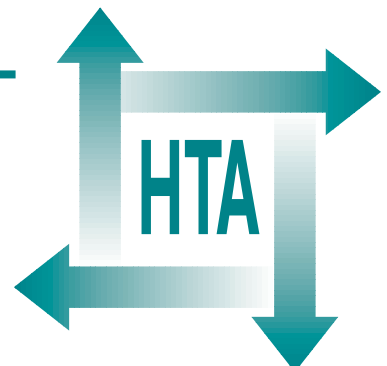


Implications of socio-cultural contexts for the ethics of clinical trials

Richard E Ashcroft
David W Chadwick
Stephen RL Clark
Richard HT Edwards
Lucy Frith
Jane L Hutton



Health Technology Assessment
NHS R&D HTA Programme



Standing Group on Health Technology

Chair: Professor Sir Miles Irving,
Professor of Surgery, University of Manchester, Hope Hospital, Salford †

Dr Sheila Adam, Department of Health
Professor Martin Buxton, Professor of
Economics, Brunel University †

Professor Angela Coulter, Director,
Kings Fund Centre for Health Services
Development †

Professor Anthony Culyer,
Deputy Vice-Chancellor, University of York †

Dr Peter Doyle, Executive Director,
Zeneca Ltd, ACOST Committee on Medical
Research & Health

Professor John Fardon,
Professor of Surgery, University of Bristol †

Professor Charles Florey,
Department of Epidemiology & Public
Health, Ninewells Hospital & Medical
School, University of Dundee †

Professor John Gabbay, Director,
Wessex Institute for Health Research
& Development †

Dr Tony Hope, The Medical School,
University of Oxford †

Professor Howard Glennester,
Professor of Social Science &
Administration, London School of
Economics and Political Science

Professor Sir John Grimley Evans,
Department of Geriatric Medicine,
Radcliffe Infirmary, Oxford †

Mr John H James, Chief Executive,
Kensington, Chelsea & Westminster
Health Authority

Professor Richard Lilford,
Regional Director, R&D, West Midlands †

Professor Michael Maisey, Professor of
Radiological Sciences, UMDS, London

Dr Jeremy Metters, Deputy Chief
Medical Officer, Department of Health †

Mrs Gloria Oates, Chief Executive,
Oldham NHS Trust

Professor Michael Rawlins,
Wolfson Unit of Clinical Pharmacology,
University of Newcastle-upon-Tyne

Professor Martin Roland,
Professor of General Practice,
University of Manchester

Mr Hugh Ross, Chief Executive,
The United Bristol Healthcare NHS Trust †

Professor Ian Russell, Department of
Health, Sciences & Clinical Evaluation,
University of York

Professor Trevor Sheldon, Director,
NHS Centre for Reviews & Dissemination,
University of York †

Professor Mike Smith, Director,
The Research School of Medicine,
University of Leeds †

Dr Charles Swan,
Consultant Gastroenterologist,
North Staffordshire Royal Infirmary

Professor Tom Walley, Department of
Pharmacological Therapeutics,
University of Liverpool †

Dr Julie Woodin, Chief Executive,
Nottingham Health Authority †

† Current members

HTA Commissioning Board

Chair: Professor Charles Florey, Department of Epidemiology & Public Health,
Ninewells Hospital & Medical School, University of Dundee †

Professor Ian Russell, Department of
Health, Sciences & Clinical Evaluation,
University of York *

Mr Peter Bower,
Independent Management Consultant,
Newcastle-upon-Tyne †

Ms Christine Clarke, Director of
Pharmacy, Hope Hospital, Salford †

Professor David Cohen,
Professor of Health Economics,
University of Glamorgan

Mr Barrie Dowdeswell,
Chief Executive, Royal Victoria Infirmary,
Newcastle-upon-Tyne

Dr Mike Gill, Brent and Harrow
Health Authority †

Dr Jenny Hewison, Senior Lecturer,
Department of Psychology, University
of Leeds †

Dr Michael Horlington, Head of
Corporate Licensing, Smith & Nephew
Group Research Centre

Professor Sir Miles Irving (Programme
Director), Professor of Surgery, University
of Manchester, Hope Hospital, Salford †

Professor Martin Knapp, Director,
Personal Social Services Research Unit,
London School of Economics and
Political Science

Professor Theresa Marteau, Director,
Psychology & Genetics Research Group,
UMDS, London

Professor Sally McIntyre, MRC Medical
Sociology Unit, Glasgow

Professor Jon Nicholl, Director, Medical
Care Research Unit, University of Sheffield †

Dr Tim Peters, Department of Social
Medicine, University of Bristol †

Professor David Sackett,
Centre for Evidence Based Medicine, Oxford

Dr David Spiegelhalter,
MRC Biostatistics Unit, Institute of Public
Health, Cambridge

Dr Ala Szczepura, Director,
Centre for Health Services Studies,
University of Warwick †

Professor Graham Watt,
Department of General Practice,
Woodside Health Centre, Glasgow †

Professor David Williams,
Department of Clinical Engineering,
University of Liverpool

Dr Mark Williams,
Public Health Physician, Bristol

* Previous Chair

† Current members

National Coordinating Centre for Health Technology Assessment, Advisory Group

Chair: Professor John Gabbay, Wessex Institute for Health Research & Development

Professor Mike Drummond, Centre for
Health Economics, University of York

Professor Charles Florey,
Department of Epidemiology & Public Health,
University of Dundee

Professor Sir Miles Irving,
Department of Surgery, Hope Hospital, Salford

Ms Lynn Kerridge, Wessex Institute for
Health Research & Development

Dr Ruairidh Milne, Wessex Institute for
Health Research & Development

Ms Kay Pattison, Research &
Development Directorate, NHS Executive

Professor James Raftery, Health
Economics Unit, University of Birmingham

Dr Paul Roderick, Wessex Institute for
Health Research & Development

Professor Ian Russell, Department of
Health, Sciences & Clinical Evaluation,
University of York

Dr Ken Stein, Wessex Institute for Health
Research & Development

Professor Andrew Stevens,
Department of Public Health &
Epidemiology, University of Birmingham



INAHTA

How to obtain copies of this and other HTA Programme reports.

An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (<http://www.hta.ac.uk>). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

- fax (with **credit card** or **official purchase order**)
- post (with **credit card** or **official purchase order** or **cheque**)
- phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque

If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card

The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order

You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of HTA on CD?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.

Implications of socio-cultural contexts for the ethics of clinical trials

Richard E Ashcroft¹

David W Chadwick²

Stephen RL Clark³

Richard HT Edwards⁴

Lucy Frith⁵

Jane L Hutton⁶

¹ Centre for Ethics in Medicine, University of Bristol

² Department of Neurology, University of Liverpool

³ Department of Philosophy, University of Liverpool

⁴ Department of Medicine, University of Liverpool

⁵ Department of Primary Care, University of Liverpool

⁶ Department of Statistics, University of Newcastle, Newcastle-upon-Tyne

Final manuscript received June 1997

Published August 1997

This report should be referenced as follows:

Ashcroft RE, Chadwick DW, Clark SRL, Edwards RHT, Frith L, Hutton JL. Implications of socio-cultural contexts for the ethics of clinical trials. *Health Technol Assessment* 1997; 1(9).

NHS R&D HTA Programme

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

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

This report is one of a series covering acute care, diagnostics and imaging, methodology, pharmaceuticals, population screening, and primary and community care. It was identified as a priority by the Methodology Panel (see inside back cover).

The views expressed in this publication are those of the authors and not necessarily those of the Standing Group, the Commissioning Board, the Panel members or the Department of Health.

Series Editors: Andrew Stevens, Ruairidh Milne and Ken Stein
Assistant Editor: Jane Robertson

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

ISSN 1366-5278

© Crown copyright 1997

Enquiries relating to copyright should be addressed to the NCCHTA (see address given below).

Published by Core Research, Alton, on behalf of the NCCHTA.

Printed on acid-free paper in the UK by The Basingstoke Press, Basingstoke.

Copies of this report can be obtained from:

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 1703 595 639 Email: hta@soton.ac.uk
<http://www.soton.ac.uk/~hta>



Contents

List of abbreviations and glossary	i	Voluntariness	25
Executive summary	iii	Autonomy as a value	26
1. Introduction	1	Problems of the autonomy theory	28
Summary of the project proposal	1	Consent as a singular event and as a process	30
What is a clinical trial?	1	Conclusion	30
What are the basic ethical issues (as they have come to light in the history of the clinical trial)?	2	4. Cultural, economic and gender factors	31
Methodological issues for this project	3	Consent and communication reviewed	31
2. Methodological aspects of clinical trials in ethical perspective	7	Culture and communication	33
The classical clinical trial	7	Socio-cultural groups and ethics	34
Randomisation	11	Understanding refusals: the significance of culture	35
Critics of randomisation in statistical experiments	12	Cultural refusals of design and methodology: community consent	37
A review of the standard issues of ethics and the clinical trial	14	Is consent a culturally neutral concept?	40
Conclusion	18	Justice and socio-economic factors	43
Recommendations	18	Concluding recommendations	45
3. Autonomy and informed consent in the ethics of the randomised controlled trial: philosophical perspectives	19	Acknowledgements	47
Introduction	19	References	49
Voluntary consent	19	Appendix 1 Database description and summary statistics	59
Overriding consent?	21	Appendix 2 Grant holders and members of the External Advisory Group	65
“Inferring” consent	23	Health Technology Assessment reports published to date	67
Imperfect communication	24		



List of abbreviations and glossary

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.

a fortiori Literally, “by the stronger”; in an argument, something is demonstrated *a fortiori* when it is a consequence or special case of something more general which has already been demonstrated.

autonomy From the Greek, roughly meaning “self-ruling”. In Kant’s philosophy, a person is only acting morally when they act autonomously, that is, when they decide rationally that the act they perform is the right thing to do without reference to non-rational motives such as custom, habit, or outside authority. More generally, by autonomy medical ethicists mean freedom from coercion and the capacity and competence to “decide for oneself”. Alternatives to this weaker usage include free or voluntary choice and decision-making. All medical ethicists agree that patients have a right to make their own decisions regarding their health and medical care, and the majority of ethicists now identify a principle of (patient) autonomy which defines this right.

Bayesian Bayesian statistics provides explicit mathematical methods for combining expert opinion with information from data in a coherent manner, using probability calculus. In contrast, frequentist statistics use expert opinion informally in the design of, and analysis and interpretation of data from, studies.

beneficence The principle that a doctor should always act to do the patient some good.

CCT (controlled clinical trial) An experimental test of a clinical procedure or drug on human subjects (usually patients who might benefit from the novel therapy), which compares the effects of the new therapy on a patient group with the effects of the standard therapy or a placebo on a group (the control group) of present or past patients

who are in some way comparable with the treatment group.

ceteris paribus Other things being equal.

confounding Two or more explanatory factors are said to be confounded if they always occur together within a particular data set. It is not possible to assess whether only one factor, and if so, which one, is directly associated with the outcome variable. For example, if a new treatment is always given by one doctor, and the standard treatment by another doctor, it is not possible to attribute any improvement observed to the new treatment. The improvement might be due to the doctor, or to the treatment, or to some combination of the two.

epistemology The branch of philosophy dealing with the nature of knowledge and the reliability or certainty of our methods of acquiring knowledge.

ex hypothesis From the hypothesis (we have assumed correct).

ex post facto From after the fact (with hindsight). For example, after a clinical trial, one where a new therapy has been shown to be significantly more effective than the old, one might argue *ex post facto* that the trial was unnecessary because we “knew” the outcome anyway. This is a fallacy.

non-beneficence Acting against the principle of beneficence.

non-maleficence The principle that doctors must do no harm to their patient, or at the least they shall harm the patient as little as possible consistent with the principle of beneficence (for instance, most chemotherapy in cancer is harmful, but this is consistent, usually, with the aim of eradicating the tumour in order to maximise benefit to the patient in the long term).

continued

paternalism In medicine, the supposed principle that doctor (or the medical system) knows best; in effect, taking decisions for patients that are properly only the patients' to make. Paternalism breaches the right of patients to make their own choices – the principle of autonomy.

placebo A therapy (usually a drug) which has no (relevant) active ingredients – e.g. a sugar pill. The giving of a placebo aims at simulating all the conditions of medical care in a case, minus the active ingredient in the therapy. The aim of this is linked to the “placebo effect” where a patient’s condition may improve simply because they believe that they are receiving an active treatment. This effect may occur even when the patient has been told that they are not receiving a “real” treatment. Some regard treating with placebos as a deception, but it may also underline the importance of good care and psychological aspects of healing. Placebos can be used in CCTs when there is a suspicion that the effects of the new therapy

may not be due to the active ingredients in the new therapy: that is, where one suspects that the new therapy is itself “really” only a placebo.

QALY (quality-adjusted life year) A measure designed by health economists to compare the net added value in terms of health of medical interventions. Rather than saying that drug X is better than drug Y simply because it adds more years of life on average, the QALY tries to take notice of the quality of life factor. Drug Y may not make one live so long, but it may have much less drastic side-effects, for instance.

RCT (randomised controlled trial) A CCT where patients are assigned to the “treatment” and “control” groups at random.

vade-mecum Literally, “go with me”; usually a pocket handbook summarising the main information needed by a person in the practice of their profession, but also figuratively some mnemonic or catchphrase that plays the same role.



Executive summary

Background

Health technology assessment (HTA) requires scientifically rigorous experimentation involving patients as subjects. HTA itself is required so that treatment given to patients will be both effective and efficient; this requirement is itself ethical in nature. At the same time it is essential that the methods used in HTA are ethically sound. Most healthcare researchers agree that the most effective and soundest method for assessing treatments is the randomised controlled trial (RCT). However, some researchers believe that the RCT is unethical, either in essence, or for use in some forms of medical research and HTA. Furthermore, many patients seem unable to understand the principles and purposes of the RCT, a factor which is highly detrimental for the validity of informed consent. Informed consent is the key to the ethics of medical research, both in most theories and in all codes of research conduct. Many RCTs therefore risk being unethical in practice, even if ethical in principle.

Aim of report

- To survey the main objections to the RCT and its alternatives.
- To assess the philosophical and methodological basis of these objections, and of the methods recommended for addressing them.
- To identify areas where objections are founded in social or cultural factors normally overlooked in ethical argument about the RCT methodology.
- To identify alternative arguments or methods which might resolve ethical conflicts in this area.

How the research was conducted

The methods used were adapted from systematic reviews in medicine. Systematic searches of Medline, Psychlit and Sociofile CD-ROM databases; hand-searches of the major journals

in general medicine and surgery, medical ethics and philosophy; and searches of books were carried out. The literature survey was restricted to articles published or abstracted in English.

A database of the most relevant and useful materials was compiled, and is accessible on the Internet (<http://www.liv.ac.uk/~sdthomps/page1.html>).

Research findings

Understanding RCTs and their alternatives

There is some evidence of difficulty in understanding the aims and methods of RCTs, and some disquiet about elements of the RCT methodologies. These objections are well known and much discussed, and concern the use of placebo, the continuation of trials after significant differentials in benefit or harm are apparent, and randomisation.

Cultural or religious objections

There was an absence of evidence of cultural or religious objections to randomisation, placebo or other kinds of controlled prospective trials. This most likely reflects an absence of research rather than absence of objections.

Informed consent

No group had explicit objections to personal informed consent. However, there is evidence for cultural variation in the desire for information in the consent process, the degree of paternalism or authority vested in the doctor by different groups, and the role of family and others in the consent process particularly when proxy consent is required.

Ethical framework of the RCT

The ethical frameworks used for discussing the ethics of the RCT are almost exclusively the liberal-individualist rights-based approach and the related so-called "principlist" approach (based on the four principles of beneficence, non-maleficence, autonomy and justice). Alternative constructions of the foundations of the RCT ethics are possible. In most cases the practical conclusions remain the same, except in two main ways. It is possible to argue for

a collective and duty-based ethics of the RCT. This risks paternalism and worse, but has the advantage of amplifying the role played by membership of a family, or a community or society, in individual autonomy. It is also possible to expand on the liberalism of the current approach, and argue that while values may be so diverse that consensus is impossible, socially we may all agree that the RCT satisfies most people's preferences most of the time, and so is just, if imperfect. Consequently, cases where this broad principle of preference–satisfaction fails should command particular research and discussion in future. This is of special relevance to the functioning of Local (and other) Research Ethics Committees.

Conclusion

The RCT is in most respects the most effective and fairest method in HTA.

Recommendations

Each recommendation is relevant especially to some group in the healthcare sector: after each recommendation the target group is given in parentheses.

- Attention should be paid by research ethics committees to the needs and values of the major religious traditions active in their area, preferably by direct representation, or at least by recognising representatives of these traditions as experts from whom advice may be sought. (Research ethics committees, area health authorities.)
- Where possible, research programmes involving clinical trials should avoid focusing on certain socio-economic groups, unless there is a clear rationale for doing so. (Funders, trialists, ethics committees.)
- Experimental methodology should be well suited to the nature of the scientific question under consideration, rather than chosen on “philosophical” grounds. (Funders, trialists, ethics committees.)
- Further qualitative research is needed into the medical ethics of particular religious traditions, in particular Islam and other religious traditions of the Indian subcontinent. (Funders, sociologists.)
- A shift in research emphasis away from ethics from the professional viewpoint and towards lay points of view is needed. (Ethicists.)
- The connection between RCTs (and HTA) and resource allocation and justice in health care requires further research. This is already important in the USA and will become increasingly important in the UK as Health Service reform continues, and as evidence-based medicine becomes more widespread. (Ethicists, policy makers.)
- Ethical issues in non-RCT research and HTA should be addressed. This is important in areas where either the RCT is widely criticised (e.g. surgery, vaccines trials) or where the ethical utility of the consent test is generally unsatisfactory (e.g. perinatology, emergency medicine). (Ethicists, methodologists.)

Chapter I

Introduction

Summary of the project proposal

It is widely accepted that the assessment of technologies in healthcare cannot be done on the basis of animal and *in vitro* experimentation alone, but requires experimentation on human patients.¹ Experimentation on patients involves particular ethical issues.² Even where there is an ethical consensus about what these issues are, and what the ethical requirements are in respect of the proposed experiment, this consensus needs to be underwritten by sound argument.³ The principal requirement of any experiment is that it should be scientifically useful.⁴⁻⁶ This requirement is a necessary condition, although it is not sufficient on its own. Most health researchers agree that the most scientifically rigorous methodology for treatment experimentation is the randomised, controlled clinical trial (hereafter RCT).⁷⁻¹⁰ This is not accepted by all researchers, and there is evidence to suggest that randomisation and control are concepts not well understood by many patients, and that many patients are unhappy with being randomly assigned to a treatment, or with being assigned to the control group.¹¹⁻¹⁴ As a consequence, an important body of opinion has formed which argues against particular elements of RCT methodology on ethical grounds, and which has proposed a number of modifications or alternatives to RCT.¹⁴⁻¹⁹

Our hypothesis was that: (1) some of the objections to the RCT on methodological or ethical grounds might have a systematic basis, not solely attributable to misunderstanding of the aims, premises and methods of the RCT, in some particular cases or in general. (2) These objections, if they are systematic, may reflect the beliefs (political, philosophical, religious or cultural) of particular groups within British society. Should this be the case, (3) these systematic beliefs would require the NHS (through Local Research Ethics Committees) to pay special attention to the interests of such groups in assessing RCTs for their ethical adequacy. More than this, (4) these objections might be such that alternatives to the RCT should be considered more sympathetically, as health assessment technologies more widely acceptable to the ethical beliefs of *all* groups in British society. But this would also require showing that alternatives to the RCT did meet

the first requirement of human experimentation, which is scientific adequacy. Finally, then, (5) objections to the RCT might necessitate a negotiated compromise between the need for validated health technologies and the requirements of objecting groups' ethical principles.

What is a clinical trial?

The definition of a clinical trial which is most succinct is due to Sir Austin Bradford Hill:

“the test of any therapeutic procedure applied to a sick person” [20, p.3]

Most of the features of the contemporary RCT are insights into what counts as a reliable test of a therapeutic procedure. Therapy includes treatment aimed at cure or palliation, and with some extension, preventive measures and vaccines. The successes of the RCT methodology have led to its being applied beyond its original scope of testing therapeutic interventions, and the RCT is now used in a range of health technology and healthcare assessments, particularly in the area of healthcare delivery. Finally, the RCT is sometimes used reflexively to test elements of RCT technique; for example in testing the effectiveness of informed consent procedures, or in determining the relative efficiency and reliability of two different designs.

For reasons that will be discussed in the next part of this report, most clinical trials (CTs) are controlled clinical trials (CCTs). Control here means that the group selected to receive the treatment under test are matched with another group, similar in all relevant respects, except that the second group do not receive the test treatment, but instead receive either the treatment which is currently standard in this situation, a placebo, or no treatment at all (beyond ordinary hospital or primary care). The methods of constructing a CCT's control group are several. The method of historic controls involves taking the group of patients who are to receive (or are receiving) the treatment under test, and finding similar patients who in the past received equivalent care but the standard treatment (which may have been no treatment, or a treatment suspected to be ineffective, placebo or actually

harmful). The present patients are each matched with a patient whose characteristics and condition were similar, according to the records. In a fully prospective trial, patients are enrolled and assigned to the treatment group (A) or the control group (B), and the method of assignment may vary. Patients may be assigned by alternation (ABABA...; or more realistically XXXXAXXXBXAXXBXXA..., where X indicates a patient who presents, but is judged unsuitable or ineligible for the trial), or by matching (patients whose characteristics and condition are similar are paired off, and from each pair one receives the test treatment, and one the control treatment – this is the “case-controlled” study method), or by strict randomisation (eligible patients, as they enrol, are assigned at random to one or the other treatment).²⁰

The RCT is a CCT which is fully prospective and uses strict randomised assignment. The aim of any method of constructing control is to provide an unbiased assessment of the treatment’s efficacy, as compared with the control treatment, in this selected population; owing to natural variations in human subjects, and in the severity and development of the condition being treated, all CCTs are statistical in nature. The aim of the statistical design will be to produce estimates of effect or probabilities of outcomes upon which future treatment and licensing decisions may rest. The purpose of this is to ensure that patients receive effective, safe treatment, which is efficient in its use of resources.²¹

What are the basic ethical issues (as they have come to light in the history of the clinical trial)?

If we restrict our attention to RCTs (comparison of treatment effect in small groups has a long prehistory), all the pioneering trials were tests of treatment efficacy, concerned with the usefulness and safety of novel drugs. The most famous example is undoubtedly the streptomycin trial for a cure for tuberculosis.^{22–24} As noted above, the uses of the RCT are by no means restricted to the testing of new drugs, whose powers of treatment are unknown. Nonetheless the focus of ethical debate on CCTs has concentrated on the ethics of prescribing experimental treatment (that is, treatments whose efficacy or safety are not yet known), within the context of a controlled experiment. Strictly speaking, there are two questions here which should be kept analytically distinct, although they are interrelated in practice. Some ethical questions concern the rights and

wrongs of using experimental treatments in various situations. Others concern the enrolment of individual patients into experimental designs oriented to comparing groups of patients considered collectively, and the scientifically motivated constraints on individual choice within the trial.^{25,26} This second group of questions remains pertinent even if the treatments used in the trial are all well-understood, useful and safe, and the point of the trial is to determine relative effectiveness or efficiency.

Because the chief focus of ethical debate has been on the nature of the CCT as a sort of experiment in the strongest form – a prospective experiment using groups of patients, in which at least one group are receiving an experimental treatment – the ethical system has been the Nuremberg-Helsinki paradigm for determining the ethical legitimacy of experimentation upon human subjects.^{27–34} The chief concern here is that patients should be enrolled into experiments only with their free (not coerced) voluntary consent, and only with full knowledge of the risks they will undergo.³⁵ This will be discussed in detail in the third part of this report, where the doctrines of consent (informed, voluntary or autonomous) which are used as filters or protective standards are examined. The key elements of this paradigm include proportionality of risk and benefit to the patients enrolled in both arms of the trial; some appropriate standard of free consent to being enrolled; and that the trial should be useful, scientifically important, reliable in design, and competently run and analysed.

Some other ethical issues have been added to these requirements, enlarging the scope of the paradigm without substantially altering its spirit. These are captured in the famous “Four Principles of Biomedical Ethics” proposed by Beauchamp and Childress.³⁶ These are labelled Beneficence, Non-maleficence, (respect for) Autonomy and Justice. Of each treatment, and of the experimental protocol itself, we may ask, in turn: does it do any good? Does it do any harm? If so, are the risks of harm commensurate with the chances of the hoped-for benefit? Are patients given sufficient information, and unprejudiced guidance, so that their consent is genuine? Are they consenting to the experimental treatment or to the experimental protocol as a whole? Is the trial protocol fair in its enrolment and selection methods? And is the method of assignment within the trial fair to the participants?

The main ethical issues which concern the CCT are as follows. Is the experiment actually necessary?

That is, are we really uncertain as to the merits of the “novel” treatment, so that we need to test it? Is it ethical to subject patients to a treatment which may be harmful, ineffective, or less effective than some other treatment? In the fully prospective trial this cuts both ways – the relatively ineffective treatment may be the new or the old treatment. If we have sufficient evidence to test the treatment at all, some authors argue that that is already enough evidence to use the treatment, without the need for further testing.³⁷ Using the standard treatment would be unethical because, *ex hypothesi*, it is less effective or more harmful than the new treatment. Conversely, it is possibly unethical to give patients a treatment which we do not know to be effective when there is a standard treatment available which we have been able to use in the past. To handle these problems, Freedman and others developed the concept of “ equipoise ” to give an account of the ethically sound approach to take to evidence about treatments.^{38–41} Related to this, there is the problem of what to do when some treatment in the trial becomes “obviously” superior in the light of evidence before the trial is complete.⁴² Can it be ethical to keep some patients on a placebo (or other) regime when the novel treatment is “obviously” effective? Can it be ethical to keep some patients receiving the new treatment once it has become obvious that it is ineffective or harmful? Much of the debate here hinges on what can count, on the different theories of statistical inference, as to obvious superiority or inferiority.^{43–45} There are some particular issues connected with randomisation: does it work? Is it ethical to assign a patient who “clearly” would do better under one treatment rather than another at random to one or the other treatment? Can patients understand randomisation well enough to consent to it? Is there anything which patients find objectionable about randomisation? Finally, particular treatments have special ethical problems connected with them, which carry implications for the ethics of CCTs of these treatments. For example, there are many complex problems of ethics associated with trials of HIV vaccines, connected with “moral hazard”.¹ Problems of this sort, which do not bear on the ethics of CCT methodology as such are beyond the scope of this study.

The major issues specific to CCTs can all be grouped under descriptions derived from the four principles; this is the value of the Beauchamp and Childress approach. The principles are very widely accepted but their status is somewhat controversial.⁴⁶ While they are useful analytically, several authors hold that they are not entirely satisfactory as justification principles. This theme

will be returned to in subsequent parts of this report. The importance of this dispute is that it is all too easy to mistake the four principles as self-justifying answers to the questions they help frame. On the one hand, this begs important questions about the foundations of the ethical theory or theories they may be taken to imply; and on the other hand, there is no self-evident method that will guide us in applying them to actual situations, such that our judgements will command consent or acceptance. These two insufficiencies are linked: the insufficiency of the foundations is evident in the insufficiency of the canons of practical application and justification.

The aim of this study is to broaden discussion of these issues, but it may be that we do not need to abandon the four principles. For if, as seems likely, no better or more substantial ethical approach can command more acceptance in our pluralistic society, we may give up on the self-evidence of the principles as sources of substantive rights and duties, while retaining them as warrants on the procedural legitimacy of our decisions. We may not be able to guarantee that our decisions are infallibly right, but we might be able to ensure that we are making these decisions in a just and accountable manner.

Methodological issues for this project

The format of this study was a systematic review of medical, social science and philosophical literature from 1990 onward, with the aim of determining the range of philosophical and religious positions with respect to the ethics of the CCT. This has a number of purposes. The first is to determine whether we can continue to use the Beauchamp and Childress principles theory as the basis for determining whether a given trial is ethical – is this theory inclusive enough? The second is to determine whether ethical debate in the medical and philosophical literature is an accurate reflection of the range of opinion expressed by patients. The third is to check that issues identified as important in the ethics of clinical trials have been adequately covered, discussed and disseminated to doctors and patients.

Systematic review in ethics

Clearly the aims and methods of a systematic review in ethics are not going to be the same as a systematic review in one of the empirical medical disciplines. There is some empirical content to ethical debates: reliable evidence of systematic

preferences or discontent about particular features of trials in the public is essential in framing practical proposals for guidelines or legislation. Also it is useless to make proposals about ethical matters that simply cannot be followed in practice for legal or procedural reasons. However, from the fact that effectively all ethicists hold that informed consent is a central plank of the ethics of clinical trials nothing can be concluded, without scrutiny of the reasons, premises and validity of the arguments used. As such, our model is not a meta-analysis of findings from a variety of studies, but rather a commission of inquiry, whose brief is to take representations from as wide a spectrum as possible, in order that a considered opinion that respects this diversity can be delivered.

Search methods

The questions framed in our hypothesis were partly philosophical and partly empirical. We needed to know whether there were in fact any common objections to the RCT methodology (or to particular trials); and we needed to assemble the interpretative and philosophical resources to make sense of them. We determined to use a modified systematic reviewing strategy to assemble a database of articles and book chapters. We used systematic searches on Medline, Psychlit and Sociofile CD-ROM databases, together with hand-searches on the most important relevant medical, bioethics and philosophy journals to assemble as wide a range of empirical and analytic material as possible and useful. Objections were sought of both direct and indirect kinds. Direct objections comprise explicit statements by patients and healthcare workers of worries, objections, and problems to do with recruitment to particular trials, compliance with protocols, and the methodology of trials. Indirect objections were limited proactive attempts on the part of the project team to extrapolate and infer objections that particular groups might make to trials, on the basis of explicit statements about topics analogous to features of trial methodology, but not directly connected to it. For instance, many religious groups object on principle to any form of gambling, whence it might be inferred that they should also object to random assignment. The absence of any objection along these lines as yet, may perhaps indicate only that this is a pitfall-in-waiting. A wide remit was adopted, on the hypothesis that careful foresight would benefit from moderate speculation.

Appendix 1 contains lists of search-terms used in the CD-ROM searches, together with the journals hand-searched and details of the time-frame of the search.

Searches for analytic material were, of necessity, much broader in scope, because the kinds of objections that might arise could have quite broad significance (economic, social, political, religious, cultural and so on), and could be taken to reflect aspects of philosophical arguments which are not normally canvassed in contemporary medical ethics, narrowly defined. Particular care was taken to discover relevant books, as these are often less well represented in electronic databases than are abstracted articles.

Statistics on our search methods and the topic headings used to organise the material are to be found in Appendix 1. In searching for articles relevant to this topic, we found a very large number of articles with relevant titles, which turned out to be irrelevant when we looked at the abstract; and so the proportion of articles which were read for relevant content was relatively low. We used two types of criteria to select articles from the subject-heading trawl. Articles dealing largely with the conceptual content of clinical methods and ethics were selected in the first months so as to construct a reliable survey of the field of RCT ethics generally, and thereafter largely on the criteria of novelty, depth or interest. Articles dealing with empirical inquiry into trials, consent, ethnography or ethical attitudes were selected for relevance. It was not our intention to analyse these studies for the reliability of their findings except in broad terms. This has to do with the nature of ethical argument. From the statistic that, say, 77% of people surveyed think that RCTs are ethical one can conclude really very little, first because opinions tell one little about their correctness (the 77% could just be wrong or confused), and second because one wants to know the reasoning behind these opinions pro and contra. Articles of this kind were usually used for the light they could throw on the kinds of argument used and the validity of these arguments. Our sister project (93/41/2) was, in addition, going to devote far more time and systematic analysis to the question of what psychological studies can contribute to ethical analysis of clinical trials.

The searching process and ongoing findings were discussed at regular intervals throughout the project by the grant holders and the research fellow. At the beginning and at the half-way period findings were presented to, and discussed with, a distinguished External Advisory Group (Appendix 2), who made recommendations about the scope of the work, the sources of material, and interpretation. The main area where substantive recommendations were made was in the examination

of the influence of specific socio-cultural factors. These recommendations are discussed in the introductory paragraphs of chapter 4, which contains material that proved hardest to interpret, and occasioned most comment from the reviewers of the draft report.

The principal issues that were discussed in the literature can be grouped under three headings.

These are: (1) Methodologies of RCTs and their alternatives; (2) Informed consent, autonomy, duties and rights; (3) Cultural and socio-economic factors affecting trials and their ethics. One chapter is devoted to each of these themes.

Chapter 2

Methodological aspects of clinical trials in ethical perspective

The role played by randomisation in CCTs is controversial in a number of different ways. In the first place, it divides the medical research community rather sharply. On the one hand, many medical researchers hold that it is often effectively unnecessary and unethical (and then there is some debate about which implies which).^{15–17,47–50} On the other hand, a large and influential section of the profession believe that in almost all cases randomisation is both ethical and necessary.^{8,9,51–56} The arguments on both sides are usually dual: both methodological and ethical. There are not that many philosophers who have written on clinical trials, but there is some literature produced almost as an afterthought in debates over the theory of statistical inference, and about Bayesian methods in epistemology.^{4,7,10–12,37,45,57–60} Finally there is some evidence that the lay public (especially patients) are unhappy about randomisation; and it is interesting whether this reflects a genuine ethical dispute with the scientists or whether it reflects a misunderstanding of the role and methodology of randomised clinical trials.⁶¹ The latter may appear less significant, but we are not sure that it is: it is just this sort of misunderstanding which destroys the authenticity of apparent informed consent.

The classical clinical trial

The classical clinical trial in medicine was devised by the medical statistician Austin Bradford Hill and his colleagues in the late 1940s in the search for a therapy for tuberculosis, drawing on ideas from Ronald Fisher's designs for agricultural field trials.^{22–24} Since the initial clinical trials many variations on the classical design have been developed, partly to handle more complex questions, partly in response to ethical worries about features of the classical trial, and partly in response to statistical and philosophical debates about the foundations of statistical inference.^{62–65} The classical design is still the most representative, however, because it is simple, relatively easy to understand and implement, and – a fact which became of great importance in from the mid 1960s – easy to explain to patients.

Evidence and treatment without comparative trials: epistemology and ethics

Suppose you have a new drug for some condition. The pharmacology of the drug indicates that *in vitro* it is effective against the disease-agent. Animal tests suggest that the drug works in animal analogues of the disease, and that the effective dose is not too close to the toxic dose in animals. (The ethics of animal testing will not be discussed here. Suffice it to say that many of these tests can be done equally well on human healthy volunteers or on altruistically minded but irreversibly terminally sick human sufferers of the disease in question – if any; and that many of the ethical objections to animal tests are the same as those that arise in human tests.) So we have *prima facie* evidence that the new drug is an effective treatment for the disease in humans. How strong is the evidence? How much reliance should we put on it?¹

The answer, of course, is – it depends. A pessimistic meta-induction on drug development suggests that this sort of evidence is not very strong testimony to the drug's effectiveness.^{10,66–69} The inferential link, to coin a phrase, between petri dishes and sick bodies is weak, and not only is it weak, we have no measure of its weakness, certainly not in general. What we do know is that the ways in which this type of evidence can be misleading are legion. However, we might feel that this drug is better than nothing so far as treating some particular patient is concerned. The scenario for this sort of decision is familiar – everything else has failed, the patient's condition is deteriorating and so forth. It is interesting to reflect on why this sort of narrative is brought into play. Doctors and surgeons speak about "heroic" interventions in such cases. The idea is that these "last ditch stands" represent limit cases where the normal ethical and pragmatic rules breakdown. In fact extreme cases are not those most likely to yield much reliable evidence about the drug's effectiveness and side-effects. To say nothing of the fact that a large proportion of treatments are aimed at non-fatal and acute conditions. The argument goes: we have no right or reason to give this new treatment to a patient in place of other treatments we have at our disposal and

about which we have more information. So we should only use it at this low level of evidence when there is nothing else.^{1,14,18,70}

Alternatively, some doctors may regard new drugs as probably superior to older treatments, and wish to rush them into use – equally using the language of heroism.^{1,14,18,71} In this case the reasoning does not have to do with the “last resort” but with the “expanding frontier” of medical-scientific progress. Ethically – such doctors argue – we are obliged to bring new advances (if that is what they are) on-stream as quickly as possible, in order that they can benefit more patients, and sooner. There is a dilemma here for trials: it may be thought unethical to run a trial if we have no sound evidence for thinking that the new drug is effective; so it might be thought best to use the drug in a few cases where it seems likely that the patients will benefit.⁷⁰ But if it works for them, it may then be thought unethical to run a trial once we – apparently – know that the drug is actually effective.^{42–44,72} The argument for trials hinges on showing that there is a grey area between a reasonable hope that the drug is effective for a few patients and a rational and justified belief that it is so for typical patients.³⁸

Suppose that in our initial attempts to use the treatment we find some improvements. What does this add to our evidence? Again, it adds something. But not a lot. We have no right to infer that the new drug caused the improvement. Informally, it looks as if there is a correlation between administration of the drug and improvement, and between non-administration and null-improvement. But, again, we cannot reliably infer that the drug was the cause of the improvements. We might look for some explanation for the improvements, and the drug would play a role in some of the causal hypotheses we invoke in framing candidate explanations. But not in all of those hypotheses: we might, for instance, suggest the famous and well-attested placebo effect (however we might choose to explain that!).^{73–77} Not only can we not directly infer that the drug was the cause of the improvements, we cannot say anything reliable about the magnitude of the effect in general. This is in part because we chose extreme cases of the disease.

There is, of course, a counter-argument to this train of thought. It is simple. If the drug (apparently) worked in the extreme cases, then it is surely going to work in the more moderate ones, and its effectiveness should be greater. This is not a convincing argument, because it presumes that the drug worked, which is what we are trying to prove. So the apparent action of the drug does not give

us reason to use the drug as a policy: however, it does give us reason to make the drug into a candidate for testing.

The counter-argument is the basis of a popular early argument against the necessity for clinical trials. Many doctors claimed that trials were unnecessary, in all but a few (if any) cases, because new drugs, found to work in a few cases could then be prescribed by physicians as they saw fit, applying their clinical judgement.^{78,79} The idea here is that training, experience and medical intuition were more effectively reliable instruments for determining how to treat particular patients than any statistical method designed to determine population statistics, which were properties of some fictional “normal man” rather than of any actual individual patient. (Note that this rests on a mistaken understanding of statistical inference: statisticians tend not to hypostatise the “population parameter” into a property of a fictional individual, although this was at one time a popular interpretation, hence its hold over most of us non-statisticians.)

This is not to be dismissed out of hand; doctors tend to be reliable judges – under most circumstances – in just the way described, at least where “routine” diagnosis, prognosis and treatment are concerned. The question begged in this argument is: how good are doctors at judging in novel situations? Accompanying the “trials are unnecessary” argument is an ethical argument. If I have reason to suppose that this drug is effective in cases of this kind, or at least, is no less effective than any other treatment I may know of, then I am obliged to prescribe it. If I do not have such reason, then I am obliged not to prescribe it. There is no room here for experimental testing.⁴⁷

This is an interesting argument, because it illustrates one of the last places where the traditional view of medicine as a practical art has any purchase. It is particularly relevant to present debate about “evidence-based medicine”. The authors do not think that, as it stands, it is right. For instance, it assumes that there is no “knife edge of uncertainty” upon which a doctor may balance in equipoise; and furthermore, it assumes that this knife edge is not in fact a fairly broad grey area. But to say why these assumptions fail to convince is a non-trivial problem in the theory of rational belief, and we leave that for future research.

Comparative trials

How much understanding do we have of the drug so far? We know that it is effective *in vitro*, and apparently in animals; and we have fragile grounds

for proposing that it seems to be effective in a small number of cases which proved resistant to alternative treatments. In other words we have enough evidence that a trial would be worth doing, on the understanding that a trial is going to provide grounds for accepting that the drug is a reliable cause of therapeutic benefit, and perhaps also that the trial will produce a reliable estimate of the strength of that effect. More modestly, we might settle for a relative indication of the superiority (inferiority or equivalence) of the new drug to the standard treatment (which if there is none, can be substituted with a placebo).

In passing, note that all our experimental work so far has contributed almost no reliable evidence for our hypothesis, if by “reliable evidence” we mean, evidence on which we can place some reliance in making a therapeutic decision or scientific assertion. This is hard to accept. To sweeten the pill, subjective Bayesians (about whom more later) will say that while none of this tentative work is much help in determining the posterior probability of the drug’s causal power, it does help in determining a sensible choice of prior distribution for the experimenter, and in designing the experiment. The classical statistician will not accept the talk about priors and posteriors, but will probably accept this as a description of the role of these pre-trial activities.⁸⁰

In fact, all trials are relative trials – that is, all trials involve a comparison between two treatment groups. To see why, let us review some of the main sources of unreliability which block naïve induction about treatment tests. First of all, the drug may have no biological effect at all, or none connected with the target condition. The observed improvements in health may be chance remissions; the biology of humans may differ significantly from the biology of animals or the combined effect of disease agent and human biology may significantly alter the effect of the drug on the disease agent, as compared with *in vitro* or animal studies. Secondly, the drug may have some effect on the disease *in vivo*, but our estimates of its effect may be misleading. Thirdly, the context, cause and effect may not be generalisable beyond a small number of cases, owing to the influence of some other environmental or physiological factor present or absent in the early subjects.

Not only are comparative trials used to manage known and unknown sources of unreliability and error, they are also intended to cope with the variability of human subjects, even *ceteris paribus* – so-called “natural variation”. This is a point

misunderstood by some critics of trials, who argue that trials can have nothing to say about treating real patients, because real patients are all different. So they are, and statistical science is designed to cope with this, so as to provide a baseline for guidance, which the doctor can use in tailoring treatment regimes to particular patients. Arguably the doctor cannot begin to do that until he has some knowledge of the behaviour of the variation’s distribution (whose properties derive from both the drug, the illness and the patient population, and so are hard to guess *a priori*).

How can these sources of unreliability in causal inference and effect estimation be managed? The basic method is to do a parallel trial comparing two basically similar groups of patients, where the only therapeutic difference is that one group receives the novel treatment, and the other group receives some alternative, but well-understood, treatment. Two types of controlled trial are standard, the first being placebo-controlled. In trials of this type, the control group is treated with a biologically neutral agent (a placebo) which simulates the procedures of treatment, while having no active causal power in itself. It is well known that the experience of being cared for by doctors and nurses can sometimes have beneficial effects on the healing process (and of course, occasionally negative effects instead). What we want to establish is that the new drug has more effect (i.e. active power plus placebo effect is greater than placebo effect alone); and this effect can be estimated in absolute terms by the drug-placebo comparison. Alternatively, the second kind of trial involves trials of the new drug against the current standard treatment, to determine whether the new drug is less, more, or equally effective.^{81–85b} This sort of trial relies on the existing treatment being known to be effective (or at least as effective as the placebo treatment), and generates an estimate of effect relative to the effectiveness of the standard treatment. It is quite common for large trials to have several arms, which compare different combinations of treatments with each other and with placebo.

Selection and allocation to treatment groups

Controlled comparison is the cornerstone of the clinical trial. But the methods used in constructing the comparison and allocating patients into treatment and control groups are various.^{20,55} You can decide that you will give all the patients in the trial the new treatment, and compare their progress with that of a similarly sized group of patients treated in the recent past, followed through medical records. This is the method of so-called historic controls. You

can assign patients to a treatment arm (new drug or placebo arms, say) by hand (picking pairs of similar patients, say) or by alternation (patients present one at a time in a sort of queue, and odd numbered patients get placebo, even get the new drug) or by random assignment to one group or the other. This last method is the method of randomisation.

Sub-grouping

At this point a few words are needed about the relations between the two groups in the trial, and about the relations between the two groups and the population they are drawn from. Since we do not know, reliably, anything about the drug's effects – although we have a reason to suppose that it has some, they are basically beneficial and they are non-negligible – there is no ground for supposing that we can construct patient groups in the trial that will match up with the set of sub-populations which the drug will affect differentially. So, unlike in population survey sampling in opinion-polling, say, we have in general no reliable method for determining *a priori* what criteria for “representativeness” we might want to impose on the patient groups.^{55,86} In most cases, therefore, we cannot construct a random sample (where we ensure that each patient has an equal chance of being selected). We are, therefore, in the position of treating the patients who are enrolled in the trial as a non-random sample, that is to say, we cannot assume that there is not some hidden (or even evident) selection principle at work. We cannot assume that our method of selection displays no systematic bias toward or away from any unknown biological character which would distort the experiment. And it is *because* of this that we need some method of making the distribution of known and unknown “confounding” variables as balanced as possible between the arms of the trial, so that the arms are alike within the trial.^{11,12,87}

Now, there are some ways in which we have to process our sample before running the trial. No trial admits just everybody: some classes of patient are usually excluded, and some may be excluded for some specific reason connected with trial in hand. This exclusion can relate to the methods of informed consent – mad subjects are excluded, typically, unless the trial is for a mental health therapy; women are often excluded on the grounds of possible damaging effects on possible foetuses; children may be excluded in part because they are deemed incompetent to give full consent, in part because their medical characteristics are often significantly different from adult medicine. These exclusions tend to match up with post-trial exclusions: but not always.

It must be remembered that most trials are intended both as therapeutic investigations and as elements of the licensing process for drugs. Since the 1950s (although the process began well before then) the issue of a doctor's judgement on prescription has been much modified by licensing of treatments – a doctor cannot prescribe what is not available or determined safe. This dovetails with earlier comments on individual inductive reasoning by doctors now having less influence than in the past. As well as exclusions, some sub-grouping is possible, in cases where we have sound reason to believe that some biological (or social or psychological) character does have relevance to the effectiveness of the treatment. So we might enrol men with a certain condition quite easily, but find fewer women patients; and continue enrolling only women after a certain point in order to get a sample size which statistical theory tells us will be large enough to make a reliable determination of effectiveness. But in effect this *a priori* sub-grouping may have to be treated as a subsidiary hypothesis.

Confounding

Control groups are, in summary, designed to screen out spurious causal inferences, and to help found estimates of treatment effect. The issue which arises now is: which method of assignment to treatment groups is best? To answer this question, we need to understand another source of unreliability, that is bias in estimation. Many factors influence the severity and progress of any disease in individual patients, and we cannot determine all of them. Particularly troublesome are the aptly named “confounding” factors, which are unknown nuisance factors which can cause unknown modifications to the disease and the treatment effect. Some of these nuisance factors may be known in type but not in degree, and others may just be unknown. One important source of confounders is the influence of the physician's conscious or unconscious choices in patient assignment – as for instance prescribing the drug to a patient whom he believes has a good chance, and withholding it in a patient whom he believes does not. Similarly, the nature of the placebo effect is such that if a patient suspects that he is (or is not) receiving the active drug, this has unpredictable but often non-negligible effects on the psychological component in healing.

It has long been standard to use some sort of “blinding” so that patient, or both doctor and patient, do not know which treatment the patient is receiving. It is usually the case that a patient will know that this is being done, for ethical reasons

to do with informed consent. Some controlling methods try to avoid this – particularly the method of historic controls, which involve all current patients, eligible for inclusion in the trial, receiving the new drug. The method of randomisation is supposed to compensate for any unconscious or conscious biases due to the physician or patients, partly by removing the element of choice in assignment, partly by spreading the bias around to minimise it. The idea is that by spreading the risk of confounding factors occurring in particular patients in one or other treatment group, the net difference between the groups will be nullified.

Randomisation

This is the basic argument for randomisation in CCTs. It is proposed as a replacement for alternation or construction methods of control-treatment group patient assignment; clearly it has no role to play if historic controls are used, because all present patients get the new drug, and all past patients are supposed to have the old drug. Randomisation only matters where there is a choice to make for each patient. And its role in these twin-armed “prospective” trials (i.e. trials, where two groups are studied over time, within the same time frame) is to eliminate certain selection biases introduced by the physician, and to balance the effects of multiple confounding variables. In other words it is a way of constructing equivalence between the two treatment groups.

Hopefully this sounds plausible and sensible. Nonetheless, it is controversial. Some of the ethical reasons why this technique is debated will be reviewed, but the methodological issues will be concentrated on thereafter.

Placebo-control

First of all, the notion of placebo-control is troubling, in part because it seems to breach the doctor’s obligation to at least *try* to do some good for the patient, and in part because, if the placebo effect works, it does so by means of a deception.^{71,82–84,85b} There are two responses to this. On the one hand, we can say that we just do not know that the new drug is anything more than a placebo itself, probably in fact a somewhat toxic one; and until we know otherwise we are not knowingly withholding effective treatment, in fact we may be withholding a useless poison. On the other hand, it may be that this treatment is effective, and so we are obliged to find out – not doing so would be withholding treatment from many more people. So far as the deception element goes, a

double-blind procedure where the doctor himself does not knowingly deceive the patient, and a proper informed consent procedure, where the patient understands that he or she has entered a sort of lottery seems to get around the need for deception. After all, it is merely by chance that this patient fell ill here and now, and was approached to enter this trial. Hundreds of others do not have even that chance; and since it is purely chance, it is not unfair. There are several interesting points here: if you live near an American teaching hospital, you are probably going to find it hard not to get enrolled into a trial sooner or later, and further, if you live near such a hospital, demographically it is probable that you are poor and so need to get treatment this way, with little consumer power; and the workings of chance, so-called, look rather like a rigged table. Also, the argument from ignorance leads to the question – when do we start knowing something? How many “positive” results do we need before we can say this is not due to chance or confounders? There is a demand for a method of stopping a trial early, when the weight of evidence seems to settle the matter early.^{42–44,72}

Non-beneficence?

The second main ethical worry about randomisation is that it forces the physician to relinquish the duty to prescribe to each patient on the merits of each case. In its simplest form, this objection can be answered by the argument from ignorance. But there is a more sophisticated version which is harder to shrug off. True, we do not know that this treatment is better, but we have enough of a belief in this treatment to conduct an experiment on the supposition that the odds are in favour of the new treatment. Else why do the experiment and take the risks with patients’ health already discussed (possible toxicity, possible non-treatment and so on)? So why do we not just treat all and only those cases which seem to us to require the new treatment, on the basis of our non-zero credence in the treatment?

This is the basis of two competing lines of thought about the clinical trial. One is the that which leads to subjective Bayesian interpretations of clinical testing, and the other is the theory of equipoise. This holds that a trial is ethical and worthwhile just in case either the particular physician, or some group of physicians known to the researcher, or the medical profession as a whole, are indifferent between the two treatments (placebo and new drug, or standard and new drug). Once equipoise is destroyed (the balance of opinion tilts one way or the other), the trial should be terminated and prescription patterns altered accordingly. There is

some ingenuity in the equipoise theory, although its constraints seem bizarre if one tries to apply the theory in practice. But it does try to formulate an account of when a trial is necessary and legitimate. In the equipoise theory, random assignment is ethical *a fortiori*, because of the way indifference between treatments (a subjective state, by the way) is taken to be normative.

Some of these arguments need to be modified slightly if the trial is not placebo-controlled, but standard-treatment-controlled. Here the worry is not that a patient may receive no treatment, but that a patient may receive a worse treatment. The twist is that where placebos do no harm, active treatments almost invariably involve some concomitant risks (a degree of toxicity, for instance). But this does not alter the substance of the argument appreciably.

These are substantive ethical worries, but it is our belief that they are of lesser significance than the following problem. What if randomisation does not do what it sets out to do? Then it seems unethical by that very fact. Alternatively, even if it does work as claimed, are the other methods significantly less effective? Also, if we do a cost-benefit analysis of the randomisation and other assignment methods (including historic controls), are RCTs still the most effective and ethical trials available?

Critics of randomisation in statistical experiments

Randomisation and confounding

The main objections to randomisation in clinical trials are summarised in some papers by Peter Urbach. Urbach is convinced that random assignment is unnecessary, because it doesn't solve the problem it is supposed to solve, and because it rests on a mistaken notion of what a clinical trial is for.^{11,12} More moderate views are held by practising Bayesian statisticians, most of whom hold that randomisation is essential but only in a limited way, a position similar to that held by David Papineau.¹⁰ The consequences of the strong and moderate Bayesian positions are the same: if randomisation never works, or only works sometimes, then in any particular experiment, the claim that randomisation does not work in *this* case can be pressed, and anyone who objects to randomisation on ethical grounds will want to do so. Of course, the onus is on them (or at least the statisticians among them) to give an alternative experimental design which is both fair and reliable.

One common objection to randomisation is that it is blind to known confounding factors, and so may in fact increase, rather than reduce, bias by unwittingly assigning a disproportionate number of "confounded" patients to one arm or the other. This is of course possible; and it is the sort of problem that will beset any scientific experiment in theory. Let us be clear about this, however. The randomised experiment is perfectly capable of dealing with known confounding factors. You build them into the design and then randomise. For instance, if gender is a known confounding factor, so that the probability distributions for men and women are different, then you do not randomise the whole sample (you can do so if a crude but simple hypothesis test is all that you need, however), you split the sample into two, and randomise within each. More generally there are randomised designs which can handle more or less any known pattern of confounding – if it is known. Recall that no trial can reasonably be planned without a fairly sensible model of the science behind the treatment and its putative effects. The fact most statisticians testify to, that it does not matter whether you are a classical or Bayesian in your theory of inference, is explained by the fact that most "personalist" assumptions are built into the pre-trial process of hypothesis formation and trial design.^{25,45} Randomisation is meant to handle unknown and unsuspected confounding.

So does randomisation in fact achieve this aim, that is, does it minimise the influence of unknown confounding factors on reliable causal inference and on estimation? Urbach has a number of arguments relevant to this point. He argues that randomisation may in fact increase the influence of confounders and that it cannot protect from large, unknown confounders. It can increase the influence of confounders as follows. Random assignment, because it is random, might pick disproportionately many of the confounder-influenced patients and assign them to one treatment group, increasing the probability of erroneous acceptance or rejection of a treatment. Far from screening out experimenter-introduced bias, it adds a new source of bias. This will be particularly important when the influence of the confounding factor is large. The classical theories of inference have no way of scrutinising the data to detect the unknown confounder's influence, because any differential effect will normally be attributed to the new treatment. It may be that a confounder is identified, which can be shown to be unevenly distributed between the arms, and it may be possible to show that the differential effect is attributable to this confounder and not to the

treatment difference. If, however, during or after the trial the penny drops and the confounder is identified, re-analysing the data is illegitimate; retrospectively assigning already randomised patients to newly defined sub-groups for re-analysis will produce sub-group pseudo-samples which are probably too small to permit sound inference (for mathematical reasons), and which in any case are not truly random, so that any inference made using them will be at best biased and at worst meaningless.

This is certainly a problem, but it seems that it is a problem of scepticism, rather than of methodology: of course Murphy's law, adapted for epistemology, applies to any inferential system! Randomisation is meant to distribute evenly the net effects of multiple confounders, rather than equalise the distribution of each individual confounder: which is why most practising Bayesians use randomisation anyway, but Urbach offers no replacement. Further, where classical statistics has an account of the probability of error (i.e. type I error rates), which is not dependent on knowing what the confounder is, Bayesian statistics has no equivalent: simply, we cannot assign a prior probability to an unknown confounder, nor can we interpret posterior probabilities in terms of error rates.

It is not clear that Bayesian methods of inference contribute anything to the problem of unknown confounders – because they are aimed at solving a different problem. Bayesians cannot claim to solve the problem of massive confounders or bad luck, simply because their aim is to devise a theory of adaptive learning based on personal probabilities, rather than a science of objective probabilities which we conduct experiments to determine. Hence they draw their contrasts too strongly: classical inference is concerned – for the most part – not with probabilities, but with estimates of parameters of probability distributions (means, variances and so on). Most Bayesians are aware of this, because a further criticism of the controlled trial on the classical interpretation is that it does not provide any basis for determining predictive probabilities. That is, on the one hand, the classical theorist cannot say in any case what the probability is that *this* patient will recover. On the other hand, the classical theorist can say that on this hypothesis, a certain proportion of patients will recover with a given probability (which is a statement about populations not individuals).

It is not clear what the Bayesian wants here. Many of the Bayesian criticisms of classical trials involve saying that the classical theorist claims objectivity

for his judgements, where in fact there are only subjectively reasonable opinions motivating the classical theorist's experimental design. This seems fair (which is one reason why one way out is to opt for decision theory, which tries to modify classical theory by including both personal probabilities at the points where opinion seems to be involved, and personal utilities to weight the decision-outcomes according to the costs and benefits of error and correctness). But the Bayesian is committed, as the classical theorist is not, to *personal* probabilities to apply in *changing, particular* circumstances and to assigning for each patient a new prior probability which is to reflect that patient's state of health and potential for recovery, to allow for conditionalisation with respect to the treatment.⁵⁷ This has the appearance of over-mathematisation (a standard worry about Bayesian theory is that the dynamics of belief systems just aren't mathematisable in that way: degree of belief being a metaphor not a quantity). For the Bayesian, the trial is a method of producing degrees of belief in efficacy, rather than measures of efficacy.

It seems that the Bayesian case against randomisation is not proven, simply because the arguments are either inconsequential, or global: the Bayesian assumptions about convergence of degrees of belief, "washing out the priors" and so on are founded on no more secure bases than are the classical assumptions, and both sides rule out the really alarming ways in which trials can produce misleading results by appealing to the figure of the experienced and imaginative researcher.⁸⁸⁻⁹¹ Many statisticians are happy to concede that a properly run trial involving either theory of inference will come to the same conclusion (although it is not clear how this could be proved without appeal to some special philosophical assumptions about knowledge, belief and reality).^{45,92-95}

Early termination and bias

Two final issues present themselves. The first is the issue of early termination of trials, when the evidence seems to indicate either a newly-detected confounder or an "obvious" treatment effect or failure. Strictly speaking this is not connected with randomisation, but with controlled trials on the classical theory. The problem of *ex post facto* subgroup analysis in classical theory was referred to earlier. Similar reasons to do with biased inference mean that procedures to "peek" at data and infer anything on the basis of early data will be problematic, unless one designs a trial specifically to allow this; and in effect that means a sequence of trials, each one with an adequate sample size, with a series of progressively modified investigative

hypotheses. So “peeking” at data is very cumbersome and costly. Under the Bayesian system, where the control and treatment arms are usually analysed independently, and the posterior probability can be continuously updated, this problem does not arise – bias is not an issue, because personal probability has nothing directly to do with estimation. The question of whether this is defensible is a vexed one, and left open here.

Is comparison ethical and reliable?

The second issue is ethical. If we grant that randomisation is not effective on its own, but simply an option that one may use if one likes in the context of a properly designed trial where known confounders are controlled directly, then one may conclude that random assignment is unethical to the extent that it is a barrier to active assignment of patients to the treatment group when the physician, using his knowledge of the patient’s condition and his prior probability judgement, believes it to be in their best interest.⁹⁶ One will also conclude that, in order that assignment to the control group will not be meaningless (because in the end, no one will be assigned to it except hopeless or very mild cases), one should not enrol patients into a trial, but rather use a database of past cases. Then two ethical questions arise. First, is this method safe and reliable (recall that we are basing this enrolment on a subjective prior which has no objective significance, so that if the treatment is toxic or ineffective these patients are being assigned the treatment with zero chance of getting an alternative treatment)?^{97,98} Second, is enrolling patients into a trial whose stated aim is to modify a series of posterior personal probabilities ethical?

The global reliability of Bayesian methods is difficult to determine, although they can be shown to be internally consistent by the famous Dutch Book argument (an argument which we believe to be misleading, in that individuals are at best very bad Bayesians, even with the help of statistics).^{99,100} Something can be said, however, about the methods recommended for ensuring that the construction of the trial is sound. As stated previously, many Bayesians use randomisation, although it plays a much less significant role than for classical theorists. However, the most important tool in Bayesian construction is knowledge of confounders, which are to be listed and deliberately grouped or deliberately spread evenly between the trial groups. In historically controlled trials, the Bayesian must rely on good quality (comprehensive and accurate) historic case records to construct an equivalence group. Both of these methods involve a very large amount of judgement, and so a greatly

increased risk of physician introduced bias, unless the physician is exceptionally perceptive (and so may have a very high prior anyway, which no trial could improve on very much?).⁹⁷ It is these factors – more than many others – which randomisation and blinding were devised to overcome.

As for the ethics of trials aimed at raising a personal probability, is this an appropriate endpoint? The classical trial aimed at knowledge (justified true belief, publicly presentable and rationally defensible). Provided the techniques used are reliable (within the usual constraints on scientific epistemology), the trial is supposed to deliver stable factual knowledge about the effectiveness of a treatment. It is true that one may want more: a set of probability tools for determining how to take treatment decisions for particular patients, for instance, and this is what Bayesian methods are good at. However, the Bayesian method in trials does not, it seems, deliver factual knowledge, but a policy decision for the attending physician. Nothing guarantees that other physicians will accept this; what they are invited to do is take this experimentally derived posterior for their personal prior – but what reason have they to do so? Also, there is a problem of interpreting the posterior probability. In Bayesian theory it represents a degree of belief; but belief in what? Effectiveness? Or does the probability represent an estimate of degree of effectiveness in this case? Or what? Imagine being faced with a patient in a certain condition, armed with a treatment and a personal probability of 0.8 about its effectiveness. What does this mean? The most obvious meaning is that 4 times ex 5 I should believe that it works (should we throw some dice?).^{57,59}

We would argue that Bayesian methods are fine for decision theoretic judgements which agree to take classical objective probabilities as binding priors and then assign personal utilities as weights in a decision making process. We cannot accept, however, that Bayesian methods are entirely ethical grounds for entering patients into the treatment arm of a trial. Nor do we accept that the Bayesian has compelling arguments against randomisation – unless those arguments are taken to be sceptical arguments tout court.

A review of the standard issues of ethics and the clinical trial

Most space has been devoted to analysing the statistical and epistemological arguments concerning the role of randomisation in the clinical trial,

simply because randomisation is the most puzzling (to many) – and most debated – element of the RCT methodology. Most features of the RCT are shared in common with other types of clinical trial, and it is arguable that the only ethically simple medical research on patients is the uncontrolled (or historically controlled) experiment using the innovative therapy on its own, subject to full voluntary consent by the patients. This is apparently simple, because only patients likely to do well on the novel drug are enrolled, they consent to receiving the drug, rather than to participating in the experiment (which is more complicated), and it may be supposed that if negative outcomes appear likely, the patient (or the trial as a whole) can be taken off the innovative programme fairly easily.

In fact phase II drug trials are like this, but the inferential quality of such a trial is low. We have no reliable method of estimating the effect due to the drug, as opposed to placebo effect. Phase II studies use a small number of patients, usually in a desperate condition, and the purpose of such studies is usually only to provide an estimate of the tolerable dose of the drug. Other circumstances where uncontrolled trials of treatments may be useful are studies where the quality of the evidence does not need to be very high, because the outcome is useful to know about but is not safety or cost critical. One might want a randomised study of whether taking a small dose of a substance three times per day is preferable to taking a large dose once per day. Most of the time this can be found out by some other means. The RCT gives the best quality of evidence: we do not always need to have this level of evidence to learn something useful. The sort of situation where we need this high quality evidence is the situation where randomisation will do some work for us, that is, when we are reasonable to expect confounding variables to be numerous. This is true of most pharmaceutical innovations, and of many surgical innovations too.

Before we consider why some features of the RCT are sometimes claimed to be unethical, we should remember what the alternatives are. Few quarrel (and Urbach is one of them) with the statistical superiority of randomised trials over unrandomised ones. This superiority can be illustrated by modelling techniques.^{94,95} The main consequence of the superiority of RCTs over other CCTs is that in the latter you need more patients to be enrolled into the trial to accept the same outcome with the same degree of confidence. Enrolling more patients exposes more patients to the risks of the trial (such as they are) and to the additional worry of the consent process; and means that the trial

will take longer to enrol sufficiently many patients, so that it takes longer to complete the trial, and so non-trial patients will have to wait longer (and more will be affected by the wait) to get access to the drug post-approval. In addition, just because the evidence obtained in a non-randomised study is likely to be less conclusive, the chance is that one or more further studies – involving still more patients – will be required to settle any controversy. The ethical choice our society has made is to consider the rights of the patients enrolled as taking priority over those of present and future patients not enrolled; but these other considerations mean that where a randomised trial is methodologically desirable and can recruit sufficiently many patients it is not on the face of it ethical to substitute any other form of trial.

The main points of the ethical critique of the RCT are as follows. Not all trials are necessary – sufficient proof for the efficacy and safety of the treatment already exists. Not all trials need to be controlled trials. Not all controlled trials need to be placebo-controlled trials. Not all controlled trials need to be randomised trials. Trials are sometimes continued beyond the point where true uncertainty about the merits of the new treatment remains (it is either clearly beneficial, or clearly non-beneficial, or clearly harmful, before the complete cohort has completed the protocol). Only releasing the drug inside the trial until completion of the trial means that some people who clearly would benefit from the new treatment do not receive it because they are not members of the cohort. Only licensing drugs which receive testing in a controlled trial means that some drugs which would be of benefit to people with rare conditions go unlicensed and so – for the most part – unused.

Most of these issues have been analysed and reviewed very satisfactorily by our sister project in Birmingham under Richard Lilford (NHS HTA Project 93/41/2). However, it is worth discussing them for the sake of completeness and to apply the lessons of our discussion of the statistical and epistemological basis of the trial.

Are trials necessary and useful to participating patients?

Several of these issues bear on the necessity and utility of the RCT as a universal method. As just pointed out, the RCT determines a high standard of evidence; and the appropriateness of standards varies. Just because the RCT is complex to organise and expensive – and often when done, done badly (from the point of view of actual randomisation, reliability of the methods of analysis used, or quality

of consent obtained), it is important to know when the RCT is appropriate and when it is not. It is perhaps not asked often enough what the study is meant to achieve. All the authorities agree that a trial is useless and unethical (because of the waste of money, time, patient confidence – all scarce resources best put to other uses – and the increased exposure of patients to risks) if it is not meant to answer a well-posed question to which we do not already know the answer. Not knowing the answer is what is effectively meant by “equipoise” – we do not know either way. Sometimes it may be necessary to illustrate what our uncertainty consists of; certainly any proposal should contain a good literature survey indicating what is and what is not known on the relevant point.⁶ It is important here that our definition of evidence not be circular: it is not always sufficient justification for an RCT that there has not been one yet so there is no evidence yet. This problem of the meaning of “evidence” and “sufficient evidence” is, formally, an open one in the philosophy of medicine. One reason to prefer statistical experiments is just that the concept of statistical evidence is so much better understood. This is the main plank of the case for the Cochrane Collaboration.^{5,21,101}

When people argue that an RCT is not needed because sufficient evidence already exists, they either mean that the therapy has been proved beyond reasonable doubt (evidence for which we can reasonably ask for), or that the trial need not be randomised. The arguments advanced to do with the methodological role of randomisation mean that either the critic must show that confounders are unlikely to pose any problems for the inductive inference we will need to make instead, or that randomisation would be cruel – or consent for it impossible to obtain. The case where randomisation would be cruel is a case where one might reasonably expect patients to have a preference for one treatment over another (perhaps the distribution of this preference is balanced enough for the trial to have two arms, or perhaps not), and that to give any patient the alternative might prove disastrous for that patient’s well-being; or for that patient to undergo the worry that, at random, they might receive their dispreferred option, would also be cruel.^{13,102–104} In this case randomised studies might have to be foregone altogether, or a randomised study could be run in tandem with a self-selecting case-controlled study. Cases such as these – for instance a study of the efficacy of radical mastectomy versus lumpectomy – will usually involve some major known side-effect (psychological or otherwise), so that the patient’s preference is shaped not only by the effectiveness

of the treatment with respect to the main variable (lifetime, in this case) but also by the costs associated. Here there is a case for making the outcome variable something like a quality-adjusted life year (QALY), rather than simply lifetime.

Can trials respect patient preferences?

There may be some patients who are content to be randomised, and if there are enough, it would be paternalistic not to run a randomised study on the grounds that other patients are not so content. The role of patient choice here is increasingly important, and the Zelen designs are often discussed, where patients may be pre-randomised between treatment and control arms, or where more than two arms are run in a trial, and patients can choose whether to be randomised or not, and if not can choose which treatment they would prefer.^{14,62,63,65} The fact that the latter designs involve vastly more patients, have difficulties of interpretation, and arguably often tell us more about patient hopes than preferences is troubling.⁶² If the premise of the trial is that we have no sound reason to prefer one treatment over another, so far as the chief outcome variable is concerned, then in many cases the significance of patient preference for one treatment over another may have more to do with the desperate desire to gamble now rather than wait for a more certain answer. This is not to be scorned. There are ethical problems, however. Patients who select themselves into a trial are likely to be more pushy than their fellow sufferers (not a fair criterion for selecting among eligible patients when the treatment is scarce or costly); and they are perhaps more likely to demand to switch arms if they suspect their arm is not doing as well (see below).^{14,105}

So-called randomised consent designs, where patients are randomly assigned to the treatment arm or to the standard or placebo arm; and patients in the treatment arm are asked whether they would like to receive the experimental treatment until a sufficient number say yes to analyse the data at the end, pose serious problems of consent. Patients who are in the non-treatment arm have been enrolled into an experiment, but either do not know, or do know but do not have the choice to receive the new treatment; for if they had the choice we would have an ordinary self-selected non-randomised trial.⁴⁸ If they are in a trial unknowingly, it seems that the consent condition has been breached. This may be an empty paradox – patients who are not in the trial at all are in the same position. Yet why should one group be randomly selected to have a choice and another selected not to have it? More importantly, if

consent is connected with a psychological variable that is a possible confounder (because likely to be linked to the placebo effect), this confounder has not been controlled for in any way, nor has it been randomised for. The randomised consent design is a poorly thought out model of unnecessary complexity which collapses into a self-selected treatment group controlled through an ill-matched matched pair.

A simple preference for one treatment over another, judged not on the grounds of the relevant side-costs but on a patient's guess about which treatment is more effective is not enough to warrant non-random allocation, although in selected cases the doctor may decide that higher principles of medical ethics warrant giving the patient the experimental treatment on a "named-patient" basis. This is particularly important in a related case, that of new treatments for rare conditions.¹⁰⁶ A dogmatic insistence by regulatory bodies that the RCT (or other prospective controlled trial) is the only basis for licensing a treatment does sufferers of rare diseases a severe injustice. However, some method of learning from treatment of patients under these circumstances is needed, and this is still being debated.

Do trials continue too long?

The main ethical worry about the conduct of trials that relates to methodological issues is the worry that once a trial has begun, it may continue past the point where serious doubts remain about the efficacy or safety of one of the drugs.^{40,42-44,72,107} This is one area where Bayesian statistics are supposedly superior, because they have a method for determining when this point is reached: one sets a level for the posterior probability to reach below (or above) which the trial must stop. In fact, classical statisticians also permit the trial data to be analysed on an interim basis, and also permit early stopping if one of the interim hypothesis tests indicates that the preset level of significance has been reached. The problem that must be solved is that unless one has a very large trial (and a very low type I error rate), the type I error rate of such interim analyses of smaller populations (of the subjects who have already completed) is likely to be high – possibly too high. If the interim type I rate is not too high – say it is 1% (a standard choice) – one may well ask, why design such a big trial (the type I rate for the complete trial being larger – say 5%)? Is a 5% rate good enough or not? It may be that a large trial can include more patients, so that if the trial is a long-term one, more people can benefit sooner. But more patients also means more people randomised to the non-experimental arm; so more people in

total running the gauntlet of uncertain risks or benefits. In fact, therefore, the kind of trial for which a classical early stopping rule is appropriate is typically the large simple trial of some preventive therapy (such as aspirin against repeat heart attacks) where the expected effect is small, but significant, and the trial is either an equivalence or a pragmatic trial, where both arms receive a treatment believed to be of some effectiveness.

The main point to remember about stopping trials is that it is only ethical if the criterion for knowledge has been met. If it has not been met, then the trial was, probably, a waste of time, and little more has been gained from it than was already known in earlier phase trials. However, we should distinguish between knowledge of benefit and knowledge of harm. Mostly, we focus on benefit, because future treatment policy rests on it. If we decide that a treatment is ineffective, or less effective than existing treatments (which might be partly a judgement about cost, too), then it will be shelved, unless and until it turns out to be possibly effective for some other condition. If we decide that a treatment is harmful (and this requires some care in definition), we will not use it again at all. Almost all drugs have some degree of toxicity or some unpleasant side-effect; harmfulness therefore means more dangerous than the disease we are treating – most chemotherapy is toxic at a level near the effective dose, but it is used because it may defeat the cancer without killing the patient first. Our criterion for harmfulness in a drug is usually coarser than our criterion for benefit, so that we will accept more false judgements that a treatment is harmful than false judgements that it is not. So we should make it easier to terminate a trial with evidence of harm than with evidence of benefit. Most data-monitoring is done with this in mind.

It is no longer even usually the case that treatment trials need to be placebo controlled. If they are, there is good evidence to suggest that patients are reasonably good at seeing through the blinding of the placebo, and compliance will probably collapse unless most patients think they are deriving some benefit anyway. Most trials are analysed on an "intention to treat" basis, because compliance with, or tolerance to, the treatment is regarded as an important feature of its effectiveness.^{108,109}

We might ask whether the termination of one arm prior to another means that some patients continue in the trial beyond the point where the effectiveness of their treatment is in question. Suppose the new treatment is harmful (we can assume that the standard treatment or placebo is not harmful,

since they are “older” and more well-known in their effects); then the trial is terminated, and every patient is switched to the safer treatment (or to none if there is none). Suppose instead, that compliance rates for the new treatment fall off but are significantly greater than zero. This may mean that the new treatment is hard to tolerate for some patients, but for the remainder is effective. Suppose, that the placebo or standard compliance rates fall off, but the new treatment arm’s does not do so (or does so more slowly).¹¹⁰ This does not by itself imply that the new treatment is more effective than the alternative – it may be more tolerable but less effective. And that would not warrant switching all the lapsed placebo or standard patients onto the novel treatment arm.

In most cases, therefore, we cannot conclude anything which warrants switching patients from their original protocol assignment prior to the end of the trial. The only reason we might have for doing so is where there is a strong patient demand for the right to exercise a preference; if that is the case the patients’ demand may be respected, conditional on various things. In the first place, they must consent to taking an untested drug, with all the additional risk that implies; secondly we must be reasonably sure that everyone has a fair chance to volunteer (subject to eligibility); thirdly some sort of co-operation between doctor and patient will be involved so that the knowledge of the progress of the randomised and non-randomised parts of the trial is shared and so the volunteer patient can update his choices.^{111,112} The patient of this type will be a co-investigator of some kind, as a result of these provisos.^{51,61}

Such a patient is apparently privileged, and has far more choice and information than most subjects in RCTs. Is this fair? It might seem not. In fact, the patient has, we expect, no greater reason to choose one drug rather than the other than the doctor does. That is, both doctor and patient should be in rational equipoise.⁴¹ The fact that the patient does not do so may be a reason to offer him the choice; or it may be a reason not to do so – it may be regarded as a withdrawal of consent. The circumstances under which patient choice might be permitted to override equipoise plus randomisation (with whatever costs in terms of quality of evidence, additional enrolments, and increased difficulty of analysis) are, as mentioned, cases where the secondary outcomes of the two treatments, *ceteris paribus*, are very different and patients have a

distinct preference for a choice, and cases where the disease is so troubling that patients would rather gamble for themselves (by guessing and choosing) than have someone (or something) make the gamble for them (by randomisation). The issue turns on what people are being asked to consent to: consent to an innovative treatment, consent to an older treatment, or consent to randomisation as treatment.

Conclusion

The beginning, middle and end of the ethics of trial design is the belief that the new treatment will turn out safe and effective, and probably superior to the alternatives, combined with the knowledge that without experimental evidence upon which reliable inference can be based it is not ethical to give the treatment to patients without their consent to acting as experimental subjects. Randomisation is a servant of this aim, and not all experiments require its use. However, in situations of equipoise and where confounders are numerous randomisation is the most satisfactory and ethical method of distributing confounders, variations, risks and benefits. There are many ethically troubling features of the RCT, but it is not clear that any alternatives to the RCT are ethically superior just because they are less epistemically reliable.

Recommendations

- Research programmes involving clinical trials should avoid systematically drawing on some socio-economic groups for their research subject, unless there is some *prima facie*, well-attested medical reason to do so, and there is a clear link between the socio-economic group in question and the medical problem under investigation.
- Experimental methodology should be well suited to the nature of the scientific question under consideration, rather than chosen on some “philosophical” grounds, simply because philosophy is neutral about most methodologies and therefore recommends pragmatism. Ethically, there is nothing to choose between “Bayesian” and “classical” designs – save on the criterion of which method will be more reliable and informative in this or that case.

Chapter 3

Autonomy and informed consent in the ethics of the randomised controlled trial: philosophical perspectives

Introduction

There are two central principles in human experimentation ethics. The first is that the experiment should be scientifically sound and present a fair proportionality of risk to benefit to the subject. This is uncontroversial, although as we saw in chapter 2 it can be difficult to spell out this principle in detail in practical situations. The second principle is that no one should be enrolled into an experiment without their express, informed consent. In what follows we examine the arguments used to defend this principle, and the arguments used to defend departures from it (including the ways in which departures are sometimes tacitly brought about sans argument). The legal context of the consent doctrine, which is not specific to clinical experimentation, and which is in any case well known is not discussed. Nor do we discuss in depth the arguments about consent by minors or the mentally ill, because these are covered in detail by our sister project (93/41/2) and because the “socio-cultural” dimensions of the debates about consent bear upon the very idea of consent and the kinds of subject who can give it validly. As discussed below, some cultures restrict the class of “competent subjects” further than Western cultures do, and some cultures regard consent as problematic even for “competent” subjects.

The randomised CCT is a type of experiment on human subjects. As such, it falls within the domain of the “Nuremberg Code”, and the “World Medical Association Declaration of Helsinki”.^{28,35} Both of these codes were framed with the Nuremberg War Crimes trials in mind, and sought to specify minimal conditions on human experimentation, such that basic human rights should be protected and respected in all experiments which use human beings as subjects. The aim of these codes is essentially protective; and the philosophical premise of the rights which are described – or perhaps stipulated or constituted – by these declarations is individualist.^{111,112} In other words, each individual’s well-being and integrity take precedence over the interests of the social body, especially the fraction

of the social body which is the state.^{113,114} This is, of course, directly targeted against totalitarian doctrines which hold that on certain occasions, or for certain groups of subjects, the interests of the state (or the remainder of the social body) are taken to be rights, and take precedence over those of the individual subject.

We will concentrate discussion on the Nuremberg codes provisions, because it is the simplest, clearest and oldest relevant code on ethics of experimentation. The later Helsinki codes preserve substantially the same position, but devote much more attention to explaining the notions of risk and benefit, which clarifies some considerations about fair risks for incompetent subjects. Arguably the Helsinki codes weaken the force of the Nuremberg principles, however, and for clarity about the stakes in the debates on consent we concentrate on their original expression in the Nuremberg code.

Voluntary consent

The first principle of the Nuremberg code states that for research to be ethical, “the voluntary consent of the human subject is absolutely essential”. In other words, each and every subject in the experiment must give their voluntary consent to be part of the experiment. As this stands it is very unclear what is required; is it enough to say to a subject “would you like to take part in an experiment?” without saying any more? and would an affirmative reply constitute consent in the required sense? Not yet, because the test of voluntariness may not be passed. As this test of voluntariness is the nub of the matter, we cannot leave it with the investigating physician’s own satisfaction that the patient (or healthy volunteer) has consented voluntarily. Indeed, remembering that the Nuremberg Code has a legal dimension as well as an ethical one, some criterion assessable by a third party is required.¹¹⁵

Not only is the principle much more vague than its simplicity seems to imply, it has also some medically

puzzling features. It seems to rule out any experimental procedures where the normal condition of the subject is such as to rule out voluntary, or even involuntary consent. Under this test, no experiments seem possible in emergency medicine, in perinatology, in psychiatry or clinical psychology, and probably in most paediatric medicine. Arguably, it disallows any research on pregnant women, not because the women cannot give consent, but because the foetuses cannot.^{116–121} The principle is quite explicit: and so-called proxy consent is no consent at all.^{122,123}

However, while this principle is somewhat difficult to apply, it is also apparently philosophically neutral and uncontentious. It is a piece of “ordinary language” which could be understood in a variety of philosophical senses. The principle is asserted without justification or thought of justification. If we accept the principle in the spirit in which it is posed, we do not need to worry too much about whether we are consequentialist, deontologists, Marxists or Buddhists.¹²⁴ There is no more to be said: it is one of the ground-rules. Any of these theories may be adopted, and we can construct accounts of what the principle means and how it is to be justified in each theory, but this activity tells us more about the theory, than it does about the principle. Like the commandment to do no murder, it is a core principle of our morality which we can theorise about, but may not theorise away. Therefore, the medical worries are best taken as anomalies for medicine: and if no experimentation is legitimate in those areas, so much the worse for them.

Premises of the consent requirement

Let us examine the premises of the argument. In the first place, we took it that the principle of voluntary consent is a moral rule. Next, the principle takes as read the principle of individualism as mentioned at the outset. Third, there is a clear distinction between experimental and other sorts of medical care.^{125–127} Fourth, there is the presumption that human subjects need protecting.¹¹¹

If we want to avoid the conclusion that much medical research will become impossible if we grant the principle of voluntary consent, then we will need to weaken or discard one or more of these premises. Before we do this, let us reflect on what this principle does not say.

Nothing philosophical is asserted about voluntariness or autonomy or personhood: but it is clear that each human subject – whatever we take that to

mean – must voluntarily consent to taking part in the experiment, whatever voluntary consent is.^{128–130} The words here have, at least, their common-sense meaning. So, for example, an unconscious patient has not consented.^{131–134} Nor has a member of a football club consented to participate, simply because his club chairman has indicated that his club as a corporate body will participate in the experiment. Only human subjects are mentioned in the principle, and whatever a collective is, it is not a human subject. This is an important point, because the other domain in which consent is an important concept is the domain of political theory, where consent is precisely a matter of collectives, and an individual’s right to withdraw political consent is very problematic. If this right exists, the citizen’s power to exercise it is very limited. In summary, the principle of voluntary consent is not – or not as it stands – a principle of informed consent or of autonomy. Each of these popular reformulations of the principle are attempts to escape some of the puzzles of the principle of voluntary consent as it stands, either as substitutes or as amplifications which block some of the more paradoxical features of the raw principle.

The principle makes no claim to sufficiency. We can easily imagine “experiments” where a number of human subjects voluntarily consent to take part, but we would not (as outsiders) regard these experiments as ethical. The authors of the Nuremberg Code reflect this point, by following the principle of voluntary consent with a series of nine other principles. The bulk of these concern experimental risks and scientific utility and competence. The final two principles state the right of the subject to leave the experiment at any time (subject to a condition which will be discussed later) and the obligation of the researcher to terminate the experiment if the experiment becomes, in its process, dangerous to the subject. This last principle, stating the investigators duty to terminate an experiment early under certain conditions, will prove troublesome when we look at RCTs.

The final element about which the Nuremberg Code is silent is the element which the Helsinki Declaration faces directly: the nature of specifically medical obligations to patient subjects in biomedical research. Nothing in the Nuremberg Code is intended to have specific relevance to this issue. This is slightly puzzling because the Nuremberg Code is addressed to the medical profession and speaks of “Permissible *Medical* Experiments”. But nothing is said concerning the experimenter’s obligations *vis à vis* the Hippocratic code of medical ethics (or indeed any other *vade-mecum* of medical

obligations, responsibilities and purposes). The authors of the Code state that most experiments, to the best of their belief, do “conform to the ethics of the medical profession generally”.

Note at this point that medical ethics is conceived not on an individual basis but a collective one: the duties of the doctor are framed as elements of a professional ethic, not as duties analytically derivable from the concept of medicine. There is something of a tension in later developments of medical ethics between perspectives which emphasise the collective and traditional, or socio-legal, foundations of medical right, and those which emphasise supposedly self-evident principles of medical good practice (substantively or procedurally justified).

Consent, experiment and treatment

The question of the relationship between the principle of voluntary consent and the ethics of routine medical practice is open, so far as the Nuremberg Code indicates. It may be that the principle of voluntary consent is an additional and independent principle which supplements those of medical ethics in experimental contexts. Or it could be that the principle of voluntary consent is logically independent of the ordinary principles of medical ethics, and the possibility exists that the two sets of principles will conflict in some situation. Or it could be that the principle of voluntary consent applies in all experimental situations involving human subjects, and the principles of medical ethics amplify and supplement this principle in just those cases where the experiment has some medical significance; for instance where the human subject has been enrolled into the experiment *qua* patient.

Most of the experiments (or pseudo-experiments) which the authors of the Code had in mind were experiments of no direct medical merit *for the subjects* (not all of the experiments were medically uninformative, although many were, and there has been some debate about whether the use of the results of these experiments was legitimate, given the way in which the results were obtained). Many were of no direct medical relevance at all, being natural-historical or physiological in character. As such, these experiments could not be considered part of normal or innovative medical care. The point of the principle of voluntary consent was to ensure that experiments of this kind were legitimate, subject to consent. Naturally, in many cases the conduct of these experiments would require medical help to be on hand, or indeed that the investigator be a medical professional. Whether all such experiments had to be carried out under

the scrutiny and professional ethics of the medical profession is probably an issue in disciplinary politics rather than law or ethics. On the one hand, so as far as ethics is concerned we can rule out the first possibility that human experimentation is a specialised branch of medicine, and should be governed by medical ethics as supplemented by the principle of voluntary consent. On the other hand, we can accept without further comment the argument that the principle applies to all human subject experiments, but needs supplementing with the ethics of medical care when the experiment is carried out using subjects who are patients (even if their patienthood has nothing to do directly with the topic of the experiment). Or can we?

Is consent consistent with beneficence?

The second possibility (having dismissed the first and accepted the third) is that the principle of voluntary consent conflicts – either always or on occasion – with sound medical ethics. We saw that the raw principle seems to conflict with medicine in some common cases (children, the mentally incompetent, etc.) Many writers have argued that medical experiments – especially the RCT – involve a conflict of principles, or, on many accounts, of roles.^{47,104,135a,135b} The role conflict they have in mind is the conflict between the investigator as doctor and the investigator as scientist; and to complicate matters further we could balance that with a conflict of roles between the individual as patient and the individual as subject. To our knowledge, no one refers to the latter conflict in these terms, although in medical sociology and history writers are familiar with the “sick role” (and its decline), and increasingly authors involved with patient advocacy issues (especially in AIDS research) are insisting that patients should have the right to choose the subject role.¹³⁶ To further muddy the waters, the conflict of roles is conceived as a conflict of role-founded duties; and so we can complete the picture by inquiring about role-founded rights.

Overriding consent?

Does duty override consent?

Given the protection-oriented nature of the Nuremberg Code it is natural to emphasise the duties of the investigating physician and the rights of the patient-subject. Also, in context, it is natural to suppose that arguments about the rights of the physician and the duties of the patient-subject are to be resisted. The sort of duty which could be conceived and which the authors of the Code want to resist is a duty on the part of the patient

to society at large.^{111,112,137,138} What the authors presumably want to resist here is not the idea that I may regard myself as owing a duty to my fellow citizens, or to my species, but that society may impose such a duty upon me, with attendant sanctions. A natural analogy might be drawn between the duties a soldier owes to his state and the duties a patient might be taken to owe; and in particular the duties a citizen owes to the state in the sense of an obligation to undergo military conscription. The core of the obligation to undergo conscription is the so-called “free rider” problem, where individuals enjoy the use of some social good (for instance civil liberty) without contributing to the social (and economic) costs necessary for the maintenance of that good. Conscription aims, among other things, to distribute fairly the chances of paying with injury or death the military costs of a state’s liberty, in such a way as to avoid the free rider problems that may be judged to arise if a war is fought with only voluntary enlistment. A similar argument concerns the development of new drugs. Drug development always involves testing for safety and efficacy on human beings. Since some people will be needed to be subjects for any given innovative treatment, is someone who persistently refuses to take part in drug testing as a subject, but who benefits from the outcomes of such testing, to be regarded as immoral? And if they are, what social sanctions might be merited? Related to this is the argument that convicted criminals might be regarded as owing some measure of participation in human experimentation as part of their “debt to society”, either because they have partially forfeited their right to refuse consent, or as a full or partial substitute for their penal servitude.^{113,139–141}

The relevance of these arguments, which have an alarming sound to the liberal ear, is that many of them were tacitly or explicitly accepted in many states at the time the Nuremberg Code was being framed. And furthermore, the statist character of these arguments may be regarded as tendentious, but the moral arguments from analogy to what most liberal democracies (and perhaps all states) are prepared to accept are not trivial to refute. It is better to understand the refusal to press the analogy as founded not on self-vindicating moral principles, but on a stipulation that this is the set of moral standards in this limited area which the global community will now adopt and commit ourselves to abide by. The problem with this is that the principles of the Nuremberg Code were in part intended to be self-evident moral principles, against which the activities of figures such as Dr Josef Mengele could be judged. Later revelations about experiments carried out by

Allied states following (tacitly or explicitly) the analogy between conscription and a “duty” to participate in experimentation only underline the ironies of the Nuremberg stipulations; they do not, for all that, detract from the rightness of those stipulations.^{142–145}

Duty and voluntary action

The gap that must be kept open is the gap between recognition that one may morally be under some partial obligation to take part in human experiments in the medical field and a statist position where this duty can be imposed upon citizens. One argument which may assist us is the argument that whereas military and fiscal obligations are citizenship duties, rather than social duties; and the putative duty to participate in medical experiments is if anything, social, and not connected with citizenship. The analogy here that could be stressed is between the need for suitable subjects for medical experiments and the need for volunteer blood-donors. Another analogy may be with duties to charitable giving and to voluntary work in the community. Duties of this kind admit of a variety of interpretations, although most people will admit them, whatever their rationale for doing so. It might be that the religious tenets one adheres to stress charitable giving, for instance. A key feature of duties of this kind is that typically they are only regarded as meaningfully satisfied when the duty is voluntarily performed. There is a complication here: many states partially replace this duty with another kind of duty, the duty to pay progressive taxes as a redistributive measure, or as part of a welfare programme. This sort of enforceable duty is sometimes argued to be destructive of charitable virtues, and many resent doing under obligation what they would happily do out of charity. This type of argument is often made by communitarians.

So once again we return to voluntariness, as referred to in the Nuremberg Code, where we first met it as a barrier to coerced participation, and now we meet it as what makes participation morally significant. This consideration was not in the minds of the authors of the code, however. At this point we should underline the claim that the statist argument about obligations to participate, and the state’s right to demand participation rests on an elision of citizen and social duties. It is the defining characteristic of totalitarianism that it conflates the political and social spheres; and so the refusal to accept human experimentation without voluntary consent is all of a piece with the authors of the Code’s rejection of National Socialist ideology. We should recall in this connection two of the statist’s arguments. The first is the argument from

the economic free-rider problem; and the second is the construction a statist may put on consent by analogy with consent to be governed.

Free riding

The relevance of the first of these arguments will become plain if we consider that the free-rider problem is drawn from economic theory, rather than pure political theory; and this draws our attention to the point that the free-rider problem is a problem for any collective organisation, not only the state. It is also relevant to systems of health-care considered as partially or fully autonomous of the state apparatus. Typically insurance-funded healthcare systems handle free ridership *vis à vis* medical experimentation not by penalising non-participants, but by rewarding participants with partial or total waiver of treatment fees. In fact this oversimplifies: hospitals do not charge patients in trials for the costs of the drug under trial, recovering the cost either from some research agency, or in kind from the drug companies. Many insurance companies will not pay for experimental treatments, but only for accepted treatments, and the costs of the experiment are borne not by the subjects, but by future patients and present and future taxpayers. This raises the issue of whether this waiver of payment should be understood as an inducement to participate, and more of that in a moment. Healthcare systems, such as the National Health Service, which impose no costs on patients have no financial mechanism for encouraging patients not to be free riders, and rely instead on a mixture of desperation, altruism, and (perhaps) paternalism to encourage participation. And the social risk which accompanies this method is that the parallel membership of the British state and the British NHS which is enjoyed by all citizens of the UK might encourage an investigator to treat this not as parallel membership of two institutions, but as membership of a single institution, thus eliding the citizen and social duties. This, arguably, took place in the US in the notorious Tuskegee experiments, and this interpretation might be put on the cases reported by Beecher and Pappworth in their famous “human guinea pig” exposes of the 1960s.^{139,140,145} These works were of great importance in establishing the “informed consent” test in research ethics, as relevant not only in court judgements about totalitarian regimes, but also in liberal democratic states.

“Inferring” consent

The relevance of the second argument is as follows. Is there an analogy between political consent and

consent to participation in a medical experiment? In political theory only some minority positions hold that the consent of the people to be governed is irrelevant to the legitimacy of the state (a minority nowadays, that is!) However, with the exception of anarchists and some theorists of direct democracy (as exemplified, perhaps, by the Swiss), almost all democratic theorists regard consent as a variable which only needs to be measured relatively infrequently, and can be assumed to behave smoothly between measurements. Consent to any particular political decision or piece of legislation is taken to be consequent on the so-called electoral mandate: and this is an assumption with bite. It is never normally regarded as a sufficient argument in court that I cannot be regarded as guilty under some law unless I accept that law as binding upon me.

One might make an analogy between this and the medical case as follows. We have separated out the medical and the state spheres, let us assume, but surely once a patient presents himself he can be taken to have consented to be treated, whatever that may involve. And if the treatment administered is experimental, but consistent with what some reasonable doctor might do in the circumstances (and this is, very roughly, the “Bolam” test applied in English law), then the spirit of the consent can be said to have been respected.

“Medically indicated” treatment

Various elements of medical phraseology reflect this theory of what role consent plays, in particular the concept of “medically indicated treatment”. Where there is a choice of treatments, with differing effects, but which are probably indifferent with respect to their efficacy with respect to the patient’s primary condition, then the doctor may ask the patient’s opinion about which course of treatment they would prefer. While the doctor may discuss the treatment preferences with the patient well before this point is reached, there is no expectation that this is morally or legally required. This perspective on the role of consent and the doctor’s expertise is frequently known as paternalist, because it is founded upon the notion that “doctor knows best”.^{146,147} While it has a paternalist flavour, however, if it is problematic that is because the notion of consent is notoriously difficult to pin down, particularly in the medical context.^{148–150} Even the paradigm of competent consent – informed, voluntary and autonomous consent by an educated and reflective adult – has an inferential component, for instance in surgery, especially under general anaesthetic (or even prior to its administration, where something like an advance directive is implied).

It is relatively easy to block the inference to consent in the case of the prisoner; the statist might say that the prisoner consents to his punishment, which consists in giving up certain civil rights for a period, and from this we can infer that this consent covers limited medical experimentation (of a severity commensurate with the measure of punishment being meted out). That this inference needs blocking is explicitly recognised in the Helsinki declaration, where experimentation using prisoners as subjects (even as volunteer subjects) is regarded as unethical because it takes advantage of their vulnerable position. Also, we should distinguish inference to consent which is based on a counterfactual reconstruction of what this subject would say – if they were conscious or mentally competent – from inferred consent of the cognitive type; and both of these kinds of consent need to be distinguished from inferred consent based on what we can call role-expectation.

Cognitive inference

Cognitive inferred consent is my consent for you to do a certain procedure under an accurate description for laymen, from which it can be inferred that whatever is technically necessary to fill in the detail in carrying out that procedure is consented to as well, even though I cannot explicitly be said to consent to it. This sort of consent involves an element of trust in the competence and expertise of the doctor, which involves in its turn a standard of “what reasonable medical opinion would accept”. There is a continuum here with my acceptance that the doctor has correctly diagnosed my condition, without my need to verify this myself. I have a right to expect that the doctor knows what he is doing, and why he is doing it.

Counterfactual inference

Counterfactual reconstruction of consent also builds on inference from what the patient explicitly consents to prior to operating, or prior to temporary incompetence. It is involved in situations where some course of action has been consented to, and some additional course of action may become indicated, or perhaps convenient, in the course of treatment, when the patient is unable to be consulted. A typical example might be appendectomy in the course of some operation on the digestive tract unconnected with appendix problems; this is sometimes done as a preventive measure, and for convenience, although this is less commonly done without prior consent than it used to be. In any case, it is risky to extend consent in this way because the extension is so unreliable, as the recent case shows of a surgeon carrying out a “medically indicated” abortion in the course of some surgery,

without prior consent. In many cases this inference will be straightforwardly illegal, under criminal law, because it involves an illicit “touch”, that is, a common assault (or worse). This extension quickly shades into what I claim is illegitimate inference to consent, viz. consent inferred from role-expectation.

Paternalism

In this case, rather than building in a limited way on consent to some specific course of action, a doctor may judge that simply because a patient has put himself into his hands, the patient may be taken to have certain expectations of what a doctor is, and infers the patient’s consent to whatever the doctor deems necessary without further consultation. This is the essence of medical paternalism. In fact, it has only been agreed that medical paternalism is ethically unsatisfactory in relatively recent times. Less than 20 years ago, articles in the *Journal of Medical Ethics* (the leading journal in the subject in the UK, frequently read and contributed to by the medical professions as well as the bioethics community) were published making the defence of paternalism (not in so many words!) on the grounds that “informed consent” was *prima facie* impossible, and so consent could be obtained by the investigating doctor referring himself to the patient’s appointed medical representative.¹⁴⁷ Occasional defences of paternalism are still published, usually based on some argument about information and comprehension.

Imperfect communication

Arguments of this kind have an important truth, as consultation of empirical articles about actual patient comprehension indicate. Patients, for a variety of reasons, linguistic, educational, psychological and social, frequently do not fully comprehend what they are being asked to consent to, or why, or in what their consent consists, or how far it extends.^{13,151} This is so on most tests – the most telling being the test of recollection: can they, after a decent short interval recall what they have consented to?^{152,153} Whether one is entitled to conclude from this that the consent process is a waste of time, or dispensable at any rate, is a moot point, and one that has occupied much space in the medical and ethical journals. Our opinion is that there is something suspicious about drawing absolute conclusions concerning the utility of patient consent from facts about the difficulty of achieving it. This is especially to be resisted when much of that difficulty may be regarded as founded upon imperfections in communication.

Linguistic barriers

These imperfections may be regarded as being of three kinds. The first kind is contingent, where some individual or group of patients is unable to understand the information given, either because the information is insufficiently informative, or because the language used is obscure, or because, simply, the patient or doctor is not fully at home in the language being used (perhaps, as in a case reported in the *British Medical Journal* recently, they are first generation immigrants from Vietnam who have learnt English late in life).¹⁵⁴ Here all that is required is that efforts be made to ensure that these contingent imperfections in communication are removed.

Cognitive barriers

The second kind of imperfection might be regarded as necessary: simply, no non-medical professional can reasonably be expected to understand the details of the medical procedure, and so basing the requirement for consent upon a requirement that the patient understand those details would make consent almost impossible to obtain. Consequent upon that would be the necessity of abandoning the experiment.^{135b} However, the number of experiments where the patient cannot be given a balanced and comprehensible description of the experiment, such that he understands and can make a decision about consent must be vanishingly small.

Social distortions

The third kind of imperfection may be regarded as contingent but “structural”; that is the contingency relates not to any facts about the individual patient, doctor or treatment, but to social facts. The sort of social facts which are relevant are facts connected with social structure and what Habermas calls “systematic distortions in communication”, which are founded in power relations.¹⁵⁵ Examples of this include: patients not understanding that they are entitled not to give consent; patients not understanding the scientific purpose of the trial and supposing that the novel innovation is (a) more effective and (b) will be administered to them (when they may be randomised to the alternative arm); patients interest in consent to being treated not being equivalent to the doctor’s interest in consent to advance medical knowledge; differential attitudes in particular socio-cultural groups to the need for consensual decision-making and appropriate processes for making decisions; differential capacities and opportunities to exercise patients’ rights.^{135b,156–172b}

All of these “distortions” to the process of giving voluntary consent can be related in part to social

structural factors, and as such are properly the domain of social research rather than philosophy or medicine. However, there are three main points to be noted here. The first is that the social context of the consent process (both the micro-context of the sick patient in the interview room in the surgery or hospital, and the wider social, political, cultural and economic contexts of the patient) is relevant to the quality and significance of consent. The second is that consent is obtained in a situation where power is involved in quite complex ways. And the third is that consent is a sort of action (technically, a speech act of a certain kind), such that there are conditions under which verbal consent fails to be consent in the relevant way.

Voluntariness

Reflective choice and desperation

The Nuremberg Code gives an explicit gloss to the meaning of “voluntary consent” which indicates that the authors recognized that consent was an action involving understanding. The paragraph reads:

“This [sc. voluntary consent] means that the person involved should have legal capacity to give consent; should be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, overreaching, or ulterior form of constraint or coercion; and should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision. The latter element requires that before the acceptance of an affirmative decision by the experimental subject there should be made known to him the nature, duration, and purpose of the experiment; the method and means by which it is to be conducted; all inconveniences and hazards reasonably to be expected; and the effects upon his health or person which may possibly come from his participation in the experiment.”

This statement tells us quite a lot about the meaning of voluntariness. It tells us that consent is genuine only when free from intentional duress, and only when the giver is in a position to understand the significance and extent of what he is assenting to. In some ways this makes the consent requirement even more restrictive than the naked formulation, because it adds additional tests: notably the core of what later is known as “informed consent”. Most of the literature on informed

consent – and it is very extensive – concentrates on this question of what informed consent should be said to consist in. But it is also interesting that some tests we might set for assent to be consent are not mentioned, here or in any of the subsequent codes. For instance, we might regard consent given under conditions of desperation as no more genuine than consent given under conditions of duress, and the ways in which desperation can be socially generated are numerous – not only the gravity and severity of an illness, but also economic need, for instance. Consent under desperation usually contains an intention that the novel treatment be received, and so (in the RCT) does not intend randomised assignment.¹⁰³

That this is so is illustrated by the subversion of randomisation by AIDS sufferers in certain treatment trials in the late 1980s. This is a fine point. Arguably, these patients acted unethically in giving apparent consent to enrol under the treatment protocol, thus rendering the data in these trials almost useless (although usable to some extent under some interpretations), and perhaps necessitating further trials to retest the hypothesis. However, on their part the argument that to be offered a choice between getting the drug, probability 0.5, and getting nothing was not a fair set of alternatives under the circumstances. That this is so has been recognised increasingly in AIDS trials, although multi-armed trials are considerably more expensive, require greater quantities of the probably rare, possibly dangerous experimental drug, and need the enrolment of proportionately more patients.¹⁴

Checking up on consent

That the tests an experimental procedure should pass are more restrictive than those we place upon “ordinary” treatment is not surprising, but what are these tests designed to achieve? As noted above, the tests on consent are meant to distinguish valid consent from invalid pseudo-consents, specifying relevant features of each; and consent itself is meant to ensure that patients are protected from undergoing risks and harms without their knowledge and agreement. Their force, in the Nuremberg Code at least, is to force doctors to seek consent, a matter which the code is quite explicit about, making it a duty upon doctors in the third paragraph of the first section of the Code:

“The duty and responsibility for ascertaining the quality of the consent rests upon each individual who initiates, directs or engages in the experiment. It is a personal duty and responsibility which may not be delegated to another with impunity”.

A slightly curious feature of this formulation is that it makes of each doctor – in the first instance – her own gatekeeper. Later, both in Britain and in the US, an additional institution was created, the Local Research Ethics Committee (LREC) or Institutional Review Board, to oversee the implementation of this requirement and to assess all research for their ethical status (at least *prima facie*).^{173–175} However, as yet no mechanism exists for ensuring that the researcher will actually do what he says he will in his proposal, and the “with impunity” sentence in the Code is the weaker for this omission.^{148,149} Certain mechanisms exist for enforcing this protective rule, notably the public sanction of the medical journals, which may refuse to publish studies conducted without valid consent processes, and the possibility of medical negligence torts in the case of experimental procedures carried out sans consent.^{176–178} Out-and-out fraud with respect to consent is uncommon, so far as we know, and two doctors who forged signatures on consent forms were recently struck off by the General Medical Council’s professional conduct committee.^{179,180}

Autonomy as a value

What the Nuremberg principle does not set out to do is protect patient autonomy. This is a later invention, related to the famous four principles of healthcare ethics, as discussed by Tom Beauchamp and James Childress.^{36,181} Autonomy is best looked at in connection with the intentional content of consent which will be examined in a moment, but this is mentioned here because many of the considerations discussed above concerning failures of the consent act, based on social structural features and the power relations in the medical situation are not wholly relevant to the Nuremberg formulation. This has an inner and an outer aspect, the inner aspect bearing on patient autonomy, and the outer aspect bearing on justice (another of Beauchamp and Childress’s principles.) The Nuremberg Code seeks to protect the patient’s physical well-being (and psychological well-being insofar as that is a medical topic); and it uses consent as both a protective and a limiting rule. The risks the patient is to undergo, it implies, are the patient’s to take, not the doctor’s. And if the doctor imposes those risks on a patient, he, and not the patient is responsible for the harms that ensue, if any. Conversely, if the patient consents to those risks, that is the patient’s business, and arguably the patient has consented to a contract, under some fairly stringent conditions, but in fact those conditions are the same as obtain in routine medical practice.

All that is needed is that the patient understand the nature of the contract he is making.

The relevance of the possibility of “distorted communication” is to this possibility of understanding. The structural basis of the distortion is relevant also to the issue of justice, which is not an issue treated by the Nuremberg Code or its successors. The Nuremberg Code requires consent not only to receiving an experimental treatment, but also to the experimental context of that treatment. It may be thought that some of the Nuremberg Code’s provisions are excessive: can a patient really be required to know and understand the methods to be used in the experiment? Answer: yes, under some accurate lay description (in other words a lot of the “technicalities” fall under the heading of “cognitive inferred consent” discussed above). Which means, among other things, that the patient should be made able to understand such elements of the drug trial as control, placebo (or standard) treatment, randomisation (the basic ideas, not the maths); and consent indicates, and is conditional upon, consent to these methodological aspects of the trial. Much heat and light has been expended on arguing that a patient cannot be in a position to understand the science, and that understanding the science is what is required for informed consent. It would be more accurate, and important, to point out that patients may not be giving true informed consent because there is a structural problem with communication than because of any informational incapacity, which is one reason to prefer the Nuremberg formulation over later formulations which refer to informed consent.

Emotional stress

The structural problems that are involved are principally concerned with firstly, the emotional difficulties with being in the patient position, and secondly with the structurally imposed situation of choice. Being a patient (or indeed, being the “guardian” of a patient who is a child or mentally incapacitated) is traumatic (often – perhaps this is exaggerated? Many trials involve treatments or technologies that are far from the dramatic cases usually discussed!). The decision one is asked to make is complex – and the Nuremberg Code’s authors were wise to refer to the need for “understanding and enlightened” decisions by subjects, rather than merely “informed” ones. In general it would be unreasonable to expect patients to consent to much more than the experimental treatment itself; and there is some evidence that most patients are in fact only consenting to that, rather than the whole experimental package of innovation plus control plus blinding plus randomisation.

However, there is also evidence that many patients report their reasons for entering trials as being based on altruism rather than a simple desire for the best available treatment (with or without the additional twist that they do not believe the investigating physician’s protestations of personal or clinical equipoise).^{166,170} Furthermore, there is evidence to suggest that the process of consent and experimental treatment are beneficial to patient well-being in some cases – particularly in cases of long-duration illness (such as cancer and AIDS). The informed consent process, however, may well be directly harmful to patients in situations of acute illness or acute stress.^{146,182} This is an area where the published evidence is frequently contradictory, but while the protective standard is voluntary consent it is clear that the consent issue cannot be fudged, and the alternatives are either to ensure voluntary consent is genuinely consent to the protocol in full, or non-participation in the trial (leaving aside the question of whether patients who refuse participation in the trial can be given the experimental treatment on an individual basis for the moment).

Socio-economic constraints on choice

The emotional stress issue has another element, which is shared with the social structural issue proper, viz., can one consent to something which is not in one’s own personal best interests? Constructing an account of “best interests” in this case is difficult. It is easy to imagine a case where someone, with full information chooses to sacrifice their own interest to the greater good. Many ethical and religious traditions would find this praiseworthy (if supererogatory). This is not the issue (although some theorists have discussed the necessity for such sacrifices, following Hans Jonas).¹³⁷ The issue is rather, if one is offered a strictly limited set of options, all of which are suboptimal globally, is any choice under those conditions consistent with the spirit of the voluntary consent rule? Is one genuinely protected by the rule if one is artificially in the position of risk? For example, suppose we have two AIDS patients, one of whom is dependent on charitable payments to cover his medication costs, and one of whom has a high-premium insurance cover and is generously provided for. And the rich patient goes to a high technology private hospital and can afford the optimum (as at present) treatment, but has the option of entering the trial; while the poor patient goes to the local university hospital and can afford only an inferior treatment, but could enter the trial and receive some treatment free. There is a good case for saying that the first patient has a balanced and undistorted set of options, where the second does not. This is not a question simply of economic justice, but of the possibility of genuine choice.¹⁸³

One way out of this dilemma is to draw on the resources of an older philosophical tradition than our rights-based one, and say that life is full of bad breaks and inequalities, and the quality of the man is demonstrated in how he deals with them.¹⁸⁴ This is a hard truth, but one that is sometimes ignored in medical ethics. However, it is arguable that it could be softened more than it is at present, and part of the importance of the argument is to point out that many healthcare experiments use what we might call socially or economically vulnerable subjects in unbalanced ways – either more than one might expect at first glance, or fewer, depending on how the trial and healthcare system is funded. Connected with this is the correlation between economic and social vulnerability on the one hand, and socio-cultural factors on the other; this is an important issue in the US where many Black Americans are enrolled into big city hospitals' trials for economic reasons, but many of them feel that first they have no choice, and second there is a “racial” explanation for their enrolment (which is related to the Tuskegee scandal).^{114,143,183,185,186}

Supposing a patient is in a situation of making a hard choice of this kind, one thing that is important is that the choice be a genuine one. For we have assumed that where informed consent cannot be obtained, the issue should not be pressed, and the patient should be given an alternative (non-experimental) treatment (be that a standard treatment, a placebo, ordinary medical care, or whatever is consistent with good medical practice and ethics). It might be the case, as mentioned above, that we wish to ensure that a particular patient receives the experimental treatment (should we think it medically indicated in this case, and we have good reason – more consent? – to think that the patient consents to the treatment but not to the experiment in full). This is often done, both in the situation described, and in the situation where a patient enters the trial but cannot comply with the protocol over time. Furthermore, it is often the case that a patient will be allowed to continue receiving the relevant medication after the trial has been discontinued (either at completion, or if the trial has been terminated early for some reason).

In the last case, there is good precedent for this; it is commonly done; and the only moral reservation one might have is where this is held out in the consent process as a sort of “carrot” to persuade the patient to enter. This would be unusual in this form, because in randomised trials the patient is promised nothing other than the chance of being randomised to the treatment, and the hypothetical possibility of continuation if randomised to the

innovation. The non-compliance case is trickier, because it might be regarded as an incentive not to comply. The case where the patient has a choice of receiving the treatment through refusing to participate in randomisation seems trickier still. Not only is there an incentive not to accept randomisation (in case the patient believes the new treatment to be more effective, which in any case might indicate less than full comprehension of the point of the trial – viz. the existence of equipoise), this option seems to prejudice the fairness of the trial to its actual participants: for they undergo the risk of not receiving the new treatment. Of course, if the new treatment turns out to be less effective, then the non-randomised innovation arm has lost its bet. And it is this bet against nature which makes the trial a fair way of assigning risks.

Returning to the question of whether it is possible to freely consent to something which is in fact against one's own best interests (on some calculation, and presuming we have no clear information about the superiority of the new treatment), there is another side to the issue of structural distortion of choice, communication, and decision-making. Some psychological studies seem to indicate that certain kinds of people are habitually disposed to taking risks, and some to “altruism”.^{187,188} Let us suppose that these characteristics are not confounders for most trials. Is it ethical to involve these people in trials disproportionately? In fact, this is more of an issue in the case where risk-takers (or the risk-averse, conversely) and altruists (or anti-altruists) are “guardians” (responsible for giving proxy consent), and are in fact subjecting someone else to risks.¹⁸⁷ In the case of personal enrolment we would argue that these are facts about such people's moral characters, and must be regarded as part of their consent-forming behaviour, rather than a relevant barrier to accepting their consent. In other words, it is a fact about how they make their choices, not a flaw in the voluntariness of those choices.

Problems of the autonomy theory

It is at this point that some remarks about autonomy may usefully be made. The term has been avoided for a number of reasons. The main one is that it seems to be a concept which adds nothing effective to the concept of voluntariness included in the Nuremberg Code, but which has promoted an enormous amount of confusing, confused, and ritualistic writing in the medical ethics literature. The second reason to handle it with care is that it is a concept with a specific philosophical meaning and heritage,

which in a survey and practical discussion should be avoided except in the conclusion of an argument. The third is that where beneficence and non-maleficence seem to have some analytic connection with the very idea of medicine, autonomy does not (although a term sometimes used synonymously – “respect for persons” – might, although this too is philosophically problematic); nor for that matter does “justice”. If autonomy is connected with medicine’s aims and values, this is a fact of recent date, within a specific cultural and historical tradition, and which requires both argument, and recognition that its adoption is stipulative not *a priori*. In summary, it is a particular interpretation of what medical care for people might involve, and a particular interpretation of what is meant by voluntariness.

Autonomy is a theory

In most cases our rejection of autonomy as the basis of the protective test is only a rejection of some of its philosophical connotations, as should be clear from the foregoing remarks about voluntary consent. There are indeed some areas where the concept of autonomy might be thought useful in considering the patient as a moral agent, rather than simply a person choosing between technically-framed rational courses of action. This is the case when thinking about the decisions a person may make in the context of their “nature” – if a person makes an “uncharacteristic” choice, we have reason to doubt that the choice has been made in a reflective way, and thus that their choice may not be fully “autonomous” in the philosophical sense. The use of the term also marks a limit which the investigating physician has a duty to be sensitive to and respect: the physician should not badger a patient any more than he should threaten him. A decision is made by a rational, self-governing individual (other things being equal); autonomy here being a synonym for self-government, or “making up one’s own mind and not letting someone else do it for you”. Hence the adjacent idea where autonomy is meant relatively: I made my choice autonomously, meaning I made my choice independent of any pressure or suggestion from someone else. Here it is increasingly difficult to spell out what this should mean, and also it is tendentious.^{189,190}

Autonomy and individualism

The theory of autonomy almost always implies strict individualism (although there are exceptions). Most informed consent theorists assume that in the end the patient must make his own choice, which entails excluding the patient’s family and friends from the process, except under carefully controlled, and usually marginal, conditions.^{190–192} Some autonomy theorists recall

that many people can only make hard choices through a process of dialogue with their family and friends; most do not; and those that do have to give a fairly elaborate account of how this fact is consistent with autonomy theory.^{191–194} In fact, autonomy theory, rather than being the essence of ethical legitimacy, is founded in a cluster of cultural traditions related to liberal individualism; and while it is appropriate to use the theory heuristically in caring for people who subscribe to that tradition, and indeed on other occasions too as a method for determining what respecting other traditions might be said to involve, it is not a more appropriate foundation for the protective rule of consent than simple voluntariness. In other words, autonomy is a derived principle, not a basic one, and its scope is consequently somewhat more limited and not of universal utility or applicability.

Autonomy and character

In thinking about the patient who makes choices based on some personal disposition it is often argued, sometimes rightly, that the reason we should accept this is to do with respecting their autonomy. This is somewhat paternalist in an inverted way: we want to satisfy ourselves that they have made their choice on grounds we can accept ourselves, be that acceptance direct (we agree with them) or indirect (we accept their right to choose in that way, or that conclusion, if not their conclusion, or way of choosing). There is a limited sense in which we have every right to expect their choices to be rational: patients who make capricious or unsoundly thought out choices are very likely not to comply with the treatment protocol, and so are a drain on the trial’s resources and prevent “more deserving” patients from getting the benefits of the trial.¹²⁹ There is some difficulty here: many trials might be aimed at populations who have low compliance rates (people with schizophrenia, or with alcohol dependency or the homeless for instance), and furthermore the low compliance rate is part of the treatment we wish to understand, rather than a moral failing in the non-complying patients).^{105,152,160,172a} However, this is an area where there is *some* duty incumbent on the participants.¹¹² Be that as it may (and it is an area that deserves further examination), the autonomy theory may throw some light on why informed decision-making is not merely protective but also often a positive benefit in itself.¹⁹⁵ If this is so, it is a psychological fact, rather than a philosophical one. In addition, it is consistent with a variety of philosophical theories (including virtue ethics, Marxism, Protestant Christianity, Kantian and utilitarian varieties of liberalism, to name but a few).¹⁹⁶

Autonomy, families and culture

If this is the role and significance of consent, there can be no serious objection to involving patients' families in the consent process, if that is what the patient wishes. The only purpose in excluding them is based on the possibility that the patient's family may exert improper influence upon the patient.^{187,194,197} Yet cases (and there are many) where the patient is from a family or community-oriented culture, rather than from an individualist culture, surely indicate that the patient's normal consent-forming process involves his reference-group, and their exclusion damages that process. Related to this is the point that patients from cultures which value or expect paternalism (and very good evidence is needed for this, if the tide is not to be turned back to paternalism as the norm in the medical profession) and place a high degree of systematic trust and reliance in the physician's expertise need to have this respected in the consent process.^{198–201} This does not imply withholding information; it may imply delivering it in a different manner, but this is a point deserving considerable debate and further research.

Consent as a singular event and as a process

The crucial point about voluntary consent is that the individual consents to what is being offered. As noted several times above, this means there is a gap between what the patient believes himself to be consenting to, and what the investigator believes (and wishes) him to be consenting to.¹⁶⁹ As the Nuremberg Code insists, the responsibility for bridging this gap is the investigator's. However, a crucial feature of the medical experiment is that the conditions under which the experiment commences change over time: at the end of the experiment the fact may be established that one treatment is superior to the other. Whether any inference can be made about the proper belief to hold about this fact between the start and end of the whole trial is a difficult issue (which is discussed in chapter 2). However, it should be noted that the patient consents to accept the clinician's equipoise at the outset, and should this condition change, arguably the applicability of the original consent changes too.²⁰¹ This implies that consent may not be a single act which holds good for the duration of the trial, but may be a series of acts, or indeed a process.

We have spoken of the "process of consent" elsewhere, where we meant the process of deciding whether to consent and of obtaining consent from each patient; here we wish to imply that the initial consent may not close the process, which continues throughout the patient's involvement in the trial. This is recognised to some extent in the Nuremberg Code, which insists that a subject shall be free to leave the experiment at any time if the experiment becomes for some reason intolerable. Also required in the Nuremberg Code, however, is the patient's understanding in advance that things may change during the course of the experiment; this is implied in the patient's understanding of the purpose and methodology of the experiment. In order to achieve compliance it may be that strong emphasis should be put on the preference for consent to apply for the duration of the trial, if given (subject to the intolerability clause). The issue of whether the patient has a right to continuous information about the progress of the trial, consequent upon his right to renew or discontinue his consent, is vexed and open.¹⁰⁷ One solution may be to distinguish in-trial and pre-trial consent, where pre-trial consent is consent to the experiment, and in-trial consent is consent to the treatment process the doctor has chosen (as in ordinary consent to routine medicine). The pre-trial consent process would need to be a stricter filter than ordinary voluntary consent has been, because of the switch in the meaning of the consent once the patient's treatment begins, and the need for the patient to agree to this in advance. The switch to "routine" consent in-trial might also remove some of the difficulties attendant on not informing the patients which arm they have been assigned to.

Conclusion

In conclusion, we have shown how much of what is required by ordinary informed consent theory was clearly and usefully expressed in the Nuremberg Code. We have shown how many structural and cultural factors are not only relevant to the theory and practice of informed consent in clinical trials, but also are best served by the pragmatic features of a Nuremberg-based ethics (rather than a "principlist" one). Informed, voluntary consent is and should continue to be the sine qua non of clinical research: but this aim will be better served by attention to the details of obtaining it in different situations than by philosophical debate over the autonomy interpretation.

Chapter 4

Cultural, economic and gender factors

As described in the Introduction, the aim of this study was to complete a systematic review of the literature on ethical issues in clinical trials of new treatments, paying particular attention to research into the influence of social, economic and cultural factors in ethics. As a review, its function is to survey what work has been done, to summarise the best work, to assess this work critically, to draw conclusions, suggest further directions for research and recommend what best practice is. By far the most part of the literature on ethical issues in clinical trials discusses ethical issues in trial methodology (as discussed in chapter 2) and in the theory and practice of informed consent (as discussed in chapter 3). Relatively little work has been done on qualitative analysis of patients and communities attitudes to trials, and of the work that has been done, the emphasis has been placed on issues of access to trials and of comprehension and capacity to understand. Thus it is possible that certain cultural groups have clear reasons for disputing or favouring aspects of trial methodology: but the research that has been done very largely ignores patients' and citizens' reasoning, concentrating rather narrowly on simple "yes, no, wasn't asked". This latter topic is important in addressing many of the problems trialists face, but does not allow for much deep understanding or foresight.

The kind of studies that have been published, and in consequence the studies this review has been able to analyse, have been written mostly by members of the medical and healthcare professions, with contributions by social scientists, philosophers and lawyers with an interest in the field. Sometimes papers which were stimulating at first reading, because of their critical stance, turned out to be unusable because their suggestions about alternative methods would have led to biased or inconclusive research. In many cases, criticisms were not really addressed to trials, but to experimentation as such, or to the whole modernist medical "world-view". Interesting studies of non-Western approaches to medicine were read, but applying their findings to trials proved impossible without further dedicated research.

In order to be useful, this chapter has to concentrate on trials situations within the UK, while drawing on other similar health services' findings (especially

the US). It is certainly true that the context of healthcare delivery (NHS? Medicare? Insurance-funding?) has important influence on the experience of patients in trials and on justice issues, as discussed *passim* and returned to below. By far the most important contextual factor is shared by all of the studies we have been able to draw on: they take place in liberal, Western democracies with "developed" economies and huge scientific research programmes. On the world stage, there are hugely significant issues regarding the exporting of trials outside this context. We took the view that from the point of view of utility to the NHS and to the British social and political context we would have to concentrate on examples from societies similar our own and the role of cultural difference within those societies. Unfortunately, most of the literature surveyed was similarly narrow in its focus.

The combination of this limitation of scope and the shortcomings of the research literature (whatever its balancing benefits) mean that a reviewer of this report was right to say that this chapter is rather ethnocentric and "biomedical" in its focus. We concede this point readily, but suggest that it is an inevitable flaw of a review study of this kind. The most obvious way to remedy this flaw (detailed qualitative ethnographic research) was beyond the scope of this study, and it is one of the chief recommendations of this study that such research be done. This chapter aims to provide a framework for reconstructing where the social, cultural and economic factors which may underpin differences regarding trials may be found. We have tried to assemble the material in a way which reflects the researchers' intentions fairly, but which begins to go beyond the "biomedical" framework. The main principle applied is the "Lack of Evidence is not Evidence of Lack"; our intention in constructing our framework is to try to suggest situations in which we lack evidence (and it could usefully be sought) and situations where we might fairly conclude that no discussion really does imply no issue to discuss.

Consent and communication reviewed

It is our contention that the vast majority of ethical problems thrown up by trials in ordinary practice

are not in the first instance the problems which methodologists and ethicists identify and debate. It is possible that consistent and rationally acceptable arguments can be made for the ethical soundness of most RCT designs, subject to the basic requirements of the therapeutic utility of the trial, statistical reliability, and the consent and safety of the participants. All of these requirements need exegesis, of course, and the vast bulk of the literature on the subject is devoted to precisely this task. There are serious ethical issues concerning clinical trials, concerning the rights and wrongs of randomisation, control, compliance, early termination, inclusion and exclusion of subjects, as discussed in our earlier papers. Yet if we look at controversial trials like the ECMO trial, or the letters pages of the *British Medical Journal*, or the large number of patient-subject attitude surveys, the predominant problems are practical ones relating to the obtaining of consent.

The practical problem is this: if the consent process is such that most patients do not reliably grasp the nature of what they are consenting to, then their acceptance of participation may not amount to consent at all. Furthermore, refusal or acceptance of participation cannot be reliably interpreted as a reflective judgement on the ethics of the trial (or of this type of trial). For example, refusal to participate can indicate a decision not to take the particular risk this trial represents (opting for an alternative, presumably more acceptable risk – and how aware is the patient that all treatment choices involve some measure of risk?) Or it might represent ethical rejection of this trial. Or it might represent ethical rejection of all trials of this type. Conversely, acceptance of participation might mask ethical rejection of the trial, but a decision that pragmatically it represents the best (or only real) option under the circumstances, so that the patient regards his doctor and his treatment with some resentment. Consent (or its refusal) is an act full of meaning, and it is probable that no two patients consent or refuse for the same set of reasons.

That consent is meaningful concerns the investigator only up to a point, since, as discussed in the chapter on autonomy, we cannot, paternalistically, expect to know not only that the patient has made a choice, but also that this choice has been made for the “right” reasons. We are interested in the main in the patient’s safety, not the patient’s virtue. Yet we are obliged, for the same reason, to ensure that the patient is consenting to what is being offered, rather than to something else the patient may imagine he is being offered.

These points are reiterated because a review of the literature on patients’ attitudes to trials, and on the mechanics of informed consent, does not make encouraging reading if we are concerned about the adequacy of informed consent in many trials. The purpose informed consent is meant to fulfil is, as discussed in chapter 3, protective. Its aim is to prevent patients being coerced into participating in experiments, and more generally, to prevent patients, who are above all persons, from being exploited in the name of some other interest (future patients, society, scientific progress); and this protective function is independent of any features of the trial itself. A randomised trial of nectar against ambrosia for relative felicitous power would be unethical if the subjects were enrolled involuntarily (someone should tell the grim reaper!) The issue of whether consent is sufficient for the ethical soundness of the trial is less clear-cut, although one might well argue – if one were very tough-minded – that a trial of euthanasia methods on willing volunteers was ethical just in case the volunteers were really willing. Yet the point is that if the protective function of the consent process misfires, because consent is not obtained satisfactorily, then the trial is unethical on that count alone. It may also be the case that some trials are unethical intrinsically – they should not even be offered to patients, because they put patients in a situation of moral hazard. That is, patients might be offered a choice which any reasonable person would (or should) refuse, but the imperfections of the communication process and of human judgement might lead some patients to accept.

One of the functions of research ethics committees is to ensure that choices such as these are anticipated and prevented. Yet the stress here falls on anticipation, because there is no mechanism which ensures that the commitment to informed consent is fulfilled in practice, in conformity with both the letter and the spirit of informed consent. There has been some discussion in the US of “research audit” and spot-checking site visits. This would be a costly and unpopular solution to a problem which is relatively rare: that is to say, deliberate fraud. If the actual problem has more to do with failures of communication between researcher and patient, then this is more appropriately solved by training for researchers and allocation of more time to the consent interview. Ethically, the issue is straightforward: if we agree that informed consent is a necessary safeguard, then we incur a duty to ensure that the safeguard functions effectively.

Culture and communication

The chief aim of this study was to examine the research and debates about the ethics of randomised trials from the perspective of the social and cultural contexts in which trials take place. The most obvious way in which socio-cultural differences can affect the ethical situation of a clinical trial is as a source of failures of communication. We have gone over the ground of informed consent once again to indicate the way in which a trial can fail to be ethical in its practice, even if ethical in theory, simply because the consent process misfires. The ways in which communication can misfire in the consent process can be very simple.

Linguistic differences

If the patient and doctor do not share a common mother tongue, communication of the detail of the trial in a suitable lay description may easily fail. A recent example reported in the *British Medical Journal* was a trial where many of the subjects were Vietnamese immigrants to the UK, many of whom had not mastered English.¹⁵⁴ There is evidence to suggest that many of these subjects cannot be said to have given informed consent simply because they cannot have understood fully what they were being asked to consent to. How serious is this? Perhaps we could conjecture that had these subjects understood, they would still have consented. This is beside the point: a properly designed trial would have taken this population into account, and have taken steps to ensure that a competent translator was on hand. Also, counterfactual and retrospective consent is no such thing. In some cases this is a failure of etiquette (if I borrow your car without asking first I am not necessarily guilty of theft, but you have good reason to be cross); in other cases it is more than that. Cases where proxy consent is required and allowed are strictly marked out, carefully scrutinised, and publicly accountable. And no just society will regard linguistic incompetence as equivalent to mental or moral incompetence. This is one area where simple watchfulness by doctors and research ethics committees will prevent many misfires.

Conceptual and behavioural differences

A second kind of culturally induced misfire is well covered in psychiatric literature, but has more general relevance. Here the misfire is conceptual. In the psychiatric case, where what the patient says is frequently taken to be part of the symptomatology, there is a considerable literature not only about ways of getting informed consent and of constructing proxy consent, but also in “trans-cultural” psychology.^{203–207} Psychiatry is about

identification, diagnosis, treatment and management of pathologies of behaviour, which include linguistic behaviour. However, the concept of pathology has a social content, as well as a naturalistic content. In other words, what may be odd behaviour to you may be normal behaviour in my culture and society; and the relations between odd behaviours and psychiatric pathology may very easily vary between cultures. In consequence, interpretation of behaviour and inference to diagnosis and treatment is a matter of even greater skill and sensitivity across cultures than it is within one, but fortunately it is a difficulty that can be remedied with knowledge. There is now a large literature examining these variations from an ethnographic point of view. These issues are not only relevant in psychiatry. Researchers are increasingly aware of the importance of health-behaviours and attitudes to health, disease and medicine, which are relevant not only to diagnosis, but also to treatment.^{208–218}

This has relevance to informed consent, not as an additional problem, but as an additional factor to be borne in mind when seeking to enrol patients in trials. As described these cultural factors are no more nor less of a *practical* problem in trial enrolment than they are in ordinary treatment and consultations. The *ethical* point is that enrolment in a trial requires somewhat higher standards of communication and comprehension in dialogue than ordinary treatment simply to respect the additional risks and need for protection incurred in the trial situation. It is to be hoped that many of the cultural barriers to communication will have been faced and overcome in the diagnostic process, yet these factors remain relevant through the consent process and the trial itself.^{153,154,219}

Institution-based misunderstanding

As well as the conceptual misfires, there is also a culturally based problem which is not concerned directly with communication. Patients in trials often have more, and more protracted contact with the medical institution than patients with the same condition outside the trial. To the extent that this can be a frightening and disorienting experience, this can be a factor which may cause some patients to refuse consent (even when, other things being equal, they might be inclined to consent), or to give consent perhaps to hasten the end of the interview, where otherwise they might not. This discomfort with the setting of the consent interview may distort the communication, in ways analogous to the “structural distortions” as mentioned in chapter 3. It has to do with the institutional context of that communication. Attention is drawn to it here because it is a cultural factor, albeit one more

to do with the institutional culture of medicine than with the cultural context of the patient. The reasons which may cause this discomfort are many. Erving Goffman famously describes hospitals as one of the “total institutions” which take their members and users over into a social world whose rules are so different and all-encompassing compared to those which normally apply that the user may become disoriented, anxious and passive or violent.²²⁰ This may overstate matters in general, but probably applies in many individual cases. If the patient being recruited is already in a culturally alien environment, the hospital or surgery may well add to this alienation, prompting decisions and choices that under more ordinary circumstances the subject may not make.^{221–230}

In this connection it is worth remarking that the sorts of “cultural” factor that may apply are many and may include nationality, gender, social status, socio-economic class (as a subjective experience), religion and world-view, or historical factors, as well as “culture” in the more precise anthropological sense. How these differences are expressed, and how they bear on the trial and its recruitment, varies from situation to situation.

The evidence for the role of these sorts of factors is patchy, *but the lack of evidence is not evidence of lack*. In addition, being ill is hardly the best condition for many patients to give informed consent, so many of these additional factors represent problems similar to those we expect to face in recruiting to clinical trials. Greater awareness of these factors and strategies for dealing with them is required in all branches of medicine, not simply in research. One of the questions this study posed was: do these factors have ethical significance?

Socio-cultural groups and ethics

As noted above, the main ethical issue raised by culturally based problems in communication is that where the patient’s comprehension of the trial is compromised, their consent may also be compromised, and the consent act may misfire, with the consequence that the patient is enrolled unethically. One dangerous consequence of this unethical enrolment is that, even if no physical harm befalls any patient enrolled unethically *because* of this particular cultural factor, there is likely to be a group effect. Suppose there is some cultural factor in the make-up of Somali Muslims, for instance, which causes misfiring consents; and this factor causes Somali Muslims to enrol where they would otherwise not do so; then the effect, if not the

intention, will be to enrol many Somali Muslims unethically, because of this factor. And in consequence, Somali Muslims will be the victims, however unwittingly, of unethical treatment because they are Somali Muslims.^{200,231–235} This is group discrimination. A more realistic example is the case of poor African-Americans, who occasionally seem to be disproportionately included (or excluded) from studies in the US. There is a fallacy made in these cases, which is that this discrimination is *de facto* racial discrimination, when in fact it is economic – but no less problematic for all that. This discrimination is haphazard, however, because for historical reasons, African-Americans are suspicious of the American medical establishment, so are often under-represented in trials. Further, while many trials enrol mainly poor subjects, some, unintentionally, enrol mainly rich subjects who use their economic and social muscle to get access to what they perceive as “state-of-the-art” treatments. In such cases the poor, who in the US are often disproportionately also African-Americans are excluded from the trial by pressure of numbers, and again seem to suffer discrimination; again this is economic.^{221–223,227–230} We will return to economic and distributive justice in the closing part of this chapter.

Intentional and unintentional exclusions

If cultural factors are barriers to effective communication in the consent process, and failure to overcome these barriers damages the quality of the consent, there is an obligation to overcome these barriers; and if this effort fails, the protective obligation motivating the consent theory requires this patient not to be enrolled. This does not warrant excluding them as a group, unless there is a clear reason why membership of this group makes overcoming this barrier impossible in all cases. To exclude a group of *eligible* subjects from being asked, individually, to participate is patently unjust, because it makes their membership of this group more important than their individual ability to make judgements for themselves. If the argument is that some group is justifiably excluded, then they, and society as a whole, has a right to know the reason, and to debate it. However, unintentional but systematic exclusion of some group is something actively to be avoided.^{194,199,236–240}

On the one hand, the activity of overcoming cultural barriers to effective inclusion may pay dividends for recruitment to the study, if by overcoming some misapprehension, members of the target group decide that enrolment is in each individual’s interests after all. On the other hand, the opposite effect is no less likely. There is something of a gamble for

the recruiting physician in this process: it may be that this enhanced consent process heightens awareness of the risks to be undergone or the benefits available. However, it is unlikely that this process will transform a patient who is normally risk-averse into a risk-seeker, or vice versa. The risks of enhancing psychosomatic elements in the disease, or placebo-type effects under treatment are probably more significant than the moral risk of causing someone to act against their character by giving them “too much” information (rather than “too little” or actually subjectively misleading information). The risks of psychological effects of the consent process may be thought of as confounders, inside the trial, which randomisation is meant to distribute between the arms so as to neutralise their overall effects. The persistence of these psychological effects in patients who do not join the trial is ethically more interesting, as such subjects undergo some psychological risk without any obvious pay-back. This is not an issue that we have seen discussed.

Understanding refusals: the significance of culture

Refusal and ethical disapproval

The ethical significance of cultural barriers to effective communication arguably adds nothing extra to the debate about RCTs that has not already been discussed in connection with consent. Some points are underlined by this issue however. The first is that the consent process is ethically essential and in a sense intellectually straightforward, but psychologically and institutionally it is complex, and requires skill and sensitivity. The second point is that the reason for much of this complexity is that while it is sometimes thought that the ethical issue about consent is a purely protective norm to regulate the activities of physicians doing research, it is also a locus of ethical choice for the patient. The patient is making a decision not only about which risks and chances he wishes to undergo, as a shared technical judgement with his doctor about a preferred course of treatment, but also about the place of this choice in his life and projects; and what the morally good choice would be for him to make. Many patients interviewed about their reason for entering a trial name “altruism”, after all. This is not a factor which should shape the doctor’s attitude to his patient overly; but it does demand respect. The third, and final point, made here is that the consent rule is not only a morally regulative rule, but also a socially constitutive rule, in that it mobilises certain social values about respect for the individual, about the protection of the vulnerable, and about the fair distribution

of risks and benefits. As a social rule, it is affected by, and can itself affect, perhaps remove, the distortions to communication which many social injustices create and rely upon.

The nature of the activity of overcoming cultural barriers to the consent process is open to a bias, as follows. If we ask for consent from someone (who may, but need not, be a member of a different cultural group), and they refuse it, we might be inclined to suppose that this refusal is based upon failure to understand the choice, and we may devote additional effort to explaining the choice to this person. In some cases we may be right; in other cases we may in effect be coercing this person to change their mind; and in many cases we are simply mistaking a genuinely comprehending refusal for incomprehension. However, if we ask for consent from someone, and we get it, it is less likely that we would question this acceptance in the same way. The sources of this asymmetry are not difficult to pick out. In the first place, in offering the trial to this subject, whom we have already decided is eligible, we have judged that this trial would benefit this subject; and the refusal seems to indicate a judgement otherwise, which we may wish to “correct”, either because we think we are right, or because we are uncomfortable with the idea that we have made an ethical misjudgement. Secondly, if we take the problem of communication between doctor and patient seriously, especially when this communication is across cultures, we may be sensitive to the possibility that we have not made the offer clear.

In clinical trials, as elsewhere in life, no means no. But no can also have wider meanings. Patient refusal might mean, “On reflection, I would prefer not to enter this trial”, and – we hope – most refusals are of this kind. The bulk of the literature on consent presumes that this is so, although many studies have looked at what sort of reasons patients have for a refusal of this kind, with the idea of improving trial designs. Yet in this study we were more interested in some other, more critical kinds of refusal. Patient refusal might mean, “I do not want to participate in this trial because I believe this trial to be unethical”.

There are some cases where a patient may in fact participate in a trial he believes to be unethical, and this has some interesting features. It may be that he regards some features of the trial as unethical but not others: for instance he may quarrel with randomisation but not with undergoing the risk of an unproved therapy, and so enter the trial in the hope of getting the experimental drug, on the

grounds that some chance is better than none in this case. He may even seek actively to subvert the protocol, on his own or in collaboration with like-minded others. It may be that a person judges the trial to be unethical because it deliberately excludes some group of which the person is not a member, and so on. Ethical disapproval of a trial which one enters anyway and complies with is a matter for the patient's conscience. Ethical disapproval combined with active non- or mal-compliance is almost certainly wrong in itself, since almost certainly it damages whatever scientific integrity the trial retains in spite of its supposed moral failings. The consequences of wrecking a trial – whether the researchers discover this or not – are potentially very severe: an effective drug may go unlicensed for even longer, or an ineffective or unsafe drug may be deemed effective and safe. Furthermore, consent has a secondary function as a guarantee that the patient understands the protocol and will, so long as the patient is able, comply with it. In other words, there is a sort of implied contract, with the researcher, and also with the other patients, who, among other things, have been given reason to suppose that the trial will be valid, which is partly secured by all participants acting in accordance with the protocol so long as their health and safety allow. Deliberate and planned non-compliance is a breach of their trust in the experiment.¹⁵⁷

So let us consider the case, upon which the above is parasitic, in which the patient refuses consent because the trial is regarded as unethical.²⁴¹ This might be because the patient's evaluation of the trial, on the same or similar principles as used by the researcher and the Research Ethics Committee, happens to disagree with the official evaluation.^{242–249} In this situation, the particular ethical judgements are challenged, although the principles underlying them are not, and disputes of this kind can be managed using the usual machinery of the medical and legal, and political institutions, the legitimacy of which both parties in the dispute presumably affirm. If they do not do so, the dispute turns into a dispute of another kind, and falls outside our present scope, because it is a dispute about the legitimacy of the social institutions we have to arbitrate value disputes of this sort.²⁵⁰ We will return to this issue when we conclude this chapter by examining the difference between procedural and substantive methods of ethics.

Kinds of cultural refusal: conditional and absolute

The kind of judgement that some or all clinical trials are unethical which this study expected to find is the sort which does not rest on the

same or similar principles as those affirmed by the researcher and the ethics committee. We expected that other cultures might have objections to the RCT which either supplemented or perhaps conflicted with the “minimalist” principles embodied in the Nuremberg Code and its successors, and which were defended in chapter 3. Refusals based on principles of this kind might be of two degrees, conditional and absolute, and refer to particular trials or to trials of some general design type.

Conditional refusals are exemplified by the Jehovah's Witnesses' refusals of blood transfusions.^{198,239} A trial which involved blood transfusions in some essential way would be regarded as unethical by Jehovah's Witnesses (although probably not by anyone else); but this judgement would be conditional in the sense that they would regard it as unethical only for members of their sect. In the same way, a trial which involved a breach of the Jewish *kashrut* regulations is unethical, more accurately, sinful, for practising Jews, but not, on their account, for other humans.^{199,251–255}

Absolute refusals are exemplified by the Hippocratic injunction against procuring abortion.²⁵⁶ This maintains that abortion is simply wrong for everybody, but since doctors are the group of people most able to procure abortions the injunction has special relevance to them. So a trial which involved in some essential way abortion (or perhaps use of its by-products – for instance, foetal tissue) would be unethical tout court, even though our institutions have determined otherwise. Some world-views and religions hold that certain actions are contrary to natural law, or divine commandment, and apparent rational dissent from these indicates only that reason is wanting or stands in need of correction.²⁵¹

Content of refusals: topic and design

Conditional refusals of the cultural kind are relatively easy to handle. We may make a distinction between refusals which object to the *topic* of the trial, that is, what the trial is testing (the drug or procedure itself), and refusals which object to the trial *design*. Conditional refusals of the former kind are worth knowing about, because future patients from the same cultural group may well similarly refuse treatment involving this drug or procedure, and an alternative may be required. Conditional refusals which object to the trial design are harder to imagine, but we may imagine a hypothetical religion which holds that random assignment is sufficiently like gambling as to be prohibited to members of the religion's priestly caste, or to

women, although legitimate for everyone else. In this case we have a group which is systematically excluded, and this is only a problem if this exclusion conflicts with some other principle we may have, or if the excluded group insist on exclusion, but demand some alternative to the trial. We will return to this in a moment when we consider the reasons which might underlie absolute refusals.

Absolute refusals of some treatment or procedure entail in the first instance only that patients who voluntarily profess this refusal shall not receive this treatment or procedure. There is no *prima facie* reason why this group should legislate for everyone else.²³⁶ They offer us a moral problem, however, because they may be right, and so we as a society are under some general obligation to examine and reflect upon this refusal. This is not true of conditional refusals, which even the refusers themselves maintain are rules binding only on members (although they may wish to encourage membership!). The social problem posed by absolute refusal has to do with whether this group are militant in their refusal or not. If they are militant, then they may take steps to impose their refusal in ways which are not consistent with other social values we adhere to; and our refusal of this militancy will be absolute in its turn. This problem is bubbling away in the case of abortion.

Cultural refusals of design and methodology: community consent

For our purposes, we were interested in refusals both conditional and absolute of the methodology of trials, rather than of particular treatments or procedures. This is not because refusals linked to particular treatments are unimportant: far from it. Our survey of literature treating medical ethical traditions based on religious ethical systems, and our survey of literature treating cultural attitudes to health, disease and healing, indicates that particular treatments are often problematic. However, a treatment regarded as problematic by some cultural group will be so regarded whether or not the treatment is taken in a clinical trial. Ethical review of trials of treatments with a potential to be problematic, in the region a Research Ethics Committee (REC) has responsibility for, will need to be alert to possible recruitment problems and of the need for sensitivity in the seeking of informed consent. The independence of the cultural status of a treatment from the cultural status of the trial methodology places the former outside of the scope of this review, although it is of some

indirect relevance to ethical problems about selection of subjects.

Do any cultural groups propose absolute refusal of the RCT methodology, on grounds based in their culture?^{231,257-262} Our survey of the literature found no evidence that any do. Criticism of the RCT returns over and over to the issues surveyed in chapter 2, and do not invoke additional or supporting “cultural” reasons for objections. Criticism tends to be more piecemeal – American women may object to the 1970s Food and Drug Administration guidelines about exclusions from drug trials of the “pregnable, pregnant or once-pregnable”, but they do not object to trials as such – in fact they objected to the guideline because they wanted to take part in trials.^{116-121,263-268} Again, women may object to certain trials of different surgical and medical strategies for treatment of breast cancer because they object to the range of choices being offered, or to randomisation. But the same women may not object to randomised trials of chemotherapy against placebo, once the decision has been made that chemotherapy (rather than surgery or radiotherapy) is the best strategy for these women’s treatment, individual by individual.^{195,269} The nature of these objections is not necessarily connected with the trial alone, but also has to do with women’s wishing to have more say over their own bodies and to make their own choices, and randomisation seems to take back one of the choices which the women’s movement has fought for – the right for women to self-determination over their own bodies. The likelihood that illness has already compromised this power of self-determination, and that entry into the medical institution has alienated the patient still further from her sense of being in control of the situation make the significance of the right to choose even greater. Randomisation is problematic not because of its scientific function, but because of its contingent sociological significance.

Let us review the features of the trial to which cultural objections may be relevant. These are: (1) the RCT is a human subject experiment. (2) Some patients receive an experimental treatment, whose risks and benefits are incompletely known, while other patients receive no treatment, or placebo, or a standard treatment, which may, in addition, be known to be ineffective. (3) Patients are enrolled into a trial, often with some confused expectations about what they will receive, and are usually assigned at random to an arm of the trial. (4) Patients are expected to comply with their treatment, cannot always expect to know anything about the progress of the trial, and have little say over whether they

can switch arms in the trial (almost invariably they cannot before the trial ends or is terminated). (5) The main ethical safeguard for the patient is informed consent, which is usually taken to involve individual autonomy and some assumptions about the capacity to exercise it.

The RCT as human subject experiment

That the RCT (and its alternatives) is a type of human-subject experiment is an issue which received a lot of attention in the 1960s and 1970s, notably in the famous “Belmont Report”, where several efforts were made to trace the distinctions between invasive and non-invasive techniques, between therapeutic and non-therapeutic experiments and between experiments, innovations and standard practices in medicine.^{35,125–127} Establishing clear distinctions proved fairly difficult. However, everyone agrees that Nuremberg-like provisions specify the main features of what is required of an ethical experiment involving human subjects. One of the main examples the Belmont commission was set up to solve was the famous Tuskegee observational study of progressive syphilis, which notoriously did not involve any benefit to the subjects themselves, beyond a hot meal at each observation visit, although a satisfactory therapy was available, nor was consent sought for or given by the subjects. One consequence of this study was that many African-Americans were, and are, highly suspicious of enrolment in human-subject experiments, including controlled trials either in medicine or the social services.^{114,221,223} This may be taken to be a cultural absolute refusal of clinical trials.

What is involved here is not an ethical refusal of the idea of a clinical trial, but a failure of trust in the system creating and administering these trials.¹⁵⁷ Non-participants who do not enrol for this reason are expressing the opinion that they have no reason to accept the *bona fides* of the investigating physician. A similar objection is expressed in the refusal to be a “little human guinea pig”.^{18,145} In both cases, what is being expressed is a belief that the physician or scientist does not regard his subjects as fully human and equal, and a belief that experiments use humans as means rather than as ends.

This failure of trust is a historical and sociological phenomenon which demands respect, not only for individuals but also for their communities, and is one source of the movement in certain communities (AIDS patients, the Maori nation in New Zealand, the Inuit in the Northern Territories in Canada) for the recognition of a kind of group

autonomy as well as individual autonomy.^{14,192,226,237} This represents a major revision to the Nuremberg-style ethics of experimentation. It raises the important question of social justice, as it bears on the selection of subjects for research. In particular an RCT has hitherto been regarded as ethical if it is scientifically valid, fair to its participants, and protective of their safety and autonomy. This further issue of communities which have in the past been collective victims of some unethical medical practice (particularly experiment) makes us ask: can an experiment be regarded as ethical if it is not socially just?

The RCT as controlled comparison

The same issues arise when one considers the ethics of controlled experiments: the usual question applies, whether it is ethical to give a patient a treatment which is known to be ineffective or only a placebo, even if we do not actually know which treatment is the ineffective one, because of blinding, randomisation, and lack of scientific evidence (which is the motive for the trial). The Tuskegee-type experiment simply makes this question more urgent for certain groups and particular patients. The role for community consent is to ensure that the physician can assure the community of the validity and fairness of the RCT, so that the community and physician can rebuild the trust needed for enrolment to begin. On the one hand, community consent is consent to approach members of the community, and in no way entails that members of the community will consent to enter the trial as a result. On the other hand, most liberals will want to know whether a community has the authority to give or withhold consent to approach its members, and in particular whether community’s withholding their consent involves excluding members of the community from participation in the trial or from being given the choice at all.^{202,236,239,240} This is probably a misunderstanding of what community consent ought to involve, although it remains a problem in any event. Community consent ought to involve no more than good public relations between the trial and the communities where it takes place; most communities are not so constituted that they have a local leviathan who can grant or withhold consent in the same way that a person can. The case of the Inuit peoples and their relations with the Canadian health establishment are unusual because they are nations (but not nation states) who have maintained a degree of state-like autonomy in most of their affairs.²⁷⁰ This makes an ethical issue simultaneously political, as in fact the Tuskegee case suggests, but the two issues require different solutions.

The role of community consent is, on the one hand, to assist in reparation for historic political injustice (where necessary). On the other hand, however, it is similar to the role of a state-appointed commission of inquiry or research ethics committee. Many of the same issues arise in the case of multinational – or even single-country multicentre trials as arise in the case of culturally different groups.^{260,261,271–273} The community consent transfers some of the role of the institution-linked REC away from what is perceived to be the “establishment” into the hands of the people who have lost faith in the establishment’s wish and will to protect them as they should.

Randomisation and compliance

The subject which, at first sight, one might expect most debate about from a cross-cultural perspective is randomisation. In fact we have no evidence at all that any cultural group objects to it any more or less than any other. We did hypothesise that randomisation might be linked to gambling or to life-insurance by some cultures; this would not be unnatural as the logic of randomisation, decision theory and risk assessment is derived from these sources.²⁴⁷ However, while many cultures do have proscriptions against gambling, these relate to the chances of unfair or disproportionate winnings or losses, to distraction of the player from social, family or sacred duty, and to the risk that the gambler will replace God with Fate as his deity. None of these seem to apply to randomisation in the trial. In any case, who is gambling in the trial? The patient? Perhaps, although the bet is – in pragmatic or equivalence trials at least – intended to be a no-lose one, relative to the out-of-trial situation. The doctor? Most religions allow people in situations of uncertainty to draw lots. The objection that the doctor is not or should not be as uncertain as all that in all patients’ cases (he should treat them as individuals, and so on) remains, as it does from the “scientific” point of view surveyed in chapter 2. Granted the premise that the doctor is in equipoise about the merits of the treatment, drawing lots in each patient’s case is legitimate, certainly in all the Abrahamic religions. The problem here is that we are speculating – we found no literature on the subject of the theology of gambling or lots and experimental randomisation. It may, however, be an issue in the future. Certainly it would be well worth while linking research into the sociology and anthropology of risk, chance and fate to the issues raised in this report.

The issue mentioned above about randomisation and some drastic surgical procedures (any irreversible treatment) in connection with breast

cancer is not in fact specifically a gender-related issue, because it would be no less problematic in trials of lobotomy or testectomy. That particular procedures and treatments are of great significance to particular cultural groups is of course very important, however. The point here will be to construct trials which have sensible outcome goals in both arms of the trial, so that patients will be indifferent between the known effects of each arm where possible.²⁷⁵ Where this is not possible, they should be counselled about the differential accompanying costs and risks.²⁶⁹

The other main socio-cultural factor concerning randomisation relates to its fairness as a method of assigning a scarce novel therapy. We will return to this when we discuss justice issues more generally. The issue of the expectation that a patient who enrolls will comply not only with the treatment but also with the protocol has, so far as we can manage to find no special cultural issues relating to it.¹⁰⁵

The main lesson of this survey of the relevance of cultural factors to ethical debates about randomised, controlled trials is that on the one hand no culture seems to have any special argument against the legitimacy of the trial methodology. The ethical problems of the RCT and its alternatives which have been identified within the medical and statistics professions seem to be a reliable compendium of the problems which are to be debated concerning RCTs. On the other hand, because the RCT does not take place in a social, economic, or cultural vacuum, it cuts across many problematic areas which bear on particular trials in complex and occasionally unpredictable ways. We did not discover any new reasons to question the legitimacy of the RCT, which is to say that as a general rule it seems ethically sound. However, if the social nexus of particular RCTs and the populations they draw on varies with reference to historical, social, gender, economic and religious factors, it is clear that the general ethical validity of the RCT only goes a certain distance. There are two main safeguards which are intended to ensure that particular RCTs remain ethical, are local in nature, and should, in principle, be much more responsive to these contextual factors. These are, once again the principle of voluntary consent, and the Local Research Ethics Committee.

Consent

The principle of voluntary consent reflects, among other things, the fact that what is ethical in general outline may not be ethical or appropriate for some individuals or groups. By ensuring that each individual is offered a choice, and can say no, and

that saying no incurs no punitive penalty, the principle should ensure that unsuspected locally relevant ethical objections are respected. Researchers should keep an eye open for patterns of refusal, to detect whether there is some systematic factor which needs bearing in mind in future. Systematic factors which are local are the sort of thing which an LREC ought to be good at identifying, because it is based in the region it serves, and because, ideally, it should be adequately representative of the region it serves. The LREC is obliged not only to determine whether the RCT is soundly designed and *prima facie* ethical, but also whether it is appropriately adapted to the area it will take place in.

Is consent a culturally neutral concept?

While the principle of voluntary consent and the role of the LREC together should seem to guarantee that a trial will be ethically and culturally tolerable for its subjects, there is an important question about their effectiveness. Just as the RCT is in general terms ethically acceptable and rationally justified, but may come to grief in particular socio-cultural situations, the principle of voluntary consent and the LREC mechanism seem ethically acceptable and rationally justified – so can they come to grief in the same way?

As discussed in chapter 3, the principle of voluntary consent has the appearance of being an essentially liberal principle, and so vulnerable to attack from non-liberal intellectual or cultural perspectives, or indeed from the internal contradictions of actual liberal-democratic states. I went some way to showing that voluntary consent was not dependent in any strong sense upon the full liberal notion of autonomy, as exemplified by Kant's theory; instead voluntary consent need only mean, in its quite ordinary sense, making up one's own mind as best one can, without coercion.²⁷⁶ Furthermore, the principle was asserted for protective reasons in the first instance, not because it was a good principle in its own right: it is not intended to be adopted by subjects as a moral maxim for their own conduct, but rather it is to be adopted by society and practised by individuals as a defence against tyranny. Since the Nuremberg code the sense of the protection has broadened to encompass protection against taking risks that have not been reflected upon.

Individualism

Some of the literature about informed consent from a cultural perspective has argued that it places

undue stress upon the *ideal* of the free and autonomous individual subject. This is a charge which is sometimes fair: enthusiastic interpreters of the principle in accordance with full Kantian autonomy arguably do exaggerate the normative merits of this mythical individual. Furthermore, to the extent that this individual is only imaginary, critics of informed consent who maintain that it is cruel and unreasonable to expect ordinary sick individuals to behave as if they were Kantian individuals have a point. On the one hand, the conditions for informed consent should not be so strict that no one could reasonably meet them in the situations where they are most likely to be faced with them! On the other hand, they need to be fairly strict if the protective function is to be fulfilled.

Which individuals?

The issue concerning the connection between individual autonomy and consent which is relevant to cultural factors is as follows. Do all cultures regard the word of any particular patient as sufficient to ensure that the protective test has been passed? Do any cultures regard the test as inappropriate, perhaps substituting some other protective test? In the first case, what we take to be voluntary consent given by some patient may not be regarded as such by other members of the patient's cultural group. In the second case, members of some cultural group may regard some or all of the process of obtaining consent to be unethical, and may require some other method of ensuring patient safety and integrity.^{231,234}

The first case – where individual consent is not regarded as enough in all cases – is in fact familiar. In several cases we do not allow informed consent from members of some classes of individual to stand on its own: children, the mentally impaired, and perhaps some institutionally vulnerable subjects (prisoners, students, subordinates of researchers). The main issue children or mentally impaired subjects pertains to whether they are capable – as we presume all adults are – of taking a considered decision about the risks and benefits they may choose to incur in their present situation. The main issue relating to the type of subject we call “institutionally vulnerable” is the risk of feeling coerced to enter a trial which under other situations one would refuse.^{277–284}

In either of these types of case we regard the individuals in question as either lacking in the competence to choose – that is to say, their words do not have the right authority – or that they would have the competence to choose, but the appropriate context for that choice to be genuinely free is

lacking. In the case where competence or authority is lacking, we can either debar such individuals from participating in this (and any similar) trial, or we can appoint an individual who we and the patient (where possible) believe will have the required authority and competence. The sort of person who would be appropriate might be a close family member, a priest, or an officer of the court. Yet whether these representatives are reliable substitutes for the patient's own judgement is never clear, and precisely because they are not the patient, their judgement will always lack final authority.

The categories in our society of the types of patient who cannot give full consent, and the measures we have for determining proxy consent are pointed out because in some respects these categories are "soft": it has long been understood by historians that "childhood" was a mid-nineteenth century invention, for instance; and that "madness" is very socially and culturally fluid; and that women's rights to property ownership, to the franchise, and to self-determination are only patchily recognised in the world today.

It is not hard to imagine cultures in which a woman's consent is regarded as only as dependable as a child's, so that a woman could be entered into a clinical trial only with her husband or father's consent (perhaps even where this contradicts what the woman says). We have no evidence that any culture takes this view. However, examination of the guidelines which have from time to time been promulgated to regulate clinical research shows that women's power to consent has frequently been nullified by regulations which exclude women (or some subset of women) from trials relevant to their health at the outset, because they are "ineligible" for reasons not solely attributable to biology. Is this because of sex discrimination? Perhaps, although it seems well-intended (and the situation has changed in any case). A more likely reason is that it has to do with defending the researcher and the drug proprietor against damages suits raised by future offspring of the women in the trial whose development may be harmed.

The role of protective guidelines and LRECs is to prevent patients being offered participation in trials which are substantively unethical, not to offer patients more protection than they would choose for themselves. Excluding subjects on some principle for which there is no defensible scientific reason, and where there is no opportunity for public debate about the ethical principles, is straightforward paternalism. On the other hand, over-literal and bureaucratic interpretation of

these guidelines by physicians or LRECs is equally prone to problems. For example, it is a mistake to assume that merely getting as many patients as is necessary to say "yes", as quickly as possible, surely does not respect their individual integrity.¹³⁰

We have tried to show how complex the ethical decisions are which patients must make, as well as those made by physicians and LRECs. The informed consent is not an end in itself.

Individuals and their families

One mistake in this area which has cultural significance is to over-stress the individual's role in decision-making. While the decision to give consent has to be taken, in the end, by the individual, few of us make momentous decisions without consulting family or friends. Possibly there is some truth in the idea that northern Europeans are more individualistic than southern Europeans, for example. Certainly there is evidence that the quality of informed consent obtained from American patients of Mediterranean cultural origin is diminished where such patients are unable to consult their families.^{192-194,199,201,204,285,286} In cases where the patient is able to go away and think about the choice for some time this problem probably does not arise, since the patient can then consult with his family. Where this is not possible – because the decision is required quickly, or because the patient is hospitalised – the individual who is culturally inclined to place his interests in the context of the interests of his family will need to have his family with him to help think through the decision. This is of course an additional source of problems: the family may disagree among themselves, or with the patient.¹⁹⁴ In constructing proxy consent it must be remembered that in family-oriented cultures it may not always be the case that other members of the family will place the individual's safety and interests first. All of this requires some sensitivity and knowledge of the sociology of families in particular cultures, and, more practically, a knowledge not only of the patient alone but of the family too.

These considerations are important not because they offer an alternative construction or replacement for individual-centred informed consent, but because they fill out some details in the what obtaining that consent will involve. In the last instance, the individual patient's word should carry most weight, simply because the whole point of voluntary consent is to protect individuals from groups who think their interests are superior to the individuals, or their knowledge of the individual's interests is better than the individual's own self-knowledge. However, precisely this point should lead us to question whether the physician's

and the LREC's and perhaps the courts' judgements about what is in individual patients' interests are necessarily more well-founded than the judgements of the patients' families.

The source of the mistake that is sometimes made, to the effect that patient's individual consent means decision-making should not include their family is an mistake about autonomy: philosophically it might be supposed that taking advice from my family will make my choice heteronomous. Philosophically this would be wrong; autonomy is often best served by the rational seeking and taking of advice, in order to avoid the risk of taking decisions rashly, unreflectively, or in the grip of great pain or untutored emotion. We should distinguish the idea of a family as a block to autonomy (which can certainly occur easily) and the idea of a family as part of the background conditions for autonomous choice. The role of the physician in the consent process is to help the patient make the best decision he can – and that will usually involve recognising that the patient is a member of a family. However the principle stands, that the decision is the patient's to make, not any one else's.

Is consent cruel?

We now turn to the question of whether any culture regards consent as an excessively cruel means of protecting patients.^{199,231,255,287,288} Here we do not consider the content of the consent. That is, we do not ask about whether patients are occasionally asked to consent to something that is unfair or cruel. It might be argued that asking patients to consent to be randomised between radical mastectomy and lumpectomy would be cruel, for instance. This is the sort of question which LRECs are meant to deal with, and it is discussed in chapter 2 on the methodology of trials. Rather, we ask whether in general there are cultural reasons to suspect that asking for consent at all will be distressing for patients. Sometimes this comes close to the issue, just discussed, about whether all cultures agree on the categories of people able to give full consent. For instance, if we insist that someone with a certain kind of mental handicap is, in this instance, competent to give consent, but in fact they find this actually distressing, this is a good reason to treat the patient as ineligible for the trial (and decide about whether they could be suited to the experimental treatment outside the trial on other grounds). In hard cases like this, we might retrospectively ask, was this person actually competent? Is asking someone who is incompetent for consent which they cannot give wrong? That depends on the incompetence. For instance, if a male doctor asks a female patient for her consent to perform an intimate examination, this may be distressing for

many women, but even more so, when that woman comes from a culture where she is not allowed to display her genitalia to a man who is not her husband. Intellectually she may be able to give consent, culturally she may not (and emotionally may not want to do so); and this situation is potentially shaming for her.

Expectations about doctors

In fact, seeking consent is closely connected to the relationship between doctor and patient, and how this is conceived in various cultures. Some authors report, for instance, that in Japan and Korea there is a strong expectation that the doctor should tell the patient what to do; being asked by the doctor what the patient wishes to do is disorientating; and in the long run, diminishes the trust the patient has in the doctor's ability to perform the doctor role.¹⁹⁹ In Britain where medicine is still not fully consumerised, some expectation is still placed on the doctor that the doctor will act paternalistically.¹⁵⁴ In Italy, patients frequently shop around for diagnoses and medical tests between consultants, whom they may approach directly, regarding their general practitioner as another specialist (and not a high status one); and something similar is the case in the US.²¹⁶ Informed consent is an act which takes place in these highly variable contexts.¹⁵⁶

The challenge here is to find an adaptation of the informed consent paradigm which will preserve its protective role while making it appropriate to the patient's expectation of what the doctor will do. A key element here is the paradox of scientific medicine: on the one hand, patients expect that doctor's knowledge is always increasing, but on the other hand, the chance is continually rising that any patient will be asked to join a trial, the premise of which is that something important is not known.^{289,290} There is, to our knowledge, no research on how to adapt informed consent to the patient's desired level of physician's authority, although there is considerable research about how to raise consumer choice in medicine. The social context of the marketisation of medicine in the West is clear enough. The moral point that people should be encouraged to a mature appreciation of what they can change and what they cannot (in the short-term, their illness and the state of medical knowledge), and to sound thinking about choices in the domain where they can change things, is also commonplace. However, people's health behaviour is strongly shaped by their trust in the medical system ("from cradle to grave") and their trust in the knowledge, integrity and judgement of the doctor. The principle we have chosen is that the values of protection and of individual choice are more important than the value of a caring and

paternalist medical profession; and this choice has consequences we have to live with.²⁹⁰ Use of the patient's supposed wish to have moral choices made for them to play down informed consent – not in principle, but in individual cases – is an alibi for backsliding. Nonetheless, it is also reasonable to worry that informed consent's purpose for some doctors is as a protection not for their patients but for themselves: "it wasn't my fault – you knew the risks". In such situations evasion of an expert's responsibility has been mistaken for avoidance of paternalism.

Justice and socio-economic factors

We now turn to socio-economic factors and issues of social justice in the RCT. Almost all the ethical issues discussed have focused on issues that arise once a study has been designed, a scientifically appropriate population has been identified, and criteria for eligibility have been determined which are consistent with existing guidelines on good practice in trials. We have analysed the ways in which socio-cultural factors are relevant to enrolment into the trial, and discussed ways in which methodological features of the trial may have differential acceptability in different cultures. There are also issues relating to the trial as a method of healthcare delivery in comparison with similar non-trial treatment strategies.

Inducement

In 1990, the Royal College of Physicians recommended that:

- “40. Improved care should not be offered as an inducement to participate.
- 41. Payments to patients are generally undesirable but are occasionally acceptable in studies which are long and tedious. Payments to patients should not be for undergoing risk and should not be such as to persuade patients to volunteer against their better judgement.
- 42. Any payments to be made to patients should be reviewed by the Research Ethics Committee.”²⁹¹

These guidelines are easy enough to interpret and apply in healthcare systems which are free at the point of use. In healthcare systems where this is not the case, for example where patients are billed for their care, and cover the bills by means of insurance payments or their own savings, entry into a trial is an inducement on its own, simply because they receive free treatment where they would otherwise have to pay (either directly or through increased insurance premiums or both).^{292–294} Insurance companies typically will not pay for

experimental therapies, the patient receives the treatment free because no one could afford the scarce innovative treatment if the patient had to bear its unit cost.¹⁸⁵ Hence members of the sizeable proportion of the US population who have no health insurance cover at all – even from the State – are disproportionately induced to enter trials in a way which gives us cause to wonder whether they are persuaded to act against their better judgement (although sometimes it is rational to accept a risk in the expectation of a profit). This is a particular danger because clinical trials are frequently performed in urban hospitals (especially teaching hospitals) which are often located in areas of relative economic deprivation.^{185,186,222,224,225,229,294–300}

In any healthcare situation the Royal College's first recommendation is hard to take literally, simply because of the prospect of receiving better care – among other things one has a chance of receiving a superior therapy, and the probability is that participation in the trial will involve additional contact with the health system, which may be in itself an inducement for many patients (and perhaps off-putting for others).^{263,301–306}

Together these factors which the Royal College drew attention to raise the question of whether participation in a trial may be considered a good in itself, which presents issues in distributive justice. On the one hand, do trials spread risks fairly among the population, or are there unfair inclusions of some classes of vulnerable subjects? On the other hand, do trials spread benefits fairly among the population, or are there unfair exclusions of some needy subjects or unfair inclusions of the wealthy?

Distribution of illness, wealth and trials

This issue bears on the economic epidemiology of health and disease. If the truism that illness is no respecter of persons (sc. their wealth or status) were correct, then the distribution of chances of entering a trial might well be random, and so independent of wealth. However, this is not the case: many diseases are differentially linked to wealth distribution. We might therefore wonder whether the risks and benefits of trial participation exaggerate these health trends. The ethical issues connected with this are best studied in connection with the study of economic justice on the one hand, and the study of healthcare rationing on the other.^{292–307} Most of the ethical significance of the political economy of trial recruitment is a consequence of those issues, which are beyond the scope of this chapter. Two issues are especially relevant to the RCT: the fact that the risks of the trial may be unfairly distributed, and the fact that

randomisation might be considered a form of resource allocation method.

One way to allocate a scarce resource is to assign it at random; it is particularly useful when either the possible recipients are equally deserving, or again when there are different determinations of what “desert” is in the target population and so “desert” is decided to be an unhelpful or confusing criterion. It is possible to understand – if one is a patient – that randomisation is a sort of assignment to the novel treatment by lottery. This is a mistake, of course, because that is neither its intention, nor could it be – because the treatment may be no better than the alternative (or worse). The quantity of the drug is indeed scarce, but there is enough for all the treatment group at least. This understanding of the role of randomisation may not be uncommon, and should be corrected.

The fact that no one, or only a few, outside of the trial can receive the treatment, unless perhaps they are continuing a course of the drug having completed their participation in the trial, means that patients for whom the treatment is of probable rather than simply possible benefit (as judged by the physician) have only a small chance of receiving the drug. However, the tough-minded line here is that it is their misfortune to have presented before the drug has been licensed, and not to have been selected, or to have consented, to enter the trial. All that can reasonably be hoped for is a fair chance to enter the trial.

Inducement again

As we saw when discussing community autonomy, social activism concerning recruitment to trials may have unintended consequences. Many American trials have experienced problems recruiting, and so have mounted social outreach programmes to improve recruitment.^{222,229,230} Often this is for the unobjectionable reason that the benefits of the trial will mostly be received by the target community, and so a reliable trial and a fair one will need to draw its subjects mostly from that community. Furthermore, just as there is nothing unethical in compensating a doctor for the inconvenience of managing a trial, there is nothing wrong with compensating subjects for any inconvenience they may undergo in participating in the trial – where that inconvenience is not connected with the topic of the trial. So laying on a minibus and a hot meal as compensation or circumvention of inconvenience is generally reasonable. But it is hard to tell where this turns into an inducement to participate.

The American poor, who are often also members of ethnic minorities, might well view this outreach

activity with some suspicion as a method of finding subjects to be “experimented on”, or as a technique of social control. The distance between active recruitment to extend the benefits of the trial and active recruitment to load the bulk of risks on the target population is all in the intention, which is to say, not very far.

The usual dilemma of trials: whether they represent an expected risk or an expected benefit to the patient plays havoc with any argument about the economic justice of the trial. It is as well to be aware that it is an issue for many patients; and because there are real, but weak, links between low income, low education, and ethnicity (especially in the US, where ethnic group and economic class are closely linked) which make for vulnerability and suspicion of “authority”, the possibility of injustice is always present.

In most cases the social injustice, like the risks and benefits of trial participation, are unpredictable. All that can reasonably be expected of a trial manager is that the best efforts are made to ensure a fair chance of enrolment for patients in the relevant population; that selection is made in such a way that the findings of the trial will be reliable and meaningful; and that some degree of explicitness is given to what is meant by “fairness”. Fairness might mean – to each according to his illness; to each according to his need; but not, hopefully, to each according to his desert.²⁹⁹ The fact that illness and need both have economic correlates is troubling to some extent, but is the way of the world. In the end, the risks of participation can be avoided by non-participation (refusal of consent). The efforts of healthcare professionals may be needed to make this an economically viable option.

Economic status, education and comprehension

A final issue concerning the economic justice of trials is the role of educational level. Naturally the well-educated will have a greater chance of understanding the consent process; it is unclear whether there is any constant link between educational level and trial consent. The evidence is conflicting, arguably because other factors come into play. Low educational level might imply greater trust in the doctor, or it might imply suspicion, for example.^{225,227} Educational level might be mistaken for degree of capacity for autonomous consent. There is a ring of plausibility to this: we might suppose the well-educated have a richer conception of their life chances and hopes and fears, and so when they make a choice, it is a commitment with greater significance and more durability. This can

be read between the lines of the literature on this topic – and more patronising rubbish we have yet to come across. The only consequence of lower educational level is that more care might be needed to give an accurate and comprehensible account of the choices available to the patient. So far as the quality of the choice is concerned, the care of the physician to be clear is far more significant.

To conclude this chapter: it is clear that many of the possible relevant socio-cultural factors are on the one hand relevant to RCTs in the same way as they are relevant to all healthcare. There are few issues which bear specifically on the RCT. Nearly all relevant issues have to do, in the end, with informed consent; and most have to do with how to deepen our understanding of what that consists of, so that we can secure its legitimacy as a protective rule. We have stressed that its role is protective, and that whatever merits we may be able to discern in it under some or other philosophical theory (for instance, the theory of moral autonomy), the importance of the rule does not stand or fall with such interpretations. The purpose of the ethical framework of the RCT is not to fix in advance which trials are ethical and which are not – as if it were possible to do so. Rather it is to construct a procedure such that while our cultural pre-suppositions may differ, we can all agree that the decision we make is ethical, however we differ about the reason why it is. In the case of human experimentation, the final determinant of ethical participation by a patient is their consent to participate. While we have broadened the account of the conditions under which consent is freely given, and seen that some attempts to broaden it further (as in the economic case) are subject to disagreement, the principal points remain: patients should be given choices, and the only people who can make those choices are the patients themselves, with the help of their friends, families, communities and physicians when they need it. Once we have separated out trials which are scientifically unnecessary, incompetent, cruel or involve deception, all other trials are in themselves ethically neutral, and represent the fairest context for patients to choose treatments when good evidence is lacking.

Concluding recommendations

- Attention should be paid by research ethics committees to the needs and values of the major religious traditions active in their area, preferably by direct representation, or at least

by recognising representatives of these traditions as experts from whom advice may be sought.

- Research programmes involving clinical trials should avoid systematically drawing on some socio-economic groups for their research subject, unless there is some *prima facie*, well-attested medical reason to do so, and there is a clear link between the socio-economic group in question and the medical problem under investigation.
- Further qualitative research is needed into the medical ethics of particular religious traditions, in particular Islam and the religious traditions of the Indian subcontinent. Materials here are lacking for any informed judgement.
- A shift in research emphasis away from ethics from the professional (medical, legal, scientific) viewpoint and toward the lay point of view is needed. Determining what patients and their families think of trials, particularly in the illuminating cases where recruitment proves difficult, is hard to do, on the basis of the present literature. Most literature presumes misunderstanding of the aims of trials or treatments, where in fact there may be understanding, but disagreement.

The RCT is, and will remain, in most respects the most effective and fairest method in Health Technology Assessment. There is no evidence for any systematic unfairness or misperception in the RCT methodology itself, at least in the British context, mainly because the economic factors applicable in the American healthcare delivery context do not obtain. Yet awareness of the sources of possible systematic unfairness should be raised, in order that this situation continue. One important way for this awareness to be increased would be to compile reviews and research into non-Christian traditions in medical ethics, particularly in those traditions well represented in the British Isles, and to disseminate this information to the healthcare professions. It is unlikely that any broad regulatory changes are necessary, but greater sensitivity will certainly contribute to the popularity of RCTs among patients, as well as among doctors. Where systematic unfairness does obtain, it obtains in the content, objects and scope of medical research – not in the methodology as such. The role of gender has not been much highlighted in this report, except in the American context, because UK regulations and the RCT methodology are gender-neutral. Enrolment and research priority setting may not be.



Acknowledgements

This work was funded by NHS R&D Health Technology Assessment Programme, grant number 93/41/4.

Dr Ashcroft thanks all the grant holders and members of the External Advisory Group for their invaluable assistance while working on this project. He also thanks the Department of Philosophy of

the University of Liverpool for providing a welcoming and intellectually stimulating environment and for hosting the project. He especially thanks the project Research Assistant, Ms Susan D Thompson, for carrying out the bulk of the searching tasks, administering the project, managing the database and preparing the search statistics, for many helpful suggestions and for her support.



References

Note: a full reference list is available online at <http://www.liv.ac.uk/~sdthomps/page1.html/> or in hard copy form on request from the first author.

1. Kerns TA. Ethical issues in HIV vaccine trials. Basingstoke: Macmillan, 1997.
2. Hill Sir AB. Medical ethics and controlled trials. *BMJ* 1963;**1**:1043–9.
3. Anon. The controlled clinical trial: a consensus? *Lancet* 1987;**5**:47–8.
4. Mike V. Towards an ethics of evidence – and beyond: observations on technology and illness. *Res Phil Technol* 1989;**9**:101–13.
5. Chalmers I. The Cochrane Collaboration: Preparing, maintaining and disseminating systematic reviews of the effects of health care. *Ann NY Acad Sci* 1993;**703**:156–65.
6. Herxheimer A. Clinical trials: two neglected ethical issues. *J Med Ethics* 1993;**19**:211–18.
7. Mike V. Philosophers assess randomised clinical trials: the need for dialogue. *Controlled Clinical Trials* 1989;**10**:244–53.
8. Leber P. Is there an alternative to the randomised controlled trial? *Psychopharmac Bull* 1991;**27**:3–8.
9. Kaufman D. Cancer therapy and the randomised clinical trial: good medicine? *Cancer* 1993;**72**:2801–4.
10. Papineau D. The virtues of randomisation. *Br J Phil Sci* 1994;**45**:712–15.
11. Urbach P. Randomisation and the design of experiments. *Phil Sci* 1987;**52**:256–73.
12. Urbach P. The value of randomisation and control in clinical trials. *Statistics in Medicine* 1993;**12**:1421–41.
13. Silverman WA, Altman DG. Patients' preferences and randomised trials. *Lancet* 1996;**347**:171–4.
14. Epstein S. Democratic science? AIDS activism and the contested construction of knowledge. *Socialist Review* 1991;**21**:35–64.
15. Berkowitz S. Ethical issues in the case of surgical repair of cleft palate. *Cleft Palate – Cranio-facial J* 1995;**32**:271–81.
16. Charlton BG. Randomised clinical trials: the worst kind of epidemiology? *Nature Medicine* 1995;**1**:1101–2.
17. Gehan EA, Freireich EJ. Non-randomised controls in cancer clinical trials. *N Engl J Med* 1974;**290**:198–203.
18. Hare RM, editor. Little human guinea pigs. In: Essays in bioethics. Oxford: Oxford University Press, 1993:131–46.
19. Starzl TE, Donner A, Eliasziw M, Stitt L, Meier P, Fung JJ, *et al.* Randomised trialomania? The multicentre liver transplant trials of tacrolimus. *Lancet* 1995;**346**:1346–50.
20. Hill Sir AB. Statistical methods in clinical and preventive medicine. Edinburgh: E & S Livingstone, 1962.
21. Cochrane AL. Effectiveness and efficiency: random reflections on health services. London: Nuffield Provincial Hospitals Trust, 1971.
22. Armitage P. Bradford Hill and the randomised controlled trial. *Pharmaceutical Medicine* 1992;**6**:23–7.
23. Doll R. Sir Austin Bradford Hill and the progress of medical science. *BMJ* 1992;**305**:1521–6.
24. Lock S. The randomised controlled trial: a British invention. In: Lawrence G, editor. Technologies of modern medicine. Proceedings of a seminar held at the Science Museum, London, March 1993. London: Science Museum, 1994:81–7.
25. Palmer CR. Ethics and statistical methodology in clinical trials. *J Med Ethics* 1993;**19**:219–22.
26. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in clinical trials. *J Chron Dis* 1967;**20**:637–48.
27. Annas GJ. The changing landscape of human experimentation: Nuremberg, Helsinki and beyond. *Health Matrix* 1992;**2**:119–40.
28. Annas GJ, Grodin MA, editors. The Nazi Doctors and the Nuremberg Code: human rights in human experimentation. Oxford: Oxford University Press, 1992.
29. Harris S. Japanese biological warfare research on humans: a case study of microbiology and ethics. *Ann NY Acad Sci* 1992;**666**:21–52.
30. Howard-Jones N. Human experimentation in historical and ethical perspectives. *Soc Sci Med* 1982;**16**:1429–48.
31. Lederer S. Subjected to science: human experimentation in America before the Second World War. Baltimore: Johns Hopkins University Press, 1995.

32. Scherzer A. Lessons from the Holocaust for American medicine. *J Med Assoc Georgia* 1994;**83**:211–6.
33. Shevell MI, Evans BK. The “Schaltenbrand Experiment”, Wuerzburg 1940: scientific, historical and ethical perspectives. *Neurology* 1994;**44**:350–6.
34. Advisory Commission on Human Radiation Experiments Research Ethics and the medical profession. *JAMA* 1996;**276**:403–9.
35. Levine RJ. Ethics and regulation of clinical research. Baltimore: Urban & Schwarzenberg, 1986.
36. Beauchamp TL, Childress JF. Principles of biomedical ethics, Fourth edn. Oxford: Oxford University Press, 1994.
37. Mayo O. Comments on “Randomisation and the design of experiments” by Peter Urbach. *Phil Sci* 1987;**54**:592–6.
38. Freedman B. Equipoise and the ethics of clinical research. *N Engl J Med* 1987;**317**:141–5.
39. Lilford RJ, Jackson J. Equipoise and the ethics of randomisation. *J R Soc Med* 1995;**88**:552–9.
40. Johnson N, Lilford RJ, Brazier W. At what level of collective equipoise does a clinical trial become ethical? *J Med Ethics* 1991;**17**:30–4.
41. Alderson P. Equipoise as a means of managing uncertainty: personal, communal and proxy. *J Med Ethics* 1996;**22**:135–9.
42. Baum M, Houghton J, Abrams K. Early stopping rules: clinical perspectives and ethical considerations. *Statistics in Medicine* 1994;**13**:1459–69.
43. Berry DA. Interim analyses in clinical trials: classical versus Bayesian approaches. *Statistics in Medicine* 1985;**4**:521–6.
44. George SL, Li C, 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**:1313–23.
45. Hutton JL. The ethics of randomised controlled trials: a matter of statistical belief? *Health Care Analysis* 1996;**4**:95–102.
46. Clouser KD, Gert B. A critique of principlism. *J Med Phil* 1990;**15**:219–36.
47. Gifford F. The conflict between randomised clinical trials and the therapeutic obligation. *J Med Phil* 1986;**11**:347–66.
48. Kodish E, Lantos JD, Siegler MD. Ethical considerations in randomised controlled clinical trials. *Cancer* 1990;**65**:2400–4.
49. Levine RJ. Ethics of clinical trials: Do they help the patient? *Cancer* 1993;**72**:2805–10.
50. Royall RM. Ethics and statistics in randomised clinical trials. *Statistical Science* 1991;**6**:52–88.
51. Baum M. Clinical trials – a brave new partnership: a response to Mrs Thornton. *J Med Ethics* 1994;**20**:23–5.
52. Chalmers TC. Randomised clinical trials in surgery. In: Varco RL and Delany LJP, editors. Controversy in surgery. Philadelphia: WB Saunders, 1976:3–11.
53. Gross M. Innovations in surgery: a proposal for phased clinical trials. *J Bone Joint Surgery [Br]* 1993;**75-B**:351–4.
54. Rosner F. The ethics of randomised clinical trials. *Am J Med* 1987;**82**:283–90.
55. Senn SJ. A personal view of some controversies in allocating treatment to patients in clinical trials. *Statistics in Medicine* 1995;**14**:2661–74.
56. Simon R. Randomised clinical trials in oncology. *Cancer* 1994;**74**:2614–19.
57. Jeffrey RC. How reasonable is it to base preferences on estimates of chance? In: Mellor DH, editor. Science, belief and behaviour: essays in honour of RB Braithwaite. Cambridge: Cambridge University Press, 1980:179–87.
58. Levi I. Four themes in statistical explanation. In: Harper WL and Skyrms B, editors. Causation in decision, belief change and statistics. Proceedings of the Irvine Conference on Probability and Causation, Vol. II. Dordrecht: Kluwer Academic Publishers, 1988:195–222.
59. Mayo DG. Behaviouristic, evidentialist, and learning models of statistical testing. *Phil Sci* 1985;**52**:493–516.
60. Mike V. Understanding uncertainties in medical evidence: professional and public responsibilities. In: Mayo DG and Hollander R, editors. Acceptable evidence: science and values in hazard management. Cambridge: Cambridge University Press, 1991:115–36.
61. Thornton H. Clinical trials – a brave new partnership? *J Med Ethics* 1994;**20**:19–22.
62. Altman DG, Whitehead J, Parmar MKB, Stening SP, Fayers PM, Machin D. Randomised consent designs in cancer clinical trials. *European J Cancer* 1995;**31A**:1934–44.
63. Ellenberg SS. Randomisation designs in comparative clinical trials. *N Engl J Med* 1984;**310**:1404–8.
64. Simon R. A decade of progress in statistical methodology for clinical trials. *Statistics in Medicine* 1991;**10**:1789–817.
65. Zelen M. Randomised consent designs for clinical trials: an update. *Statistics in Medicine* 1990;**9**:645–56.
66. Papineau D. Review article: Correlations and causes. *Br J Phil Sci* 1991;**42**:397–412.

67. Feinstein AR. Epidemiologic analyses of causation: the unlearned scientific lessons of randomised trials. *J Clin Epidemiol* 1989;**42**:481–9.
68. Giere RN. Knowledge, values and technological decisions: a decision theoretic approach. In: Mayo DG and Hollander R, editors. *Acceptable evidence: science and values in hazard management*. Cambridge: Cambridge University Press, 1991: 183–203.
69. Schaffner KF. Causing harm: Epidemiological and physiological concepts of causation. In: Mayo DG and Hollander R, editors. *Acceptable evidence: science and values in hazard management*. Cambridge: Cambridge University Press, 1991:204–17.
70. Ross DC. Using severity rather than randomisation for assignment in clinical trials: Monte Carlo tests and practical illustrations of the Robbins–Zhang method. *J Psychiatr Res* 1995;**29**:315–32.
71. Lockwood M, Anscombe GEM. Sins of omission? The non-treatment of controls in clinical trials. *Aristotelian Society* 1983;**LVII** suppl:207–27.
72. Pocock SJ. Statistical and ethical issues in monitoring clinical trials. *Statistics in Medicine* 1993;**12**:1459–75.
73. Elander G, Hermeren G. Placebo effects and randomised clinical trials. *Theoretical Medicine* 1995;**16**:171–82.
74. de Heyn PP, d’Hooge R. Placebos in clinical practice and research. *J Med Ethics* 1996;**22**:140–6.
75. Paterson C. Placebo effects: psychological, sociological and general practice research may elucidate effects. *BMJ* 1995;**311**:1640.
76. Shorter E. *From paralysis to fatigue: a history of psychosomatic illness in the modern era*. New York: The Free Press, 1992.
77. Sullivan MD. Placebo controls and epistemic control in orthodox medicine. *J Med Phil* 1993;**18**:213–31.
78. Hill Sir AB. The clinical trial. *Br Med Bull* 1951;**7**:278–82.
79. Hill Sir AB. The clinical trial. *N Engl J Med* 1952;**247**:113–9.
80. Abt K. Planning controlled clinical trials on the basis of descriptive data. *Statistics in Medicine* 1991;**10**:777–95.
81. Clark PI, Leaverton PE. Scientific and ethical issues in the use of placebo controls in clinical trials. *Ann Rev Public Health* 1994;**15**:19–38.
82. Cleophas TJM. Clinical trials: specific problems associated with the use of a placebo-control group. *J Mol Med* 1995;**73**:421–4.
83. Collier J. Confusion over use of placebos in clinical trials: better guidelines needed. *Br Med J* 1995;**311**:821–2.
84. Rothman KJ, Michels KB. The continuing unethical use of placebo controls. *N Engl J Med* 1994;**331**:394–8.
85. (a) Rothman KJ. Placebo mania: as medical knowledge accumulates, the number of placebo trials should fall. *BMJ* 1996;**313**:3–4.
(b) Orr RD. Ethical use of placebos in clinical trials. *J Family Practice* 1996;**42**:85–6.
86. Charlton BG. Mega-trials: methodological issues and clinical implications. *J R Coll Physicians* 1995;**29**:96–100.
87. Datta M. You cannot exclude the explanation you have not considered. *Lancet* 1993;**342**:345–7.
88. Berry DA. A case for Bayesianism in clinical trials. *Statistics in Medicine* 1993;**12**:1377–404.
89. Freedman L. Bayesian statistical methods: a natural way to assess clinical evidence. *BMJ* 1996;**313**:569–70.
90. Whitehead J. The case for frequentism in clinical trials. *Statistics in Medicine* 1993;**12**:1405–19.
91. Zelen M, Parker RA. Case-control studies and Bayesian inference. *Statistics in Medicine* 1986;**5**:261–9.
92. D’Agostino RB, Kwan H. Measuring effectiveness: what to expect without a randomised control group. *Medical Care* 1995;**33**:AS95–AS105.
93. Ratain MJ, Mick R, Schilsky RL, Siegler M. Statistical and ethical issues in the design and conduct of phase I and II clinical trials of new anticancer agents. *J National Cancer Institute* 1993;**85**:1637–43.
94. Schmoor C, Olschewski M, Schumacher M. Randomised and non-randomised patients in clinical trials: experiences with comprehensive cohort studies. *Statistics in Medicine* 1996;**15**:263–71.
95. 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. *JAMA* 1995;**273**:408–12.
96. Berry DA, Eick SG. Adaptive assignment versus balanced randomisation in clinical trials: a decision analysis. *Statistics in Medicine* 1995;**14**:231–46.
97. Ellenberg JH. Cohort studies: selection bias in observational and experimental studies. *Statistics in Medicine* 1994;**13**:557–67.
98. Freedman LS, Spiegelhalter DJ, Parmar MKB. The what, why, and how of Bayesian clinical trials monitoring. *Statistics in Medicine* 1994;**13**:1371–83.
99. Altman DG, Bland JM. Improving doctors’ understanding of statistics. *J R Statistical Soc A* 1991;**154** part 2:223–67.
100. Howson C, Urbach P. *Scientific reasoning: the Bayesian approach*, Second edn. La Salle, IL: Open Court, 1992.

101. Evidence-based Medicine Working Group. Evidence-based medicine: a new approach to teaching the practice of medicine. *JAMA* 1992;**268**:2420–5.
102. Logue G, Wear S. A desperate solution: individual autonomy and the double-blind controlled experiment. *J Med Phil* 1995;**20**:57–64.
103. McPherson K. The best and the enemy of the good: randomised controlled trials, uncertainty and assessing the role of patient choice in medical decision-making. *J Epidemiology & Community Health* 1994;**48**:6–15.
104. Shumm DS, Spece RG. Ethical issues and clinical trials. *Drugs* 1993;**46**:579–84.
105. Fineman N. The social construction of non-compliance: implications for cross-cultural geriatric practice. *J Cross-cultural Gerontology* 1991;**6**:219–27.
106. Lilford RJ, Thornton JG, Braunholtz D. Clinical trials and rare diseases: a way out of a conundrum. *BMJ* 1995;**311**:1621–5.
107. Sniderman AD. The governance of clinical trials. *Lancet* 1996;**347**:1387–8.
108. Newell DJ. Intention-to-treat analysis: implications for quantitative and qualitative research. *Int J Epidemiol* 1992;**21**:837–41.
109. Sheiner LB, Rubin DB. Intention-to-treat analysis and the goals of clinical. *Clinical Pharmacological Therapy* 1995;**57**:6–15.
110. Delini-Stula A, Berdah-Tordjman D. Placebo-controlled studies in acute-schizophrenia: an issue of concern. *European Psychiartry* 1994;**9**:165–73.
111. Caplan AL, editor. Is there a duty to serve as a subject in biomedical research? In: If I were a rich man could I buy a pancreas? And other essays on the ethics of healthcare, Chapter 6. Bloomington, IN: Indiana University Press, 1992.
112. Emson HE. Rights, duties and responsibilities in healthcare. *J Appl Phil* 1992;**9**:3–11.
113. Rothman DJ. Ethics and human experimentation: Henry Beecher revisited. *N Engl J Med* 1987;**317**:1195–9.
114. Jones JH. Bad blood: the Tuskegee syphilis experiment. Glencoe: Free Press, 1993.
115. Annas GJ. The Nuremberg code in US courts: ethics versus expediency. In: Annas GJ and Grodin MA, editors. The Nazi Doctors and the Nuremberg Code: human rights in human experimentation. Oxford: Oxford University Press, 1992.
116. Bush JK. The industry perspective on the inclusion of women in clinical trials. *Academic Medicine* 1994;**69**:708–15.
117. Dresser R. Wanted: single, white male for medical research. *Hastings Center Report* 1992;**22**:24–9.
118. McCarthy CR. Historical background of clinical trials involving women and minorities. *Academic Medicine* 1994;**69**:695–8.
119. Mastroianni AC, Faden R, Federman D. Women and health research: a report from the Institute of Medicine. *Kennedy Institute of Ethics J* 1994;**4**:55–61.
120. Merton V. The exclusion of the pregnant, pregnable and once-pregnable people (a.k.a. women) from biomedical research. *Am J Law Med* 1993;**XIX**:369–451.
121. Merkatz RB, Junod SW. Historical background of changes in FDA policy on the study and evaluation of drugs in women. *Academic Medicine* 1994;**69**:703–7.
122. Warren CAB, Karner TX. Permissions and the social context. *American Sociologist* 1990;116–35.
123. Lesser H. Obligation and consent. *J Med Ethics* 1989;**15**:195–6.
124. Engelhardt HT Jr. Foundations of bioethics, Second edn. Oxford: Oxford University Press, 1996.
125. Freedman B, Fuks A, Weijer C. Demarcating research and treatment: a systematic approach for the analysis of the ethics of clinical research. *Clin Res* 1992;**40**:653–60.
126. Reiser SJ. Human experimentation and the convergence of medical research and patient care. *Annals of the AAPSS* 1978;**437**:8–18.
127. Reiser SJ. Criteria for standard versus experimental therapy. *Health Affairs* 1994;**13**:127–36.
128. Allmark P. An argument against the use of the concept of ‘persons’ in health care ethics. *J Adv Nursing* 1994;**19**:29–35.
129. Gillon R. Autonomy, respect for autonomy and weakness of the will. *J Med Ethics* 1993;**19**:195–6.
130. Pellegrino ED. The relationship of autonomy and integrity in medical ethics. *Bulletin of the Pan-American Health Organisation* 1990;**24**:361–71.
131. Karlawish JHT, Hall JB. The controversy over emergency research: a review of the issues and suggestions for a resolution. *Am J Resp Crit Care Med* 1996;**153**:499–506.
132. Sheldon T. Consent is not always essential, say Dutch experts. *BMJ* 1995;**310**:1355–6.
133. Jonas C, Soutoul JH. Biomedical research in incapacitated people according to French law. *Medical Law* 1993;**12**:567–72.
134. Hodgkinson DW, Gray AJ, Dalal B, Wilson P, Szawarski Z, Sensky T, *et al.* Doctor’s legal position in treating temporarily incompetent patients. *BMJ* 1995;**311**:115–8.

135. (a) Perry CB. Conflicts of interest and the physician's duty to inform. *Am J Med* 1994;**96**:375–80.
- (b) Brownell KD, Stunkard AJ. The double-blind in danger: untoward consequences of informed consent. *Am J Psychiat* 1982;**139**:1487–9.
136. Jewson ND. The disappearance of the Sick-Man from medical cosmology, 1770–1870. *Sociology* 1976;**10**:225–44.
137. Jonas H. Philosophical reflections on experimenting with human subjects. *Daedalus* 1969;**98**:219–47.
138. Fethé C. Beyond voluntary consent: Hans Jonas on the moral requirements of human experimentation. *J Med Ethics* 1993;**19**:99–103.
139. Beecher HK. Research and the individual. London: J & A Churchill, 1970.
140. Beecher HK. Ethics and clinical research. *N Engl J Med* 1966;**274**:1354–60.
141. Popper SE, McCloskey K. Ethics in human experimentation: historical perspectives. *Military Medicine* 1995;**160**:7–11.
142. Buchanan A. Judging the past: the case of the human radiation experiments. *Hastings Center Report* 1996; **26** (May/June):25–30.
143. Burchell HB. Vicissitudes in clinical trial research: subjects, participants, patients. *Controlled Clinical Trials* 1992;**13**:185–9.
144. Evered DC, Halnan KE. Deadly experiments. *BMJ* 1995;**311**:192.
145. Pappworth MH. 'Human guinea pigs' – a history. *BMJ* 1990;**301**:1456–60.
146. Tobias JS, Souhami RL. Fully informed consent can be needlessly cruel. *BMJ* 1993;**307**:1199–201.
147. Garnham JC. Some observations on informed consent in non-therapeutic research. *J Med Ethics* 1975;**1**:138–45.
148. Byrne P. Medical research and the human subject: Problems of consent and control in the UK experience. *Ann NY Acad Sci* 1988;**530**:144–53.
149. Reiser SJ, Knudson P. Protecting research subjects after consent: the case for the 'Research Intermediary'. *IRB* 1993;**15**:10–1.
150. Silverman WA. The myth of informed consent: in daily practice and in clinical trials. *J Med Ethics* 1989;**15**:6–11.
151. Rosenzweig S. The experimental situation as a psychological problem. *Psychol Rev* 1933;**40**:337–54.
152. Daugherty 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. *J Clin Oncology* 1995;**13**:1062–72.
153. Susman EJ, Dorn LD, Fletcher JC. Participation in biomedical research: the consent process as viewed by children, adolescents, young adults and physicians. *J Pediatrics* 1992;**121**:547–52.
154. Nguyen-Van-Tam JS, Madeley RJ. Vietnamese people in study may have had language difficulties. *BMJ* 1996;**313**:48.
155. Habermas J. Communication and the evolution of society. London: Heinemann Educational, 1979.
156. Alderson P. Consent and the social context. *Nursing Ethics* 1995;**2**:347–50.
157. Alderson P. Trust in informed consent. *IME Bulletin* 1988;: 17–9.
158. Andreasson S, Parmander M, Allebeck P. A trial that failed, and the reasons why: comparing the Minnesota model with outpatient treatment and non-treatment for alcohol disorders. *Scand J Soc Med* 1990;**18**:221–4.
159. Angell M. Patients' preferences in randomised clinical trials. *N Engl J Med* 1984;**310**:1385–7.
160. Beech CL. Compliance in clinical trials. *AIDS* 1995;**9**:1–10.
161. Brownlea A. Participation: myths, realities and prognosis. *Soc Sci Med* 1987;**25**:605–14.
162. Daugherty CK, Ratain MJ, Siegler M. Pushing the envelope: informed consent in Phase I trials. *Annals of Oncology* 1995;**6**:321–3.
163. DeLuca SA, Korcusk LA, Oberstar BH, Rosenthal ML, Welsh PA, Topol EJ. Are we providing true informed consent in cardiovascular clinical trials? *J Cardiovascular Nursing* 1995;**9**(3):54–61.
164. Fox R. What do patients want from medical research? *J R Soc Med* 1996;**89**:301–2.
165. Gostin LO. Informed consent, cultural sensitivity and respect for persons. *JAMA* 1995;**274**:844–5.
166. Grimshaw JM. Clinical trials: patient perspectives. *AIDS* 1990;**4** suppl 1:S207–8.
167. Joseph RR. Viewpoints and concerns of a clinical trial participant. *Cancer* 1994;**74**:2692–3.
168. Kotwall CA, Mahoney LJ, Myers RE, Decoste L. Reasons for non-entry in randomised clinical trials for breast cancer: a single institutional study. *J Surg Oncology* 1992;**50**:125–9.
169. Lilleyman JS. Informed consent: how informed and consent to what? *Pediatric Hematology and Oncology* 1995;**12**(6):xiii–xvi.
170. Llewellyn-Thomas HA, McGreal MJ, Thiel EC, Fine S, Erlichman C. Patients' willingness to enter clinical trials: measuring the association with perceived benefit and preference for decision participation. *Soc Sci Med* 1991;**32**:35–42.

171. McGrath P. It's OK to say no! A discussion of ethical issues arising from informed consent to chemotherapy. *Cancer Nursing* 1995;**18**:97–103.
172. (a) Winn RJ. Obstacles to the accrual of patients to clinical trials in the community setting. *Seminars in Oncology* 1994;**21** (4, suppl 7):112–7.
(b) Thornton H. Many subjects in trial were not asked for consent. *BMJ* 1996;**312**:509.
173. Benson PR. The social control of human biomedical research: an overview and review of the literature. *Soc Sci Med* 1989;**29**:1–12.
174. McKay CR. The evolution of the institutional review board: a brief overview of its history. *Clinical Research and Regulatory Affairs* 1995;**12**:65–94.
175. McNeill PM. The ethics and politics of human experimentation. Cambridge: Cambridge University Press, 1993.
176. DeBakey L. Ethically questionable data: publish or reject? *Clin Res* 1974;**22**:113–21.
177. Rosner F, Bennett AJ, Cassell EJ, Farnworth PB, Halpern AL, Henry JB, *et al*. The ethics of using scientific data obtained by immoral means. *NY State J Med* 1991;**91**:54–9.
178. Smith R. Commentary: The importance of patients' consent for publication. *BMJ* 1996;**313**:6.
179. Carnall. Doctor struck off for scientific fraud. *BMJ* 1996;**312**:400.
180. Dyer O. GP struck off for fraud in drug trials. *BMJ* 1996;**312**:798.
181. Faden RR, Beauchamp TL. A history and theory of informed consent. Oxford: Oxford University Press, 1986.
182. Myers MG, Cairns JA, Singer J. The consent form as a possible cause of side effects. *Clinical Pharmacological Therapy* 1987;**42**:250–3.
183. Levinsky NG. Social, institutional and economic barriers to the exercise of patients' rights. *N Engl J Med* 1996;**334**:532–4.
184. Nussbaum MC. The therapy of desire: studies in hellenistic ethics. Princeton, NJ: Princeton University Press, 1994.
185. Antman K. Reimbursement issues facing patients, providers and payers. *Cancer* 1993;**72**:2842–5.
186. Berkman BJ, Sampson SE. Psychosocial effects of cancer economics on patients and their families. *Cancer* 1993;**72**:2846–9.
187. Harth SC, Johnstone RR, Thong YH. The psychosocial profile of parents who volunteer their children for clinical research: a controlled study. *J Med Ethics* 1992;**18**:86–93.
188. Schwartz CE, Fox BH. Who says yes? Identifying selection biases in psychosocial intervention study of multiple sclerosis. *Soc Sci Med* 1995;**40**:359–70.
189. Anderson JM. Empowering patients: issues and strategies. *Soc Sci Med* 1996;**43**:697–705.
190. Koch HJ. The concept of balanced autonomy in therapeutic and non-therapeutic trials. *Controlled Clinical Trials* 1995;**16**:182–3.
191. Wilson-Barnett J. Limited autonomy and partnership: professional relationships in health care. *J Med Ethics* 1989;**15**:12–6.
192. Zion D. Can communities protect autonomy? Ethical dilemmas in HIV preventative drug trials. *Cambridge Quarterly of Healthcare Ethics* 1995;**4**:516–23.
193. Aspinall CL. Family focused ethics. *Cleft-Palate – Cranio-facial J* 1995;**32**:507–9.
194. Anon. The case of the coercive family. *Cambridge Quarterly of Healthcare Ethics* 1995;**4**:135–42.
195. Ashcroft JJ, Leinster SJ, Slade PD. Breast cancer – patient choice of treatment: preliminary communication. *J R Soc Med* 1985;**78**:43–6.
196. Gillon R, Lloyd A. Principles of health care ethics, part I. Chichester: John Wiley, 1994:1–334.
197. Delany L, Month S, Savulescu J, Browett P, Palmer S. Altruism by proxy: volunteering children for bone marrow donation. *BMJ* 1996;**312**:240–3.
198. Finfer S, Howell S, Miller J, Willett K, Wilson-Macdonald, Wilson DH, *et al*. Managing patients who refuse blood transfusions: an ethical dilemma. *BMJ* 1994;**308**:1423–6.
199. Ishiwata R, Sakai A. The physician-patient relationship and medical ethics in Japan. *Cambridge Quarterly of Healthcare Ethics* 1994;**3**:60–6.
200. Levine RJ. Informed consent: some challenges to the universal validity of the Western model. *Law, Medicine and Healthcare* 1991;**19**:207–13.
201. Sanwal AK, Kumar S, Sahni P, Nundy P. Informed consent in Indian patients. *J R Soc Med* 1996;**89**:196–8.
202. Gifford F. Community-equipoise and the ethics of randomised clinical trials. *Bioethics* 1995;**9**:127–48.
203. Bilu Y, Witztum E. Working with Jewish ultra-orthodox patients: guidelines for a culturally sensitive therapy. *Culture, Medicine and Psychiatry* 1993;**17**:197–233.
204. Gerber L. Psychotherapy with south-east Asian refugees: implications for treatment of western patients. *Am J Psychotherapy* 1994;**48**:280–93.
205. Kirmayer LJ, Young A, Robbins JM. Symptom attribution in cultural perspective. *Can J Psychiatry* 1994;**39**:584–95.
206. Littlewood R, Dein S. The effectiveness of words: religion and healing among the Lubavitch of Stamford Hill. *Culture, Medicine and Psychiatry* 1995;**19**:339–83.

207. Young A. The anthropologies of illness and sickness. *Ann Rev Anthropology* 1982;**11**:257–85.
208. Acha RA, Gureje O. The use of ethnographic methods in medical research: experience with substance use disorders. *W African Med J* 1994;**13**:146–9.
209. Bhopal RS. The interrelationship of folk, traditional and western medicine within an Asian community in Britain. *Soc Sci Med* 1986;**22**:99–105.
210. Bhopal RS. Bhye bhaddi: a food and health concept of Punjabi Asians. *Soc Sci Med* 1986;**23**:687–8.
211. Browner CH, Ortiz de Montellano BR, Rubel AJ. A methodology for cross-cultural ethnomedical research. *Current Anthropology* 1988;**29**:681–702.
212. Heggenhougen HK, Shore L. Cultural components of behavioural epidemiology: implications for primary health care. *Soc Sci Med* 1986;**22**:1235–48.
213. McGuire MB, Kantor DJ. Belief systems and illness experiences: the case of non-medical healing groups. *Research in the Sociology of Healthcare* 1987;**6**:221–48.
214. Maretzki TW, Seidler E. Biomedicine and naturopathic healing in West Germany: a historical and ethnomedical view of a stormy relationship. *Culture, Medicine and Psychiatry* 1985;**9**:383–421.
215. Nash C. Interpreting cultural difference in medical intervention: the use of Wittgenstein's 'forms of life'. *J Clinical Ethics* 1993;**4**:188–91.
216. Payer L. *Medicine and culture: varieties of treatment in the United States, England, West Germany and France*. New York: Penguin, 1988.
217. Scheper-Hughes N. AIDS and the social body. *Soc Sci Med* 1994;**39**:991–1003.
218. Teichman M, Teichman Y, Converse J Jr, Foa UG. Interpersonal needs of drug addicts: are they similar across cultures? *Int J Addiction* 1992;**27**:281–8.
219. Pantilat SZ, Fenyvesi T, Fitzgibbons S, Kazal LA Jr, Pastorek JG, III. Patient–physician communication: respect for culture, religion and autonomy. *JAMA* 1996;**275**:107–10.
220. Goffman E. *Stigma*. Harmondsworth: Penguin, 1970.
221. Dula A. African American suspicion of the healthcare system is justified: what do we do about it? *Cambridge Quarterly of Healthcare Ethics* 1994;**3**:347–57.
222. Freeman HP. The impact of clinical trial protocols on patient care systems in a large city hospital: access for the socially disadvantaged. *Cancer* 1993;**72**:2834–8.
223. Gamble VN. A legacy of distrust: African Americans and medical research. *Am J Preventive Med* 1993;**9** suppl:35–8.
224. Lenhard RE Jr. A large private university hospital system. *Cancer* 1993;**72**:2820–3.
225. Millon-Underwood S, Sanders S, Davis M. Determinants of participation in state-of-the-art cancer prevention, early detection/screening and treatment trials among African Americans. *Cancer Nursing* 1993;**16**:25–33.
226. O'Neil JD. The cultural and political context of patient dissatisfaction in cross-cultural clinical encounters: a Canadian Inuit study. *Medical Anthropology Quarterly* 1989;**3**:325–44.
227. Roberson NL. Clinical trial participation: viewpoints from racial/ethnic groups. *Cancer* 1994;**74**:2687–91.
228. Singer M. AIDS and the health crisis of the US urban poor: the perspective of critical medical anthropology. *Soc Sci Med* 1994;**39**:931–48.
229. Sperber AD, Henkin Y, Shanty S. Methodological issues in conducting a community-based clinical drug trial. *Family Practice Res J* 1993;**13**:311–21.
230. Winn RJ. Obstacles to the accrual of patients to clinical trials in the community setting. *Seminars in Oncology* 1994;**21** suppl 7:112–7.
231. Carrese JA, Rhodes LA. Western bioethics on the Navajo reservation: benefit or harm? *JAMA* 1996;**274**:826–9.
232. Christakis NA. Ethics are local: engaging cross-cultural variation in the ethics of clinical research. *Soc Sci Med* 1992;**35**:1079–91.
233. Elliot C. Where ethics comes from and what to do about it. *Hastings Center Report* 1992;**22**:28–35.
234. Orona CJ, Koenig BA, Davis AJ. Cultural aspects of nondisclosure. *Cambridge Quarterly of Healthcare Ethics* 1994;**3**:338–46.
235. Wang V, Marsh FH. Ethical principles and cultural integrity in health care delivery: Asian ethnocultural perspectives in genetic services. *J Genetic Counselling* 1992;**1**:80–92.
236. Davis DS. It ain't necessarily so: clinicians, bioethics and religious studies. *J Clin Ethics* 1994;**5**:315–9.
237. Enquesslassie F, Nokes J, Cutts F. Communities' confidentiality should be maintained and community consent sought. *BMJ* 1996;**312**:54–5.
238. Gillon R. Biomedical ethics in Europe – a need for the POBS. *J Med Ethics* 1993;**19**:3–4.
239. Schwartz RL. Multiculturalism, medicine and the limits of autonomy: the practice of female circumcision. *Cambridge Quarterly of Healthcare Ethics* 1994;**3**:431–44.
240. Wreen MJ. Autonomy, religious values and the refusal of lifesaving treatment. *J Med Ethics* 1991;**17**:124–30.
241. Charatan F. US religious groups oppose gene patents. *BMJ* 1995;**310**:1351.
242. Alberti KGMM. Local research ethics committees: time to grab several bulls by the horns. *BMJ* 1995;**311**:639–41.

243. Cookson JB. Auditing a research ethics committee. *JR Coll Physicians* 1992;**26**:181–3.
244. Garfield P. Cross district comparison of applications to research ethics committees. *BMJ* 1995;**311**:660–1.
245. Horner JS. Criteria for decision-making in local research (ethics) committees. *Public Health* 1993;**107**:403–11.
246. Hotopf M, Wessely S, Noah N. Are ethics committees reliable? *JR Soc Med* 1995;**88**:31–3.
247. Meade TW. The trouble with ethics committees. *JR Coll Physicians* 1994;**28**:102–4.
248. Middle C, Johnson A, Petty T, Sims L, MacFarlane A. Ethics approval for a national postal survey: recent experience. *BMJ* 1995;**311**:659–60.
249. While AE. Ethics committees: impediments to research or guardians of ethical standards? *BMJ* 1995;**311**:661.
250. Warren CAB, Staples WG. Fieldwork in forbidden terrain: the state, privatisation and human subjects regulations. *American Sociologist* 1989;**20**:263–77.
251. Boyle J. Radical moral disagreement in contemporary health care: a Roman Catholic perspective. *J Med Phil* 1994;**19**:183–200.
252. Brown J. Prenatal screening in Jewish law. *J Med Ethics* 1990;**16**:75–80.
253. Rispler-Chaim V. Islamic medical ethics in the 20th century. *J Med Ethics* 1989;**15**:203–8.
254. Schostak Z. Jewish ethical guidelines for resuscitation and artificial nutrition and hydration of the dying elderly. *J Med Ethics* 1994;**20**:93–100.
255. Wu Z. Conflicts between Chinese traditional ethics and bioethics. *Cambridge Quarterly of Healthcare Ethics* 1994;**3**:367–71.
256. Veatch RM, Mason CM. Hippocratic versus Judeo-Christian medical ethics: principles in conflict. *J Religious Ethics* 1987;**15**:86–105.
257. Barry M, Molyneux M. Ethical dilemmas in malaria drug and vaccine trials: a bioethical perspective. *J Med Ethics* 1992;**18**:189–92.
258. Basch PF. Technology transfer to the developing world: does new technology have any relevance for developing countries? *Tubercle and Lung Disease* 1993;**74**:353–8.
259. Frankenberg R. Medical anthropology and development: a theoretical perspective. *Soc Sci Med* 1980;**14B**:197–207.
260. Maier-Lenz H. Implementing multicentre, multinational clinical trials. *Drug Information J* 1993;**27**:1077–81.
261. Marshall P, Thomasma DC, Bergsma J. Intercultural reasoning: the challenge for international bioethics. *Cambridge Quarterly of Healthcare Ethics* 1994;**3**:321–8.
262. Mull JD. Innovation and behaviour change: applied anthropology strategies for international health and cross-cultural medicine. *Infectious Disease Clinics of North America* 1995;**9**:245–64.
263. Oakley A. Who's afraid of the randomised controlled trial? Some dilemmas of the scientific method and 'good' research practice. *Women and Health* 1989;**15**:25–59.
264. Ritrovato CA, Dinella C. The representation of women in clinical drug trials. *Drug Information J* 1995;**29**:147–54.
265. Rogers B. Gender differences in research. *AAOHN J* 1994;**42**:30–2.
266. Wermeling DP, Selwitz AS. Current issues surrounding women and minorities in drug trials. *Annals of Pharmacotherapy* 1993;**27**:904–11.
267. Andersson F, Glasier A, Ross J, Baird DT. Attitudes of women to fetal tissue research. *J Med Ethics* 1994;**20**:36–40.
268. Rosser SV. Re-visioning clinical research: gender and the ethics of experimental design. *Hypatia* 1989;**4**:125–39.
269. Hillis JW, Wortman CB. Some determinants of public acceptance of randomised control group experimental designs. *Sociometry* 1976;**39**:91–6.
270. Kymlicka W. Liberalism, community and culture. Oxford: Oxford University Press, 1989.
271. Verdun-Jones S, Weisstub DN. Consent to human experimentation in Quebec: the application of the civil law principle of personal inviolability to protect special populations. *Int J Law Psychiatry* 1995;**18**:163–82.
272. Warnock M. A national ethics committee: to meet the growing public demand for candour. *BMJ* 1988;**297**:1626–7.
273. Watling MIL, Dewhurst JK. Current experience of central versus local ethics approval in multicentre studies. *JR Coll Physicians* 1993;**27**:399–402.
274. Hacking I. The emergence of probability. Cambridge: Cambridge University Press, 1975.
275. Kee F. Patients' prerogatives and perceptions of benefit. *BMJ* 1996;**312**:958–60.
276. Kant I. Groundwork of the metaphysics of morals.
277. Delano SJ, Zucker JL. Protecting mental health research subjects without inhibiting progress. *Hospital and Community Psychiatry* 1994;**45**:601–3.
278. Alderson P, Montgomery J. Health care choices: making decisions with children. London: Institute for Public Policy Research, 1995.
279. Berglund CA. Children in medical research: Australian ethical standards. *Child: Care, Health and Development* 1995;**21**:149–59.

280. British Pediatric Association. Guidelines for the ethical conduct of research involving children. London: British Paediatric Association, 1992.
281. Choudhry S. Review of legal instruments and codes on medical experimentation with children. *Cambridge Quarterly of Healthcare Ethics* 1994;**3**:560–73.
282. Dickenson D. Children's informed consent to treatment: is the law an ass? *J Med Ethics* 1994;**20**:205–6.
283. 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):13–9.
284. Leikin S. Minors' assent, consent or dissent to medical research. *IRB* 1992;**15**:1–7.
285. Laine C, Davidoff F. Patient-centred medicine: a professional evolution. *JAMA* 1996;**275**:152–6.
286. Katz AM, Shotter J. Hearing the patient's 'voice': toward a social poetics of diagnostic interviews. *Soc Sci Med* 1996;**43**:919–31.
287. Crigger B-J. Bioethnography: fieldwork in the lands of medical ethics. *Medical Anthropology Quarterly* 1995;**9**:400–17.
288. DeVries RG. Toward a sociology of bioethics. *Qualitative Sociology* 1995;**28**:119–28.
289. Lantos J. Informed consent: the whole truth for patients? *Cancer* 1993;**72**:2811–5.
290. Lee JM. Screening and informed consent. *N Engl J Med* 1993;**328**:438–40.
291. Royal College of Physicians. Research involving patients: summary and recommendations. *J R Coll Physicians* 1990;**24**:10–14.
292. Maynard A, Bloor K. Introducing a market to the United Kingdom's National Health Service. *N Engl J Med* 1996;**334**:604–8.
293. Newdick C. Who should we treat? Law, patients and resources in the NHS. Oxford: Oxford University Press, 1995.
294. Brennan T. Just doctoring? Medical ethics in the Liberal State. Berkeley, CA: University of California Press, 1991.
295. Cavers DF. The legal control of the clinical investigation of drugs: Some political, ethical and social questions. *Daedalus* 1969;**98**:427–48.
296. French GR. When manufacturers are unwilling to accept the risks or invest the capital: vaccine production by the Salk Institute to specification of the US army. *AIDS Research and Human Retroviruses* 1994;**10** suppl 2:S309.
297. Menzel PT. Guest book review: Just doctoring. *Am J Law Med* 1992;**XVIII**:163–70.
298. Menzel PT. Equality, autonomy and efficiency: what healthcare system should we have? *J Med Phil* 1992;**17**:33–57.
299. Van Willigenburg T. Communitarian illusions: or why the Dutch proposal for setting priorities in health care must fail. In: Seedhouse D, editor. *Reforming health care*. Chichester: John Wiley, 1995:161–5.
300. Weindling AM. Ethics and economics in health care: prognosis, a traditional alternative to futility. *BMJ* 1995;**310**:1671–2.
301. LaPuma J, Stocking CB, Rhoades WD, Darling CD. Financial terms as part of informed consent to postmarketing research. *BMJ* 1995;**310**:1660–3.
302. Brown GB. The changing audience for clinical trials. *Drug Information J* 1995;**29**:591–8.
303. Feinstein AR. The crisis in clinical research. *Bulletin of History of Medicine* 1995;**69**:288–91.
304. Freestone DS. Conflict of interests: an introduction. *J R Soc Med* 1995;**88** suppl 24:1–2.
305. Charny MC, Lewis PA, Farrow SC. Choosing who shall not be treated in the NHS. *Soc Sci Med* 1989;**28**:1331–8.
306. Hazlet TK, Sullivan SD. Professional organisations and healthcare industry support: ethical conflict? *Cambridge Quarterly of Healthcare Ethics* 1994;**3**:236–56.
307. Neaves WB, Wildenthal K. Conflict-of-interest issues surrounding faculty participation in, and ownership of, technology and drug companies. In: Cheney D, editor. *Ethical issues in research*. Frederick, MD: University Publishing Group, 1993:139–45.

Appendix I

Database description and summary statistics

There were three parts to the search strategy:

1. Search throughout known databases for articles using particular search terms.
2. Identify those journals which have the greatest number of relevant articles and hand-search these journals to find additional relevant articles not found during the electronic search.
3. Identify and search relevant internet sites in order to form a broader view of the subject through lay comment.

I. Electronic search

The electronic search identified articles written in English and was conducted on four databases:

- Medline 1990 – September 1996
- Psychlit 1990 – September 1996
- Sociofile 1974 – June 1996
- Life Sciences 1990 – June 1996

Tables 1–3 gives a breakdown of the search terms used and article retrieval rates.

TABLE 1 Medline searches

Search term	Found	Hits	Used	Search term	Found	Hits	Used
anthrop* and medic*	36	5	2	ethics & epidemiology	108	28	0
anthropology	82	13	5	ethics & medical & patient*	124	11	8
anthropology & cultural	259	13	7	ethics & observational studies	23	20	0
anthropology & medic*	187	5	2	ethics & studies	193	29	0
autonomy	29	2	0	evidence-based medicine	75	63	33
BMJ in source & ethics	104	32	17	human experimentation	149	55	34
clinical trial & participation	125	24	9	medical anthropology	35	5	2
clinical trial & evaluation	331	8	0	observational studies	100	3	2
clinical trial & informed consent	92	49	28	observational studies & surgery	10	2	0
clinical trial & methodology	22	10	6	patient advocacy	183	15	4
clinical trial & methods	685	10	2	philosophy & medicine	176	29	16
clinical trial & particip* & stats*	73	11	1	philosophy & medicine & informed consent	18	8	3
clinical trial & participation	43	38	20	placebo effects	7	1	1
clinical trial & randomization	39	8	4	QALY	20	6	1
clinical trial & refusal	6	6	4	race & health	205	15	4
clinical trial & research methods	29	11	2	randomized controlled trials & history	106	11	7
clinical trial & standards	83	61	32	randomized controlled trials & method	201	34	19
clinical trial & standards & human or patient	55	14	6	randomized controlled trials & patient	82	10	8
clinical trial & strategy	34	2	0	religion & health	201	16	6
<i>Found = number of articles identified by the search term; Hit = articles considered; Used = articles relevant and read in detail</i>							
<i>continued</i>							

TABLE 1 contd Medline searches

Search term	Found	Hits	Used	Search term	Found	Hits	Used
research design & standards	58	15	5	research design & standards	163	10	2
research & ethics	115	21	15	review & clinical trial & evaluation	165	12	1
research design & volunteer	7	4	1	review & clinical trial & methodology	11	5	1
research design	34	30	18	review & clinical trial & strategy	8	1	0
research design & double blind method	188	22	10	systematic review	43	11	6
research design & random allocation	111	35	14				

Found = number of articles identified by the search term; Hit = articles considered; Used = articles relevant and read in detail.

TABLE 2 Electronic search: databases other than Medline

Search term	Found	Hits	Used	Search term	Found	Hits	Used
Psychlit							
anthropology & cultural	243	9	3	placebo effects	44	4	1
anthropology & informed consent	1	1	0	race & illness	53	4	1
anthropology & medic*	112	3	1	randomization	108	4	4
clinical trials & methods	43	6	5	randomized clinical trial	123	7	3
ethics & epidemiology	14	4	3	research & ethics & trials	17	11	4
ethics & research & human	109	8	6	research design & standards	4	1	1
human experimentation	5	1	1	review & ct & evaluation	2	1	0
observational studies & human	37	5	1	systematic review	21	3	0
patient advocacy	16	1	0				
Sociofile							
attitudes to health	119	5	3	patient advocacy	13	1	1
clinical trials	44	3	1	philosophy & medicine	210	24	13
ethics & human & research	131	44	16	philosophy & medicine & informed consent	3	3	2
informed consent	192	13	7	randomization	98	21	7
medical anthropology	113	51	19				
Life Sciences							
anthropology	30	11	4	informed consent	33	3	3
anthropology & informed consent	2	1	0	placebo effects	8	1	1
autonomy	19	1	1	race & health	156	3	0
ethics & human	3	3	0	religion\race & health	2	2	1
ethics & medical	4	4	1	research & ethics	4	4	2
gender & health	114	2	1	research & trials	161	5	5

Found = number of articles identified by the search term; Hit = articles considered; Used = articles relevant and read in detail.

TABLE 3 Total articles obtained by electronic search

Database	Total yield	Number of hits
Medline	5903	856
Psychlit	850	73
Sociofile	759	165
Life Sciences	532	40

Hand-search

Using electronic databases 1134 articles were found in 312 journal/newspaper titles. Hand-searches were made on those journals which produced the highest numbers of relevant articles in the electronic searches (*Table 4*).

This manual search produced 19% extra articles. In addition, useful information in the form of letters, comments, editorial was found. This type of material was not originally considered in the electronic search.

Internet search

A search of the internet was made using the Netscape interface. Similar search terms were used

TABLE 4 Journal usage – demonstrating the top journals

Journal title	Total articles used
<i>British Medical Journal</i>	123
<i>Statistics in Medicine</i>	62
<i>Journal of Medical Ethics</i>	47
<i>Social Science and Medicine</i>	47
<i>The Lancet</i>	38
<i>Cancer</i>	23
<i>Journal of Medicine and Philosophy</i>	21
<i>Hastings Center Report</i>	19

as those in the original electronic database search. The internet was searched in order to try and obtain a broader perspective on the subject through lay comment. Some useful site addresses are given in Annex I and article details in Annex II.

ANNEX 1 Internet site addresses

The site address to connect to the database of articles for this project [Implications of Socio/Cultural Contexts of the Ethics of Clinical Trials] is: http://www.liv.ac.uk/~sdthomps/page1.html
http://www.gen.emory.edu/medweb/medweb.bioethicshtml MedWeb: Bioethics.
gopher://gopher.mcw.edu:72/11/Bioethics%20Texts/Practical%20Practical%20ethics%20for%20resident%20physicians Practical ethics for resident physicians.
gopher://www.pitt.edu:80/hGET%20/%7Ecaj3/CEP.html Center for Clinical ethics, University of Pittsburgh.
http://ebm.jr2.ox.ac.uk Centre for evidence based medicine.
http://ccme-mac4.bsd.uchicago.edu CCME Home page. Links to medical organizations. Ethics policies and codes. Clinical ethics.
http://ccme-mac4.bsd.uchicago.edu/CCMECourses MacLean Center for clinical medical ethics. Dept Medicine, University of Chicago.
http://ccme-mac4.bsd.uchicago.edu/CCMEPolicies University of Chicago.
http://kuhttp.cc.ukans.edu/cwis/units/medcntr/Lee/SPECIALT/HISTORY Medical matrix – history of medicine.
http://wings.buffalo.edu/faculty/research/bioethics/news13.h Centre for clinical ethics and humanities in health care. Bioethics Bulletin.
<i>continued</i>

ANNEX 1 contd Internet site addresses

<p>http://wings.buffalo.edu/faculty/research/bioethics/news6 Clinical ethics and humanities in health care/bioethics.</p>
<p>http://wings.buffalo.edu/libraries/units SUNY at Buffalo – Health Science Library. Bioethics mediagraphy.</p>
<p>http://www.callamer.com/itc/mindful/vax.html National Council for International Health AIDS Link.</p>
<p>http://www.cen.uiuc.edu/~priestle/amnesty/trick Amnesty International Web Page.</p>
<p>http://www.cre.gu.se/Homepage Centre for research ethics, Brogatan 4, S-413 01 Goteborg, Sweden.</p>
<p>http://www.gatech.edu/amnesty/source The Human Rights Source.</p>
<p>http://www.thomson.com/chaphall/cctres.html OJCCT: Clinical Trials Resource Center.</p>
<p>http://www.well.com/user/reidar/cab.html Wellcome Community Advisory Workshop.</p>

ANNEX II Article details (internet sites)

<p>http://ccme-mac4.bsd.uchicago.edu/CCMEPolicies 1989 current options of the council on ethical and judicial affairs of the American Medical Association.</p>
<p>http://ccme-mac4.bsd.uchicago.edu/CCMECourses An ethics consultation service in a teaching hospital – utilization and evaluation. Author: LaPuma-J; Stocking-CB, et al.</p>
<p>http://wings.buffalo.edu/libraries/units Bioethics mediagraphy.</p>
<p>http://www.sonic.net/cgi-bin/jpat/sortdb Do I take the eye out or leave it in? Author: Fine SL.</p>
<p>http://kuhttp.cc.ukans.edu/cwis/units/medcntr/Lee/SPECIALT/HISTORY Emory University MedWeb history of Medicine resources. CADUCEUS – history of medicine collections.</p>
<p>http://ccme-mac4.bsd.uchicago.edu/CCMEPolicies/ind Ethics policies and codes.</p>
<p>http://ebm.jr2.ox.ac.uk Evidence-based medicine: what it is and what it isn't.</p>
<p>http://www.gatech.edu/amnesty/source Human rights law: a research guide to the literature.</p>
<p>gopher://gopher.mcw.edu:72/11/Bioethics%20Texts/Practical%2 Incompetent patients.</p>
<p>http://www.uib.no/isf/people/patient.htm Patient centered method and self directed behaviour change. Author: Meland E.</p>
<p>http://www.cre.gu.se/Homepage Studies in research ethics nr. 3. Ideal and reality. Applying ethics in theory and practice. Author: Halberg M, editor.</p>
<p>http://www.cre.gu.se/Homepage Studies in research ethics nr.2. Scientific responsibility and public control. Proceedings from a Workshop 10–11 August 1992. Author: Welin S, editor.</p>
<i>continued</i>

ANNEX II contd Article details (internet sites)

<p>http://ebm.jr2.ox.ac.uk The centre for evidence-based medicine – prospectus.</p>
<p>http://ccme-mac4.bsd.uchicago.edu Topics in medical ethics and health policy.</p>
<p>http://www.callamer.com/itc/mindful/vax.html What does the developing world stand to gain from current HIV vaccine development efforts? Author: Collins, C.</p>
<p>http://www.mcgill.ca/CTRG/bfreed Book published on the web “Duty and Healing”.</p>
<p>http://www.peg.apc.org Queensland Law Reform Commission discussion paper: The concept of consent.</p>
<p>http://www.well.com/user/reidar/cab.html Workshop: Establishing a European community based clinical trial. Author: Reidar Lie.</p>

Appendix 2

Grant holders and members of the External Advisory Group

Grant holders

Dr Jane L Hutton (lead applicant)
Mathematics and Statistics
The University of Newcastle

Professor Stephen R L Clark
Department of Philosophy
The University of Liverpool

Professor David W Chadwick
Department of Neurological Science
The University of Liverpool

Professor Richard H T Edwards
Director of Research and Development
University College of Medicine, Cardiff

Ms Lucy J Frith
Department of Primary Care
University of Liverpool

Research Fellow

Dr Richard E Ashcroft
Department of Philosophy
University of Liverpool
(now: Centre for Ethics in Medicine,
University of Bristol)

Members of External Advisory Group

Mr M Akbar Ali
Liverpool

Professor Brenda Almond
Social Values Research Centre
The University of Hull

Ms Joyce Carter
Department of Public Health
University of Liverpool

Ms RT Edwards
Department of Public Health
University of Liverpool

Dr Bernadette Larkin
Consultant Psychogeriatrician
Stockport Health Care Trust
Steppinghill Hospital

Professor SJ Leinster
Department of Surgery
Faculty of Medicine
University of Liverpool

Professor Sheila AM McLean
School of Law
University of Glasgow

Dr Gordon D Murray
Medical Statistics Unit
University of Edinburgh

Professor Maggie Pearson, Director
The Health and Community Care Research Unit
University of Liverpool

Rabbi YY Rubinstein
Regional Chaplain
Salford University

Dr Ros L Smyth
Respiratory Unit
Royal Liverpool Childrens' Hospital
Alder Hey Hospital

Professor Greg G Wilkinson
Department of Psychiatry
Royal Liverpool University Hospital

Mr Simon Woods
Department of Nursing
University of Liverpool

Acute Sector Panel

Chair: Professor John Farndon, University of Bristol †

Professor Senga Bond, University of Newcastle-upon-Tyne †	Professor Richard Ellis, St James's University Hospital, Leeds †	Dr Chris McCall, General Practitioner, Dorset †	Professor Jon Nicoll, University of Sheffield †	Dr William Tarnow-Mordi, University of Dundee
Professor Ian Cameron, SE Thames RHA	Dr David Field, Leicester Royal Infirmary NHS Trust †	Professor Alan McGregor, St Thomas's Hospital, London	Professor John Norman, Southampton University	Professor Kenneth Taylor, Hammersmith Hospital, London †
Ms Lynne Clemence, Mid-Kent Health Care Trust †	Mr Ian Hammond, Hillingdon HA †	Mrs Wilma MacPherson, St Thomas's & Guy's Hospitals, London	Professor Gordon Stirrat, St Michael's Hospital, Bristol	
Professor Cam Donaldson, University of Aberdeen †	Professor Adrian Harris, Churchill Hospital, Oxford		Professor Michael Sheppard, Queen Elizabeth Hospital, Birmingham †	

Diagnostics and Imaging Panel

Chair: Professor Mike Smith, University of Leeds †

Professor Michael Maisey, Guy's & St Thomas's Hospitals, London*	Professor MA Ferguson-Smith, University of Cambridge †	Professor Donald Jeffries, St Bartholomew's Hospital, London †	Professor Colin Roberts, University of Wales College of Medicine †	Mr Stephen Thornton, Cambridge & Huntingdon Health Commission
Professor Andrew Adam, UMDS, London †	Dr Mansel Hickey, University of Manchester	Dr Andrew Moore, Editor, Bandolier †	Miss Annette Sergeant, Chase Farm Hospital, Enfield	Dr Gillian Vivian, Royal Cornwall Hospitals Trust †
Dr Pat Cooke, RDRD, Trent RHA	Professor Sean Hilton, St George's Hospital Medical School, London	Professor Chris Price, London Hospital Medical School †	Professor John Stuart, University of Birmingham	Dr Jo Walsworth-Bell, South Staffordshire Health Authority †
Ms Julia Davison, St Bartholomew's Hospital, London †	Mr John Hutton, MEDTAP Europe Inc., London †	Dr Ian Reynolds, Nottingham HA	Dr Ala Szczepura, University of Warwick †	Dr Greg Warner, General Practitioner, Hampshire †

Methodology Panel

Chair: Professor Anthony Culyer, University of York †

Mr Doug Altman, Institute of Health Sciences, Oxford †	Dr Rory Collins, University of Oxford	Dr Stephen Harrison, University of Leeds	Professor Ian Russell, University of York †	Dr David Spiegelhalter, Institute of Public Health, Cambridge †
Professor Michael Baum, Royal Marsden Hospital	Professor George Davey-Smith, University of Bristol	Mr Philip Hewitson, Leeds FHSA	Professor David Sackett, Centre for Evidence Based Medicine, Oxford †	Professor Charles Warlow, Western General Hospital, Edinburgh †
Professor Nick Black, London School of Hygiene & Tropical Medicine †	Professor Ray Fitzpatrick, University of Oxford †	Professor Richard Lilford, Regional Director, R&D, West Midlands †	Dr Maurice Slevin, St Bartholomew's Hospital, London	
Professor Martin Buxton, Brunel University †	Professor Stephen Frankel, University of Bristol	Mr Nick Mays, Kings Fund Institute, London †		

Pharmaceutical Panel

Chair: Professor Tom Walley, University of Liverpool †

Professor Michael Rawlins, University of Newcastle-upon-Tyne*	Ms Christine Clarke, Hope Hospital, Salford †	Dr Desmond Fitzgerald, Mere, Bucklow Hill, Cheshire †	Professor Trevor Jones, ABPI, London †	Dr Ross Taylor, University of Aberdeen †
Dr Colin Bradley, University of Birmingham	Mrs Julie Dent, Ealing, Hammersmith and Hounslow HA, London †	Dr Alistair Gray, Wolfson College, Oxford †	Dr Andrew Mortimore, Southampton & SW Hants Health Authority †	Dr Tim van Zwanenberg, Northern RHA
Professor Alasdair Breckenridge, RDRD, Northwest RHA	Mr Barrie Dowdeswell, Royal Victoria Infirmary, Newcastle-upon-Tyne	Professor Keith Gull, University of Manchester	Dr John Posnett, University of York	Dr Kent Woods, RDRD, Trent RO, Sheffield †
		Dr Keith Jones, Medicines Control Agency	Dr Frances Rotblat, Medicines Control Agency †	

Population Screening Panel

Chair: Professor Sir John Grimley Evans, Radcliffe Infirmary, Oxford †

Dr Sheila Adam, Department of Health*	Professor George Freeman, Charing Cross & Westminster Medical School, London	Dr Ann Ludbrook, University of Aberdeen †	Professor Catherine Peckham, Institute of Child Health, London †	Professor Nick Wald, University of London †
Dr Anne Dixon Brown, NHS Executive, Anglia & Oxford†	Dr Mike Gill, Brent & Harrow Health Authority †	Professor Alexander Markham, St James's University Hospital, Leeds †	Dr Connie Smith, Parkside NHS Trust, London †	Professor Ciaran Woodman, Centre for Cancer Epidemiology, Manchester †
Professor Dian Donnai, St Mary's Hospital, Manchester †	Dr JA Muir Gray, RDRD, Anglia & Oxford RO †	Professor Theresa Marteau, UMDS, London †	Dr Sarah Stewart-Brown, University of Oxford †	

Primary and Community Care Panel

Chair: Professor Angela Coulter, Kings Fund Centre for Health Services Development, London †

Professor Martin Roland, University of Manchester*	Professor Andrew Haines, RDRD, North Thames RHA	Professor Roger Jones, UMDS, London †	Dr Fiona Moss, North Thames British Postgraduate Medical Federation†	Dr Mary Renfrew, University of Oxford
Dr Simon Allison, University of Nottingham	Dr Nicholas Hicks, Oxfordshire Health Authority †	Mr Lionel Joyce, Chief Executive, Newcastle City Health NHS Trust †	Professor Dianne Newham, Kings College, London	Dr John Tripp, Royal Devon & Exeter Healthcare NHS Trust †
Mr Kevin Barton, Bromley Health Authority †	Professor Richard Hobbs, University of Birmingham †	Professor Martin Knapp, London School of Economics & Political Science †	Professor Gillian Parker, University of Leicester †	
Professor John Bond, University of Newcastle-upon-Tyne †	Professor Allen Hutchinson, University of Hull †	Professor Karen Luker, University of Liverpool	Dr Robert Peveler, University of Southampton †	* Previous Chair † Current members
Professor Shah Ebrahim, Royal Free Hospital, London	Mr Edward Jones, Rochdale FHSA			

Copies of this report can be obtained from:

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 1703 595 639 Email: hta@soton.ac.uk
<http://www.soton.ac.uk/~hta>

ISSN 1366-5278