, and his insistence that falsification is the only way observations can inform theory. The Bayesian stance, on the other hand, apparently has induction at its heart. Senn (1991), however, has pointed out that Bayesians make assumptions (about the model) which are not tested, and it is only within this framework that induction works.

Philosophers of science (deductive and inductive) might use clinical trials in different ways. The

former would be looking for evidence to reject the current best theory, while the latter want data to inform their beliefs about the key parameters in the model. It seems to us that both of these might be appropriate, albeit at different stages in a theory/ model's life. In an early clinical trial, the theory the scientists want to test is that the drug is possibly of clinical value, that is, possibly beneficial and without unacceptable side-effects. If a (reasonably sized) trial fails to falsify this theory, the drug may progress to later stages of development and testing. The purpose of the trial is thus to look for qualitative deviations from the 'theory' – and a deductive approach seems reasonable. In a Stage 3 clinical trial it may be already 'known' that the drug is potentially of clinical value – and a better estimate of the size of its effect is desired. Such a trial is looking to refine (rather than reject) the theory, by improving the quantitative estimate of effect – so the inductive approach seems reasonable. In practice it would be a matter of emphasis rather than 'all or nothing'; for example, radical departures from the assumed model (e.g. severe side-effects in certain subpopulations) in a Stage 3 trial might well precipitate abandonment of the trial and drug.

When considering clinical trials, the deductive approach in particular seems incompatible with the ethical point of view which regards individuals' benefits as paramount (individual ethics). It proposes testing theories to destruction, i.e. however well 'corroborated' a theory is, it should be tested in ever more precise and extreme ways. This might lead to trials of treatments already 'known' from extensive testing to be beneficial, just in case there might be some as yet unfound side-effect. Similar accusations might be levelled at the inductive approach, i.e. that this requires ever more precise estimates. However, the Bayesian methods that best suit the inductive approach also lead naturally to a technique called decision analysis, which involves examining, expected benefit (or loss). If applied to an individual patient being randomised, decision analysis will show (on the basis of the patient's prior beliefs and evaluation of the possible consequences of the treatments) whether one of the treatment options is expected to produce a

better outcome for that patient, or whether the alternative treatments are of equal benefit in prospect. This information is, of course, exactly what an individual patient acting in his own interests needs to know. Thus, while the inductive

philosophers may want more data to produce more precise estimates, the methods they use will (in theory) give clear guidance as to how much benefit, if any, a particular patient stands to lose by entering a particular trial.

Health Technology Assessment panel membership

This report was identified as a priority by the Methodology Panel.

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