SERIES

Research governance: ethical issues

Anne Slowther[1] Petra Boynton[2] Sara Shaw[3]

J R Soc Med 2006;**99**:65–72

This is the third and final paper in a series on research governance [Series editors: Trisha Greenhalgh and Sara Shaw]

SUMMARY

Healthcare research is haunted by a history of unethical studies in which profound harm was caused to vulnerable individuals. Official systems for gaining ethical approval for research, designed to prevent a repetition of these shameful examples, can prove bureaucratic and inflexible in practice. The core ethical principles of respect for autonomy, prevention of harm, promotion of benefit, and justice (which form the basis of professional codes of research conduct) must be applied flexibly to take account of contextual, methodological, personal and practical considerations. Ensuring that the design and conduct of all research is ethically sound is the responsibility of all involved—including researchers, research institutions, ethics review committees and regulatory bodies.

INTRODUCTION

Recognizing and responding to the ethical dimension of research is a fundamental part of the research governance process. Ethical codes of practice and regulatory frameworks reflect concern about actual or potential examples of unethical research. Translating these broad ethical principles into the specific context of individual research projects in different social and cultural settings poses challenges for researchers, ethics review committees, and regulatory bodies.[1] Concepts such as informed consent are open to interpretation and influence within specific social and political contexts. In France, for example, legal and ethical guidelines are less restrictive in relation to research on patients who lack competence than in other European countries, reflecting a cultural tradition that places more emphasis on therapeutic benefit than self determination.[2] In this paper, we explore the relationship between fundamental ethical principles, the ethics review process, and the conduct of medical research, with particular attention to the principle of informed consent.

[1]Clinical Research Fellow, Ethox Centre Department of Public Health and Primary Care, University of Oxford, Oxford OX3 7LF; [2]Lecturer, [3]Senior Research Fellow, Department of Primary Care and Population Sciences, University College London, London N19 5LW, UK

Correspondence to: Sara Shaw

E-mail: s.shaw@pcps.ucl.ac.uk

CORE ETHICAL PRINCIPLES FOR HEALTHCARE RESEARCH

The Nuremberg Code[3] was developed in response to the medical experiments conducted under the Nazi regime. Its main focus was on protecting research participants from harm and ensuring that they had given valid consent. Other examples of potentially harmful research on participants who were not fully informed or who had no choice whether to participate[4–6] have reinforced the need to protect research participants from harm and obtain informed consent. These are the two core principles of the Declaration of Helsinki[7] which was developed by the World Medical Association and first adopted in 1964. Its most recent version was ratified in 2000. The Helsinki declaration, and other international codes of research, has tended to be interpreted as referring to clinical or biomedical research. In recent years there has been increasing recognition of the need for ethical regulation of other forms of research (for example in the social sciences) and of activities that have not traditionally been classified as research (such as medical audit). This reflects earlier discussion in the series regarding 'what is research?', the delineation between different research-type activities and the sometimes varied application of ethical principles to these according to the label used (e.g. audit, quality improvement or research).[8] From an ethical perspective, it is the nature of the study undertaken, and the involvement of participants in the study, that generates the requirement to comply with the principles of ethical conduct, and not the label given to it. Some national and international codes of research ethics are listed in Box 1.

A third principle articulated in many ethical codes is to promote benefit. Research should benefit either research participants directly, or the wider population, and the benefit of the research should significantly outweigh the potential harm to participants. Additional ethical principles may come to light when particular examples of research practice cause concern. The principle of justice, for example, was a key concern in the debate over studies of HIV treatments in developing countries.[9,10] The principles of honesty and integrity (of researcher, research institution and research sponsor) were highlighted by the Olivieri case,

Box 1 **National and international ethical codes of conduct in healthcare research**

Declaration of Helsinki	[www.wma.net/e/policy/b3.htm]
International Ethical Guidelines for Biomedical Research Involving Human Subjects: Council for International Organizations of Medical Sciences (CIOMS) (Ref. 3)	[www.cioms.ch/frame_guidelinesnov_2002.htm]
International guidance for ethical review of epidemiological studies: CIOMS	[www.cioms.ch/frame_1991_texts_of_guidelines.htm]
Currently under revision	[www.cioms.ch/epiwebdoc.pdf]
International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice guidelines (Ref. 4)	[www.ich.org/MediaServer.iser?@ID=482&@_MODE=GLB]
Medicines for Human Use (Clinical Trials) Regulations 2004 (*Implementation of European Union Clinical Trials Directive 2001*)	[http://medicines.mhra.gov.uk/ourwork/licensingmeds/types/ctdregs_shortdesc.pdf]
The National Commission for the Protection of Human Subjects of Biomedical and Behavioural Research (US): Ethical principles and guidelines for the protection of human subjects of research	[http://ohsr.od.nih.gov/guidelines/belmont. html]
Ethical Guidelines for International Comparative Social Science Research in the framework of MOST (Management of Social Transformations) UNESCO	[www.unesco.org/most/ethical.htm]
Research ethics framework, Economic and Social Research Council, UK	[www.esrc.ac.uk/ESRCInfoCentre/Images/FSRC_Re_Ethics_Frame_tcm6-11291.pdf]
National Statement on Ethical Conduct in Research Involving Humans: National Health and Medical Research Council of Australia	[www.nhmrc.gov.au/publications/synopses /e35syn.htm]
Ethical guidelines for social science research in health: The Indian National Committee for Ethics in Social Science Research in Health	[www.hsph.harvard.edu/bioethics/guidelines/ethical.intro.html]
Guidelines on ethics in health research: Health Research Council of New Zealand	[www.hrc.govt.nz/assets/pdfs/ethgdlns.pdf]
Guidelines on Ethics for Medical Research: Medical Research Council of South Africa	[www.sahealthinfo.org/ethics/index.htm]
MRC Ethics series: Medical Research Council UK *A series of guidance on different aspects of medical research*	[www.mrc.sc.uk/index/publications/publicationsethics_and_best_practice/publicationsethics_series.htm]

in which a researcher was impeded in publishing her concerns over toxicity of a study drug in a trial funded by a pharmaceutical company.[11]

These core principles inform the duty of care that a researcher owes to research participants, and the duty that a research institution or sponsor owes to both participants and researchers. The purpose of the ethical review process is to ensure that the researcher and research sponsor are discharging their duty of care to research participants, informed by the core ethical principles set out in the national and international codes of conduct (Table 1). While the main focus of the review process is on the effect of research on the participants, there is also an ethical requirement to identify and minimize potential harm to researchers. Reports have previously documented researchers encountering physical and psychological harm during the research process.[12,13] This includes risk of exposure to disease,[14] distress, or physical and emotional abuse from participants, carers or colleagues.[15] Whilst some types of fieldwork have rightly been identified as 'dangerous',[12,13] risk and harm to researchers may also arise in areas considered 'safe'[13] and through coding or analysing data that concerns sensitive issues.[16] Researchers from ethnic or sexual minorities or who are untrained or inexperienced may be particularly vulnerable,[11,14] and in many cases researchers are offered little in the way of protection.[15]

BALANCING BENEFITS AND RISKS

A key requirement of ethical codes is that the importance of the research objective is in proportion to the inherent risk to the participant. In a clinical trial, there is a potential direct benefit to some research participants (for example, the opportunity to take a new, highly effective medicine that is not yet licensed for general use). But a clinical trial would be unethical in the absence of clinical equipoise (i.e. if the researchers knew beyond doubt that the drug was more effective than other interventions, they would not be justified in withholding it from half the participants). What the participant is being asked to do is share in the uncertainty (they *might* gain some benefit—but they might be randomized to the control arm, or the new medication might prove less effective than existing treatments, or have harmful side effects). In other words, there is rarely a guarantee of direct benefit for the individual clinical trial participant. An important rule of thumb is that a 'control'

Table 1 **Mapping ethical principles onto a research ethics application form using the standard UK form as an example**

Ethical principles informing the assessment of a research proposal	***Examples of relevant questions in the application form***
Benefit of the research	
General benefit of research to participants and society	What is the primary purpose of the study? [A4] What are the principal research questions? [A7,8] Will the study achieve its aim? [A48, A49, A51, A52] Scientific justification/critique of the study [A9, A45–47]
Specific benefit to participants	Potential benefit for research participants? [A18]
How is benefit measured and defined? By whom?	Evidence that prospective participants and 'concerned communities' have been consulted over design and details of the research [A10]
Minimizing risk of harm	
To participants	Are any procedures withheld from participants? [A11] Are participants subjected to extra clinical procedures or other non-clinical interventions? [A12, A13] Discussion of sensitive or embarrassing issues? [A14] Potential for harm to participants? [A16, A17] Inclusion and exclusion criteria [A22, A23] Are participants involved in existing research? [A25] Arrangements for compensation for negligent and non-negligent harm [A35, A36] Arrangements for monitoring conduct of study/criteria for stopping research prematurely [A57] How is personal data handled? [A31, A40–44]
To researchers	Potential for harm to researchers [A19]
Respect for autonomy of participants	
Consent	
Information and understanding of participants	Scrutiny of information sheets, consent forms and advertisements for recruitment How is emerging information fed back to participants? [A29] How will final results be made available to participants? [A37]
Avoidance of coercion	How is informed consent obtained? [A26–29] How are participants identified/approached and recruited? [A20, A21] Will participants be paid, for what, and how much? [A33, A34]
Respecting those who are unable to consent	Justification of including vulnerable groups [A24]
Confidentiality/privacy	How is confidentiality ensured? [A31, A40–44]
Justice	
Specific populations should not be disadvantaged by being excluded from research	What arrangements have been made for participants who might not adequately understand verbal explanation of written information in English, or who have special communication needs? [A29]
Participants should benefit from any positive outcomes of the research that they have contributed to	What are the arrangements for continued provision of an intervention for participants after the research has finished? [A67]
Integrity of the researchers/research institutions	
Financial incentives	Are researchers receiving personal payment or other benefits? [A60, A61] Will the organization hosting the research receive payment or benefit over the costs of the research? [A62]
Personal conflict of interest	Does any researcher have direct personal involvement with the sponsor or funder of the research? [A64]
Publication transparency	How will results of the study be reported/disseminated? [A37]

intervention should equate to best available treatment—or at the very least, to best usual care. For this reason, it is rarely acceptable to have a placebo or 'no intervention' arm when testing drugs, educational interventions, or healthcare policies except in situations where no intervention has ever been shown effective.

The main benefit of much observational research is to future patients or to society in general—for example, phase

Table 2 **Guidelines for research on persons who lack capacity to consent**

Ethical code	***Criteria for research to be permitted***
The ethical conduct of research on the mentally incapacitated MRC UK 1993 [www.mrc.ac.ukpdf-ethics-mental.pdf]	Participant does not object Therapeutic research is in the participant's best interests Non-therapeutic research, no more than negligible risk of harm and not against participant's interests Research approved by research ethics committee Independent agreement that the participant's welfare and interests have been properly safeguarded
Medical research involving children. MRC 2004 [www.mrc.ac.uk/pdf-ethics_guide_children.pdf	The relevant information cannot be gained through research with adults Parents can consent to research that has potential benefit for the child Parents can consent to non-therapeutic research if the risks are sufficiently small to be said not to go against the child's interests
International Ethical Guidelines for Biomedical Research Involving Human Subjects: Council for International Organizations of Medical Sciences (CIOMS) [www.cioms.ch/frame_guidelines_nov_2002.htm]	Applies to children and adults who lack capacity to consent: for non-therapeutic research the risks must not exceed those associated with routine medical or psychological examination of the participants If the risks exceed the above criteria then the ethics review committee must find: (1) that the research is therapeutic; (2) the risks of the research interventions are only slightly greater than those associated with routine care of the participants; (3) the objective of the research is sufficiently important to justify the increased risk, and (4) the interventions are reasonably commensurate with the clinical interventions that the subjects have experienced
Research: The Role and Responsibility of Doctors: General Medical Council 2002 [www.gmc-uk.org/standards/default.htm	Research on adults lacking capacity to consent should only take place if: • it could be of direct benefit to their health; or is of special benefit to the health of people in similar circumstances • that it will significantly improve the scientific understanding of the adult's incapacity leading to a direct benefit to them or to others with the same incapacity • the research is ethical and will not cause the participants emotional, physical or psychological harm • the person does not express objections
National Statement on Ethical Conduct in Research Involving Humans: National health and medical research council of Australia [www.nhmrc.gov.au/publications/synopses/e35syn.htm]	Research on children and young people should only be conducted if the research is important to the well being of this group and cannot be conducted on any other group The research process provides for the physical, emotional and psychological safety of the child Consent cannot be given for research which is not in the child's best interests For adults who lack capacity to consent, the research must be in their best interests and their refusal must be respected
Mental Capacity Act. UK 2005 (implementation 2007) [www.opsi.gov.uk/acts/acts2005/20050009.htm]	Research on persons lacking capacity must be connected with an impairing condition affecting that person, and it cannot be carried out on others who can consent. The burden of taking part must not be disproportionate to the potential benefit For non-therapeutic research the risk must be negligible, and that anything done will not be duly restrictive or invasive

two vaccine trials on healthy volunteers or epidemiological studies to identify risk factors for specific diseases. But being in a research study may bring indirect (secondary) benefits to the participant. Assessing these benefits, like assessing risk, is not straightforward. Secondary benefits may include closer monitoring of a patient's condition in the therapeutic research or increased feelings of self worth through knowledge that they are helping others.[17] In reviewing a proposal a research ethics committee needs to form a view on the relative risks and benefits of the research, but researchers must also carefully consider this balance at the earlier stage of developing the research protocol, as part of their duty of care to participants.

In weighing up the risk–benefit balance in research, the following should be taken into account:

- The importance, originality and topicality of the research question
- The scientific validity of the study
- The likelihood of achieving meaningful results—for example, the capacity of the study to recruit adequate numbers

Table 3 **Examples of research where consent is difficult to obtain**

Type of research	*Possible alternatives to standard informed consent in these types of research*
Emergency care research, e.g. (1) Patients in pain and distressed. Intervention required immediately. No time for consideration (Ref. 27) (2) Patient has blood or tissue sample taken on admission when unable to consent (Ref. 28)	Waived consent: The US Department of Health and Human Services has issued guidance on conditions necessary for the waiver of informed consent in emergency care situations (Ref. 29) Obtaining consent post hoc, e.g. patient can withdraw permission to use blood or tissue sample when informed of study after recovery Prior consent/assent from community from which subjects will be drawn, or from specific individuals within that group (Ref. 30)
Epidemiological research using patient records or databases, e.g. use of records of cancer patients to investigate relationship between outcome and NHS care (Ref. 31)	Community assent: General information about possible use of data given to members of the group from which the participants will be drawn (e.g. patients in a primary care practice, patients on a cancer registry). Individuals have an opportunity to refuse (Ref. 29)
Cluster randomized trials, e.g. RCT of practice based intervention to improve care of asthmatic and diabetic patients (Ref. 32)	Consent from 'guardian' of the cluster or 'cluster representation mechanism' (e.g. CEO of acute hospital or managing partner in a primary care practice) or local community reps (Ref. 33) Assent from all individuals in clusters without prior knowledge of the interventions (Ref. 34)
Future research on tissue samples or genetic material obtained as part of clinical care	Open ended consent: Participants are informed of the broad parameters of possible future research on their samples but do not consent to specific research projects (Ref. 35)
Zelen studies, where the control group is unaware of the intervention, e.g. RCT to assess effectiveness of outreach programmes post discharge for patients admitted with CVA (Ref. 36)	Modified consent: Participants are informed that there is an additional research question about which they cannot be informed as it would affect the results, but they will be informed about it at the end of the study. Therefore participants consent to not having full information at enrolment (Ref. 37)
Ethnographic studies, e.g. a study exploring the course of substance abuse in people with severe mental illness (Ref. 38)	Evolving consent: The ESRC Research Ethics Framework provides guidance on consent in participatory social science research. In this context, consent to participate is seen as an ongoing process, and is continually open to revision and question. 'Highly formalized or bureaucratic forms of consent' are avoided in favour of 'fostering relationships in which ongoing ethical regard for participants is to be sustained (Ref. 39)

RCT, Randomized clinical trial; NHS, National Health Service; CEO, Chief Executive Officer; CVA, cerebrovascular accident

- The potential impact (on the participants, the local community, the disease group, the global community)
- The potential risks to participants and researchers (discussed in paper two of this series).[17]

In the UK, it is no longer part of the remit of the research ethics committee to evaluate the science of a proposal, but they are required to obtain independent information on the risks and benefits of the proposed research. A study that involves significant risk of harm to research participants will need to show a significant potential benefit. For example, many studies of new malaria vaccines involve infecting participants with malaria via mosquito bites. The potential harm to the participants from contracting malaria if the vaccine is ineffective may be considered justifiable (provided they have given informed consent) because of the huge potential benefit to the world wide community in developing such a vaccine.

RESPECT FOR AUTONOMY AND INFORMED CONSENT

Respect for the integrity and autonomy of the individual underpins the requirement for informed consent of research participants. One of the key functions of ethical review is ensuring that consent for participation in research is properly obtained and documented. The process of obtaining consent must be sensitive to the cultural values of the potential participants if their autonomy is to be truly respected. This is particularly relevant when research is conducted in communities that may not share the cultural values of the researchers, for example research in developing countries, or with refugee populations. Valid consent for any medical procedure, be it research or clinical care, requires that: (*a*) the person is informed of the nature of the procedure, including its likely risks and benefits; (*b*) the person is competent to make the decision; and (*c*) the decision is made freely and without coercion. All three elements of the consent procedure need to be considered in the specific context of the proposed research, and all three are informed by the principle of respect for autonomy.

Information

Research participants cannot make an autonomous choice about whether to participate in a study if they do not have

information that is relevant to their making that choice. In research, as in clinical practice, there are two key factors in ensuring that consent is truly informed. One is the content of the information provided, its accuracy, comprehensiveness and clarity. The other is the process of information sharing, how it is presented, the context in which it occurs, time allowed for reflection and discussion, and the balance of power between researcher and participant. The process of information sharing will vary depending on the type of research. A questionnaire survey may require only a clear information sheet whereas a clinical trial of a new drug treatment will involve a more complex process more akin to a clinical consultation. In this situation the model of concordance may be useful.[18] Provision of information requires particular care when the research involves vulnerable groups, for example children, or when there are language and cultural differences between researcher and participant. Researchers working with Navajo interpreters using a translation of the standard consent form in a diabetes clinical trial found that the consent process caused 'embarrassment, confusion and misperceptions that promoted mistrust'.[19]

Voluntariness

Valid consent must be freely given. Researchers and research ethics committees need to consider whether the process of obtaining informed consent includes implicit or explicit coercion of participants. For example, presentation of information can emphasize benefits of participation and obfuscate risks, or payment to participants may potentially be coercive, depending on the context and amount offered. The context in which patients are approached, or asked for their consent may be coercive, for example if not enough time is allowed for participants to consider the information. A more subtle area of potential coercion is the relationship between researcher and research participant. In many instances of healthcare research the researcher is also the participant's medical carer and patients may fear that refusal to participate in a study will jeopardize their care. Health research within universities has raised concerns about the overuse of student participants and the pressure they experience due to a fear of losing course credits or upsetting their tutors.[20]

Competence

A valid consent requires that the person giving consent is competent to do so. Competence is assessed in relation to the decision being made, for example a 14 year old may be competent to consent to take part in a survey on smoking behaviour in adolescents but not competent to consent to take part in a phase two study of an HIV vaccine. The legal definition of capacity (in English law) to consent to medical treatment (which would probably also apply to research) is that the person understands the relevant information, believes the information and is able to evaluate the information and make a choice.[20] It is possible to conduct research with patients who are not competent to give consent, including children, but national and international guidelines, and in some countries specific legislation,[21] place limits on the type of research that can be carried out (see Table 2). In most cases consent or assent of a family member or someone with legal responsibility for the participant will be required. In general, research cannot be carried out on individuals who lack capacity to give consent unless it is not possible to conduct the research in any other way—for example, research on neonates or in intensive care. In these cases the research should be therapeutic (i.e. have the potential to benefit the research participants), or if non therapeutic must involve minimal harm.

RESEARCH WHERE CONSENT IS DIFFICULT OR IMPOSSIBLE TO OBTAIN

There are some situations where consent for research studies is difficult or impossible to obtain, even from people who are capable of giving it. The development of national and international regulatory frameworks for the conduct of research, the expansion of the focus of such frameworks to include different methodological paradigms—for example, social science research—and the increasing emphasis on individual informed consent within these regulatory frameworks, has raised challenges for both researchers and the research ethics community. An example of this is an increasing emphasis in UK law on consent to use stored data and tissue for research purposes which has generated heated debate within some research communities with claims that whole categories of research will become virtually no-go areas. UK guidelines for researchers have been developed in some of these areas.[22–24] More recently, there has been some movement away from a blanket ban approach to research where there is no individual consent to one where researchers are encouraged to present an argument for conducting the research with reference to: the benefits of the research; the need for this type of study; the risk of harm to participants; and the reason why individual consent cannot be obtained. There has also been an increasing interest in exploring concepts of informed consent in contexts where individual consent is difficult or impossible to obtain, and in developing alternative models of consent that may be both practically achievable and ethically justifiable in these situations. Table 3 gives some examples of these models. Thus the focus on individual informed consent has led to an evolving and richer interpretation of the concept of consent. This may facilitate ethical research by permitting some research to be

conducted without individual informed consent while not disregarding the key ethical principle of respect for autonomy.

CONCLUSIONS

In conducting healthcare research, both researchers and participants are to some extent a means to an end—the improvement of healthcare for patients and/or the general population. It is thus essential that healthcare research in all its forms is underpinned by core ethical principles that protect participants *and* researchers from harm and respect their integrity as individuals. Ethical review and governance processes play an important role in ensuring that these core principles are translated into the practice of research. There is some concern that the potential benefits of medical research are not given enough weight in the ethical review process, and that the inflexibility of informed consent requirements has led to potentially valuable research being lost.[25,26] Reducing unnecessary bureaucracy may facilitate the passage of research protocols through the ethical review process. The UK Department of Health has recently published a report on the operation of NHS research ethics committees that makes recommendations in this area.[5] As healthcare research becomes more diverse—both in the type of research and the populations studied—ethics committees, researchers and research sponsors face a continuing challenge in interpreting and balancing these principles in specific situations without severely limiting the progress of important research, which may in itself be harmful.

REFERENCES

1 Molyneux CS, Peshu N, Marsh K. Understanding of informed consent in a low-income setting: three case studies from the Kenyan Coast. *Soc Sci Med* 2004;**59**:2547–59

2 Maio G. The cultural specificity of research ethics—or why ethical debate in France is different. *J Med Ethics* 2002;**28**:147–50

3 *Nuremberg Code: Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law*, Vol. 2, 1949: 181–2

4 Jones JH. *The Tuskegee Syphilis Experiment*. New York: The Free Press, 1981

5 Beecher HH. Ethics and Clinical Research *N Engl J Med* 1966; **274**:1354–60

6 Papworth MH. *Human Guinea Pigs*. London: Routledge & Kegan Paul, 1967

7 *Declaration of Helsinki* [www.wma.net/e/policy/b3.htm]. Ferney-Voltaire: World Medical Association, 2000

8 Shaw S, Boynton PM, Greenhalgh T. Research governance: where did it come from, what does it mean? *J R Soc Med* 2005;**98**:496–502

9 Varmus H, Satcher D. Ethical complexities of conducting research in developing countries. *N Engl J Med* 1997;**337**:1003–5

10 Lurie P, Wolfe SM. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. *N Engl J Med* 1997;**337**:853–6

11 Ferris LE, Singer PA, Naylor CD. Better governance in academic health sciences centres: moving beyond the Olivieri/Apotex Affair in Toronto. *J Med Ethics* 2004;**30**:25–9

12 Williams T, Dunlap E, Johnston BD, Hamid A. Personal safety in dangerous places. *J Contemp Ethnogr* 1992;**21**:343–74

13 Lee RM. *Dangerous Fieldwork*. Thousand Oaks: Sage, 1995

14 Lankshear G. Bacteria and babies: a personal reflection on researcher risk in a hospital. In: Lee-Treweek G, Linkogle S, eds. *Danger in the Field: Risk and Ethics in Social Research*. London; New York: Routledge, 2000

15 Boynton PM. *The Research Comparison: a Practical Guide For the Social and Health Sciences*. Hove; New York: Psychology Press, 2005

16 Hadistavropoulos T, Smyth WE. Elements of risk in qualitative research. *Ethics Behav* 2005;**11**:163–74

17 Scott DA, Valery PC, Boyle FM, Bain CJ. Does research into sensitive areas do harm? Experiences of research participation after a child's diagnosis with Ewing's sarcoma. *Med J Aust* 2002;**177**:507–10

18 Stevenson FA, Cox K, Britten N, Dundar Y. A systematic review of the research on communication between patients and health care professionals about medicines: the consequences for concordance *Health Expectations* 2004;**7**:235–45

19 McCabe M, Morgan F, Curley H, Begay R, Gohdes DM. The informed consent process in a cross-cultural setting: is the process achieving the intended result? *Ethn Dis* 2005;**15**:300–4

20 Re C. (adult: refusal of medical treatment). Re C. (adult: refusal of medical treatment). 1994, High Court

21 Euricon study group. Overview of European legislation on informed consent for neonatal research. *Arch Dis Child* 2001;**84**:F70–3

22 Office of the Information Commissioner. *Use and Disclosure of Health Data: Guidance On the Application of the Data Protection Act 1998*. London: Office of the Information Commissioner, 2004

23 Medical Research Council. *Personal Information in Medical Research*. London: MRC, 2000

24 *Human Tissue Act*, 2004 [www.opsi.gov.uk/acts/acts2004/20040030.htm]

25 Cassell J, Young A. Why we should not seek individual informed consent for participation in health services research. *J Med Ethics* 2002;**28**:313–17

26 Chalmers I, Lindley RI. Double standards on informed consent to treatment. In: Doyal L, Tobias JS, eds. *Informed Consent in Medical Research*. London: BMJ books, 2001: 266–76

27 Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. *Lancet* 1988;**2**:349–60

28 Bhagwanjee S, Muckart DJ, Jeena PM, Moodley P. Does HIV status influence the outcome of patients admitted to a surgical intensive care unit? A prospective double blind study. *BMJ* 1997;**314**:1077–81

29 National Institutes of Health. Waiver of informed consent requirements in certain emergency research. *Federal Register* 1996;**61**: 51531–3

30 Lindley RI. Thrombolytic treatment for acute ischaemic stroke: consent can be ethical. *BMJ* 1998;**316**:1005–7

31 Macleod U, Ross S, Twelves C, George WD, Gillis C, Watt GC. Primary and secondary care management of women with early breast cancer from affluent and deprived areas: retrospective review of hospital and general practice records. *BMJ* 2000;**320**:1442–5

32 Feder G, Griffiths C, Highton C, Eldridge S, Spence M, Southgate L. Do clinical guidelines introduced with practice based education improve care of asthmatic and diabetic patients? A randomised controlled trial in general practices in east London. *BMJ* 1995;**311**: 1473–8

33 Medical Research Council Clinical Trials Unit. *Cluster Randomised Trials: Methodological and Ethical Issues*. London: MRC, 2000

34 Edwards SJ, Braunholtz DA, Lilford RJ, Stevens AJ. Ethical issues in the design and conduct of cluster randomised controlled trials. *BMJ* 1999;**318**:1407–9

35 Parker M, Ashcroft R, Wilkie AO, Kent A. Ethical review of research into rare genetic disorders. *BMJ* 2004;**329**:288–9

36 Dennis M, O'Rourke S, Slattery J, Staniforth T, Warlow C. Evaluation of a stroke family care worker: results of a randomised controlled trial. *BMJ* 1997;**314**:107–6

37 Boter H, van Delden JJ, de Haan RJ, Rinkel GJ. Modified informed consent procedure: consent to postponed information. *BMJ* 2003;**327**: 284–5

38 Alverson H, Alverson M, Drake RE. An ethnographic study of the longitudinal course of substance abuse among people with severe mental illness. *Commun Mental Health* 2000;**36**:557–69

39 Economic and Social Research Council. *Research Ethics Framework*. London: ESRC, 2005