

Ethics of medical research in developing countries: the role of international codes of conduct

JL Hutton Department of Statistics, The University of Newcastle, Newcastle upon Tyne, UK

Many statisticians work with informal codes of ethics, and are probably unaware of the existence or content of rules which have been drawn up to govern statistical practice. Medical statisticians will be aware of codes of conduct for medical research, and most codes of professional ethics have some dependence on evidence. Statisticians, therefore, have a valuable contribution to make to debates on ethics which concern scientific soundness, data and perceptions of risk.

A lively debate on the revision of the widely respected Declaration of Helsinki, to reflect issues arising from research in developing countries, particularly HIV research, centres on questions of study design, data analysis and assessment of risk.

Collectively owned multiprofessional work requires each of the various professions to take responsibility for the conduct of the research, and the impact that it might have. Statisticians share important responsibilities in maintaining ethical medical research in all countries.

1 Background

All social and professional groups have rules of good behaviour, although often these ethics are implicit. Many issues contribute to any discussion of ethics.^{1–53} Statisticians largely work with implicit rules, and many are probably unaware of the existence or content of rules which have been drawn up to govern statistical practice.^{3,27,41} Medical statisticians will be aware of codes of conduct for medical research, and most codes of professional ethics interact with statistics.²³

The need for regulation of the conduct of professionals who carry out experiments on human subjects was recognized a century ago, in Germany.⁴⁹ The inhumane experiments carried out by doctors under the Nazi government clearly contravened the existing laws. After the war crimes trials in Nuremberg, a code of conduct was drawn up, and there are now many international codes governing research on people.^{16,12,22,37,53} Recently, there have been proposals to change the Declaration of Helsinki (DH)⁵³ because of controversy over HIV trials. Much of the debate hinges on questions of study design, data analysis and assessment of risk. Statisticians, therefore, have a valuable contribution to make concerning scientific soundness, evidence and perceptions of risk.⁴⁵

Principles of three statistical codes of practice (Section 2.1) and three medical research codes are summarized (Section 2.2) and their style and status discussed. The motivation for the proposed revisions of the Declaration of Helsinki was trials of interventions to reduce vertical HIV transmission. These trials therefore provide the main worked example, (Section 3) and the proposed revisions of DH are discussed in

Address for correspondence: JL Hutton, Department of Statistics, The University of Newcastle, Newcastle upon Tyne NE1 7RU, UK. E-mail: J.L.Hutton@ncl.ac.uk

the light of this debate (Section 4). Counterexamples are given which challenge the proposed revisions (Section 5). Informed consent, which is important in both statistical and medical codes, is discussed in Section 6.

I suggest that statisticians share important responsibilities in maintaining ethical medical research in all countries. Collectively owned multiprofessional work requires each of the various professions to take responsibility for the conduct of the research, and the impact that it might have.

2 Rules of professional conduct

2.1 Guidelines for statisticians

The International Statistical Institute Declaration on Professional Ethics²⁷ recognizes the variety of settings in which statisticians work, and the many branches of the discipline. The Declaration is therefore an informative framework of principles, not a set of regulations. Each principle is followed by a commentary and bibliography. The intention is that statisticians who consider departing from the principles do so as a result of deliberation, not ignorance. The principles are grouped into four categories, with no category having priority: obligations to society, funders and employers, colleagues and subjects are considered.

Social obligations require statisticians to consider conflicting interests, and guard against misuse and misinterpretation of statistics, extend the scope of statistics to benefit as large a community as possible, and pursue objectivity with openness about limitations. Obligations to paymasters require clarity about roles and responsibilities; impartial assessment of alternative statistical methods; no pre-emption of outcomes, and safeguarding privileged information while revealing the statistical methods and techniques used. In return for respect for exclusive technical and professional knowledge, statisticians must be honest about the limits of their expertise.

The three obligations to colleagues described are maintaining confidence in statistics, transparency of methods, and knowing one's own ethical principles as well as those of one's collaborators. A difficult responsibility is neither '... overstating or understating the validity or generalisability of data ...' (ISI.3.3).

Individual people, households and corporate entities are the subjects to whom obligations are due. Statisticians should avoid intrusion. There is an excellent discussion of the implications of the obligation to obtain informed consent, in terms of adequacy of information and of consent. Statisticians are expected to '... adhere to the principle of obtaining informed consent directly from subjects' even if they first have to negotiate with a 'gate-keeper' who is blocking access. Careful consideration of modifications to informed consent addresses observation studies, dealing with proxies, secondary use of records and misleading potential subjects. Withholding information is deceitful, and instances when legitimate censure can be avoided because of special research requirements are rare, and difficult to justify. In such cases, *post-hoc* consent should be considered.

The interests of subjects must be protected, not merely within the study, but also with regard to subjects' relationships. Social position can hold risks:

The interests of subjects may also be harmed by virtue of their membership of a group or section of society (see Clause 1.1). So statisticians can rarely claim that a prospective inquiry is devoid of

possible harm to subjects. They may be able to claim that, as individuals, subjects will be protected by the device of anonymity. But, as members of a group or indeed as members of society itself, no subject can be exempted from the possible effects of decisions based on statistical findings.²⁷

The Royal Statistical Society (RSS) Code of Conduct⁴¹ primarily describes the professional duties of a statistician, with a view to upholding the reputation of the profession. Some of the rules do address ethical matters. Part of the context for the rules is the recognition that the general public have no easy way of judging the quality of statistical work. This implies that statisticians have a moral responsibility to others.

The 'public interest' is the focus of the first two rules. Fellows of the RSS are required to have knowledge of, and comply with, the legislation and standards 'relevant to their chosen field'. Hence, this paper is important to medical statisticians, and any statistician who referees articles or grants with a medical research component. The second rule has wide implications, as it expects Fellows to avoid any actions which damage basic human rights. Two particular issues are mentioned: that subjects of enquiries should freely give their informed consent; and that confidentiality should be respected.

The professional judgement of statisticians may be overruled. In such circumstances, the RSS code (RSS.3) requires the Fellow to indicate the likely consequences of ignoring their judgements. In addition, Fellows are to prevent their names being attached to misleading summaries of data (RSS.6). Finally, RSS.9 is worth noting in the context of cross-national studies: 'Fellows shall encourage and support fellow members in their professional development ...'.

The American Statistical Society's Ethical Guidelines for Statistical Practice³ emphasize the duty of statisticians to maintain professional integrity. In particular, they should provide honest and objective interpretation, based on evidence, with disclosure of any special interests. Statisticians have a responsibility to respondents, especially with respect to privacy, consent and confidentiality. Statistical work must be open to assessment, with the limits and source of data made clear, and the role of statistical analysis, including choice of procedures, visible. Data should be available for analysis by appropriate others. As users of statistics may be dependent on expert advice, good conduct and good communication are essential. The guideline on collecting 'only the data needed for the purpose of their inquiry' implies that studies should have clearly defined aims, in order to be well designed. There is a tendency in medical research to collect information 'while we are there'.

There are also local or application specific codes, such as those drawn up by government statisticians.

2.2 Control of human experiments

Both ISI and RSS expect statisticians in health care to be conversant with the codes of conduct relevant to this research.

Ten standards were laid down by the war crimes tribunal at Nuremberg to which physicians (or others) must conform if an experiment on human subjects is to be permissible.³⁷ Voluntary consent is the first requirement of the Nuremberg Code, and the duty to ensure the consent is of high quality rests on every person involved. This duty cannot be delegated, and the subjects must be free to leave at any time. Previous knowledge must be used in designing the experiment, and experiment must be the

only way of obtaining useful results. The risks to be taken must be carefully evaluated, and suffering minimised. Only scientifically qualified persons exercising great skill can carry out research, and they must stop the research early if any harm is likely to result from it.

The Declaration of Helsinki, made by the World Medical Association (WMA) in 1964, gives similar principles as ‘recommendations guiding physicians’, but in a different order.⁵³ Informed consent is not given the prime position (I.9–I.11), and the existence of situations in which a ‘physician considers it essential not [*sic.*] to obtain informed consent’ (II.5) is presumed. Some new provisions are included. The use of ethics committees or institutional review boards is one new principle: ‘The design and performance ... should be clearly formulated in an experimental protocol which should be transmitted to a specially appointed independent committee for consideration, comment and guidance’ (I.2). Accurate reporting of results is required, and publication of research which does not conform to the Helsinki principles is banned (I.8). Conformity to ‘generally accepted scientific principles’ (I.1) is required. A distinction between ‘therapeutic and non-therapeutic research’ is introduced (Sections II and III), to clarify that nontherapeutic research is also subject to ethical review.

In the section which addresses clinical research, physicians are stated to be free to introduce ‘new diagnostic and therapeutic measures’ outside a controlled study, on the basis of individual judgement (II.1). Physicians ‘can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient’ (II.6). Every patient ‘should be assured of the best proven diagnostic and therapeutic method’ (II.3).

The DH states that physicians are not relieved of their responsibilities under the law of their own countries. The WHO/CIOMS guidelines were framed with particular concern for developing countries,²² not to duplicate the principles already established, but to suggest how these principles might be applied. Informed consent and research on communities receive particular attention, as indicated by the excerpt below.

Subjects in developing countries

14. Rural communities in developing countries may not be conversant with the concepts and techniques of experimental medicine. It is in these communities that diseases not endemic in developed countries exact a heavy toll of illness, incapacity and death. Research on the prophylaxis and treatment of such diseases is urgently required and can be finally carried out only within the community of risk.

15. Where individual members of a community do not have the necessary awareness of the implications of participation in an experiment to give adequately informed consent directly to the investigators, it is desirable that the decision whether or not to participate should be elicited through the intermediary of a trusted community leader. The intermediary should make it clear that participation is entirely voluntary, and that any participant is entirely free to abstain or withdraw at any time from the experiment.

Community-based research

16. Where research is undertaken on a community basis – for example by experimental treatment of water supplies, by health services research or by large-scale trials of new insecticides, of new prophylactic or immunizing agents, and of nutritional adjuvants or substitutes – individual consent on a person-to-person basis may not be feasible and the ultimate decision to undertake the research will rest with the responsible public health authority.

17. Nevertheless, all possible means should be used to inform the community concerned of the aims

of the research, the advantages expected from it and any possible hazards or inconveniences. If feasible, dissenting individuals should have the option of withholding their participation. Whatever the circumstances, the ethical considerations and safeguards applied to research on individuals must be translated, in every possible respect, in the community context.

Review procedures

18. The provision for review of research involving human subjects are influenced by political institutions, the organisation of medical practice and research and the degree of autonomy accorded to medical investigators ...

19. Authority to assess safety and quality ... is most effectively vested in a multi-disciplinary advisory committee operative at the national level. ... and statisticians have important contributions to offer to these assessments. Many countries at present lack resources ... Improvement ... is dependent, in the short term, on more efficient exchange of relevant information internationally.

Externally sponsored research

27. The term externally sponsored research is here used to refer to research undertaken in a host country but initiated, financed and sometimes wholly or partly carried out by an external international or national agency with the collaboration or agreement of the appropriate authorities of the host country.

28. Such research implies two ethical imperatives:

The research protocol should be submitted to ethical review by the initiating agency. The ethical standards applied should be no less exacting than they would be for research carried out within the initiating country.

After ethical approval by the initiating agency, the appropriate authorities of the host country should, by means of an ethical review committee or otherwise, satisfy themselves that the proposed research meets their own ethical requirements.

Where externally sponsored research is initiated and financed by a pharmaceutical manufacturer, it is in the interest of the host country to require that it should be submitted with the comments of a responsible authority of the initiating country, such as a health administration, research council or academy of medicine or science.

29. An important secondary objective of externally sponsored research should be the training of health personnel of the host country to carry out similar research projects independently.

32. ... For research sponsored by pharmaceutical manufacturers, the manufacturers themselves should assume responsibility in case of accidents. This is particularly necessary in the case of externally sponsored research when the subjects are not protected by social security measures.'

The remarks CIOMS.18 and 19, on review procedures, recognize practical and political realities. As statisticians, we can welcome the recognition of our potential contribution, but even 'highly developed' countries do not have an adequate supply of statisticians to support ethics committees.⁵¹

The CIOMS.27 and 28 requirements for ethical review in both host and 'external' countries are noteworthy. As recognized under review procedures, different countries have different resources for ethics committees, which require considerable expenditure, at least of time.⁵² Concern was expressed about the independence of ethics committees in some countries at the international school from which these proceedings arise. A longer-term view of the impact of research interventions is required by CIOMS.29, and the wider social context is stressed by CIOMS.32.

There are many other national codes and guidelines which address research on humans.

2.3 The style and status of codes

The statistical codes all require statisticians to be open, while respecting confidentiality, and aware of the various interests of the societies in which they work. The ISI Declaration is particularly concerned with humility and honesty. It does not invoke professional consensus, but recognises the range of opinions within the statistical commonwealth. Perhaps these attitudes are not surprising, given widespread innumeracy and suspicion of statistics. The NC, DH and CIOMS do not stress transparency, yet much of the debate about revision of the DH is concerned with the motivation behind studies.

Statisticians are expected to be mindful of the wider context and implications of their work. Indeed, ISI recommends that statisticians take responsibility for trying ‘... to ensure that funders and employers appreciate the obligations that statisticians have not only to them, but also to society at large ...’ (ISI.2.4). Statisticians ‘... have no special entitlement to study all phenomena.’ The pursuit of knowledge cannot override other values, and statisticians must both seek to benefit the widest possible community, and recognize that study findings can lead to harm of subjects or their social group. The NC emphasis is different; protagonists must justify research on humans by asserting that ‘such experiments yield results for the good of society that are unprocurable by other methods or means of study’. Of course, strictly speaking, RSS Code only applies to Fellows of the RSS, and the ASA guidelines are similarly restricted. The ISI Declaration provides guidance for any statistician who cares to read it, and deserves to be widely known, but has no legal force. In general, most statisticians develop their professional standards without studying these codes.

The statistical codes are primarily conscious of people in society, where the medical codes summarized above focus on people as individual patients or subjects. Much discussion of medical ethics focuses on a doctor–patient dyad.⁶ The DH first states that it ‘is the mission of the physician to safeguard the health of the people’, but then focuses on the doctor–patient dyad.

The DH is often regarded as having superseded the Nuremberg Code. This replacement is not obviously a matter of merit: DH lessens the requirements of the Nuremberg Code, and so lowers the standards. At a workshop where revisions to DH were debated, the majority of participants argued for ‘a slim set of principles, not regulations, that could remain unchanged for many years at a time’. Guidelines on the application of the principles could take into account different circumstances and new issues.³⁵ This is the approach taken by ISI.

Although the DH provides ‘recommendations guiding *physicians* in biomedical research’,⁵³ it is accepted as relevant not only by physicians, but also by many nonmedical people throughout the world.³⁵ Thus, the national and international legal status of DH are not clear, nor is it clear where ownership and responsibility for change lie.⁴³ With the absence of a consensus, the issue of the ownership and freedom to change influential international research guidelines is highlighted. The WMA ‘owns’ DH, the WHO/CIOMS guidelines belong to the WHO, but what is ownership of a set of principles or guidelines? The definition of stakeholders who are expected and entitled to contribute to revisions needs to be addressed. The WMA has been criticized for restricting the range of people consulted about the proposed revisions. The USA has dominated the debate on vertical HIV transmission trials. While the integrity of

contributors is not questioned, serious consultation with those affected by the proposed revisions is needed. Although one could see DH as a WMA statement of 'responsible medical opinion', the property of the medical profession, in reality it is effectively international law with the same status as the UN Declaration of Human Rights.⁴³ As such, it requires serious consideration by Fellows of the Royal Statistical Society (RSS.2).

Although health professionals might prefer to own 'their' codes, the revisions of DH have not been proposed for medical reasons, and the debate is between ethics, including distributive justice, and economic prudence.^{5,43} In order to argue that particular principles are inappropriate, one has to present a case showing, for example, that protection of profits by patent and monopoly is more important than limiting the course of an epidemic. Even if the revision of DH were simply a matter of ethics, the application and interpretations of human rights requires law, policy and hence politics. Adjudication among groups with different interests is a political responsibility, and ways of including the public in the debate are required. Schüklenk and Ashcroft suggest that ownership of DH might be passed to the United Nations.⁴³

3 Background to the proposed change in the Declaration of Helsinki

The world AIDS epidemic has brought medical research to the attention of many people. Although some issues associated with medical research in developing countries were given serious consideration by early 1980s,²² extensive debate was started in 1997 by criticism of trials of drugs to prevent maternal transmission of HIV to infants.³¹ I shall summarize the arguments as they have developed. The more general issues will then be discussed.

3.1 The vertical HIV transmission trials

In the past 4 years, a heated debate about research in developing countries has arisen because of trials of interventions to reduce transmission of HIV from mothers to their infants (hereafter 'vertical HIV transmission'), before and after birth.

In an editorial, Lurie and Wolf³¹ noted that an intervention, the AIDS Clinical Trials Group study 076 (ACTG076) regimen of an antiretroviral drug, AZT, had been shown to be effective in 1994, but, despite this, in many later trials of vertical HIV transmission, some or all patients were not provided with antiretroviral drugs. Although ACTG076 is regarded as the acceptable standard of care in USA, a less expensive, but equally effective intervention, would be worth finding. Should trials seeking an alternative intervention use ACTG076 as the control arm? Of the 18 studies identified, the two being performed in USA provided unrestricted access to antiretroviral drugs for all patients. Only one of the remaining 16 trials (nine of which are USA funded) provided these drugs to all participants. Placebo controls are used in other trials.

Lurie and Wolf point out that there is much agreement among those who defend and oppose placebo controlled trials. They claim that the only disagreement is about what the best comparison group is. Of course, what the 'best' comparison group is depends on what the research question is. Is it legitimate to ask 'Is the shorter

ACTG076 regimen better than nothing?’, rather than ‘Is there a less expensive, more feasible regimen than ACTG076?’ Notice that this focuses attention on a single aspect of a single disease.

The adequacy of data analysis, which is addressed in N2 & N3, is raised: existing trials indicated that the ACTG076 regimen could be simplified.³¹ Lurie and Wolf therefore argue that knowledge of the likely effectiveness of simpler treatment means that the balance of risk and benefit is already in favour of the simple treatment compared to placebo. Uncertainty about the outcome is not well balanced – equipoise does not hold – hence placebo control is unethical. Two points must be considered, however. First, Msamanga demonstrates that transmission rates vary substantially over time and between countries,³⁴ so that it will be difficult to estimate the effect of treatment. Further, one needs to consider carefully what constitutes adequate evidence.²⁴ An alternative therapy, vitamin A, is not mentioned, so information on the association between vitamin A and transmission is not discussed.^{44,50}

The appropriate standard of care is that of the sponsoring country (DH.II.2, WHO/CIOMS.28). Lurie and Wolf disagree with those who claim that placebos can be used in countries which have very limited health care provision. They also disagree with the claim that a placebo-controlled trial can reach firm conclusions more rapidly, and is therefore more ethical. Their disagreement is based on particular comparisons which lead to similar sample sizes. I agree that to allow a ‘local standard of care’ comparison is to provide an incentive to use underprivileged subjects, in direct disagreement with N2: the results would not be ‘unprocurable by other methods and means of study’.

Angell states the basic principle needed to justify a trial: that there is no good reason to prefer one of the treatments to any of the other treatments in the experiment.⁴ Investigators’ primary responsibility is to their subjects, as informed consent, though crucial, is insufficient to protect subjects from the desire for a rapid answer to a research question. She points to parallels between the vertical HIV transmission trials, and the Tuskegee Study of Untreated Syphilis, in which poor African-American men were not given known effective treatment because researchers wished to observe the natural history of syphilis. The physicians argued that the men would probably not have been treated any way (particularly as the nature of their disease was concealed from them). Funding agencies in USA have argued that placebo-controlled trials are justified by the local standard of care. Angell believes placebo controlled trials might be ethical, if pre-existing evidence supported it but not on the basis of a ‘local standard of care’ argument. She thinks a motivation for invoking ‘local standard of care’ might be ‘a slavish adherence to the tenets of clinical trials’: some people require all trials to be randomized, double blind and placebo-controlled. Angell suggests that motives of business and profit also contribute to the desire to use ‘local standards of care’, in order to carry out research cheaply and quickly. We suggest the quality of the evidence sought must be evaluated in terms of the research question and social context,⁸ and trials are not always necessary.

Msamanga and Fawzi note the wider questions raised by these trials.³⁴ They provide statistics on the severity of the HIV epidemic in sub-Saharan Africa, where only \$11 per head on average is spent each year on health. In the context of preventing tuberculosis in HIV-positive people, they point out that research into practical questions, about the feasibility of delivery of treatment given the resource and training

implications, is needed (CIOMS.29). Also, other scientific issues are unresolved. African programmes require co-operation of governments, multinational companies and international agencies.

A response by Varmus and Sacher to these criticisms denies the parallels with Tuskegee on the grounds that those subjects were denied effective and affordable interventions.⁴⁸ They do not state how poor men could afford USA health care. Three principles are mentioned: respect for persons, beneficence (minimizing risk and maximizing benefit) and justice. Varmus and Sacher invoke beneficence in their claim that they can ethically support a trial in another country that would not be acceptable in the USA because the disease burden makes greater risks acceptable. They might not support a trial of an unaffordable treatment as it would be unjust. Their main reason for supporting HIV trials is economic: cheaper treatments are sought. The poverty of many nations requires the research question to be 'is simple treatment better than nothing?'. They justify the use of placebos primarily by claiming that their use ensures definite answers to questions of safety and value, and also mention speed and the local standard of care. Although Varmus and Sacher claim the USA sponsored trials comply with (unspecified) principles and guidelines, I think they do not comply with CIOMS.28: parity of standards across countries. The reasonable statement that one should not use poor populations as a test bed for 'drugs for use *solely* in developed countries' (my emphasis) should be followed by a consideration of drugs *mainly* for developed country use or *mainly* for profit. Given the health care budgets of impoverished nations, the vertical HIV transmission trials will provide knowledge effective solely for the rich. Schüklenk indicates that the research question was chosen to justify the use of placebo, but the relation of the information gathered to the purported question shows the trials were not ethical.⁴²

Bayer notes the emotional content of the initial debate and points out that the real ethical problem is not whether to use placebos, but the immorality of the world economic order.⁹ The 'maldistribution of wealth and resources' makes the vertical HIV transmission trials a focus of (emotional) outrage. The goal of reducing HIV transmission in Africa requires information on affordable, implementable interventions which will be the basis of health care policy. Matchada cites the failure, due to infrastructure barriers, to eradicate tuberculosis, despite 'free drugs'.³³ He compares expenditure by African nations on war and debt servicing with that of health care. The question of whether ACTG076 is affordable in South Africa and the wider research agenda for Africa are explored by Karim.^{28,50} Two large South African vertical HIV transmission trials, one of vitamin A and the other of antiretroviral drugs provide the context. Health service costs associated with infrastructure, HIV testing and maternal care might dominate the cost of any ACTG regimen, whereas routine vitamin A supplementation avoids such costs. Frequent home deliveries and the importance of breast feeding also restrict the feasibility of ACTG076.

Karim investigates three possible control groups for a study of interventions for vertical HIV transmissions in South Africa. He indicates that historical controls are likely to lead to invalid conclusions because of rapidly changing transmission rates. Using the ACTG076 regimen makes any study an equivalency study, and requires extrapolation to adjust for differences in factors such as viral load, concomitant disease, delivery method and breast feeding rates. The validity of such extrapolation is

crucial, and Karim regards ACTG076 as an inappropriate control. Hence he chooses the third option, placebo control, on scientific grounds, and evaluates its ethical status. Protection of people from exploitation is the starting point. Voluntary informed participation requires appreciation of ‘undue risk’ which must be judged in relation to a standard. Karim argues that the ACTG076 is not an international standard, and no otherwise available therapy is being withheld. If ACTG076 were an international standard, Karim would not regard a randomized controlled trial of treatment likely to be less effective than ACTG076 with ACTG076 as control as justifiable. However, without the international standard, placebos are justified. Fixed ethical standards have to be implemented in the context of (rapidly) changing standards of care.^{28,50}

Wider issues are raised by Annas and Grodin,⁵ who place the debate in the context of the UN Declaration of Human Rights. The goal of slowing the HIV epidemic might not be most sensibly achieved by addressing vertical transmission. Annas and Grodin suggest that whether these trials should have been done at all is a more important question than the role of placebos. They specifically ask ‘... when is medical research ethically justified in developing countries that do not have adequate health care (or on USA populations that have no access to basic health care)?’, as they are concerned about exploiting impoverished populations. Good intentions are not sufficient, even for a utilitarian justification of the HIV trials (i.e. that they could lead to future benefit). Serious plans to implement interventions shown to be beneficial are required. If treatments will not be made available, then knowledge of efficacy of a shorter regime than ACTG076 will only benefit wealthy people. There are no plans to make these HIV interventions available. Even inexpensive and effective treatments for sexually transmitted diseases, which reduce the incidence of HIV infections¹⁹ are not delivered to poor Africans; and this is merely one example.

Annas and Grodin refute the idea that some of the HIV trials can be justified as being by nationals on their own nations (Ugandans) by pointing out that cultural relativism is not generally acceptable – apartheid was criticized. It is not clear in what way these trials are ‘for the good of their [Ugandan] people’. Secondly, the USA is involved in the Ugandan trials. There is a parallel with Tuskegee, in the reliance on professional consensus as a substitute for ethical principle. This is particularly unfortunate in a profession (medicine) which has only very recently begun to include a little instruction in ethics.

Annas and Grodin conclude by commending a commitment by developed countries ‘... to take economic, social and cultural rights as seriously as political and civil rights.’⁵ The effect of exploiting medical care for commercial gain, on a world-wide scale, is investigated by Benatar.¹⁰ Theological equality of persons exists, but not socioeconomic equality.

3.2 Subsequent debate on vertical HIV transmission trials

The question ‘are ethical standards absolute?’ is discussed by Resnick in the light of the above arguments.³⁸ Resnick argues that the debate hinges on scientific rigour. He argues that ethical standards are universal, as there are general principles for all human research, but not absolute, because the application of the principles allows interpretations which depend on social or cultural factors, and economic conditions. Seven ethical concepts are listed: informed consent, beneficence to subjects, privacy,

social utility, justice, scientific rigour, and monitoring of studies and subjects.³⁸ Both proponents and opponents of placebo-controlled vertical HIV-transmission trials appear to accept these concepts, with the proponents claiming to emphasize utility and justice, rather than beneficence. Economic conditions are the primary reason given for seeking an alternative regimen.

Resnick summarizes the arguments of proponents: 'the research is ethical because it uses scientific rigour to address urgent social needs'. The necessity of placebos to assess whether anything is better than nothing, and the differences in morbidity of populations are the reasons given. The potential for economic blackmail by sponsors is recognised by Resnick. Concern for the benefit of participants seems to blind authors to the benefit for the pharmaceutical industries and their shareholders. Comparison of an \$80 treatment with placebo reduces the costs of the study considerably over a contrast between \$80 and \$800 treatments. With respect to beneficence, Resnick distinguishes between

(VB1) Denying treatment when treatment is not available to the general population, but may be available in some populations;

(VB2) Denying treatment when treatment is available to the general population.³⁸

By asserting that Tuskegee violated the requirements of informed consent, and beneficence in terms of VB2, Resnick dismisses the parallel with Tuskegee. Further, he suggests the abuse of Tuskegee could only be recognized after the event.

We found no evidence for dependence of trial ethics on sociocultural contexts.⁸ The same considerations on placebos apply to anti-epileptic drugs, but placebo-controlled trials of anti-epileptic drugs (AEDs) are not permitted in UK or USA. Contrary to Resnick's claim, new drugs tested on adults are used on children without placebo-controlled trials. Resnick fails to discuss whether women in USA suffering from anaemia and malnutrition should be offered entry to a placebo-controlled trial; whether the treatment or the cost of the treatment should be changed, and why health care professionals and infrastructure are in short supply. He does not explain his claim that placebo-controlled trials 'promote justice by providing a fair distribution of benefits and burden of research'. Although Resnick recognizes the parallel between USA industries seeking out cheap labour in the developing world, and pharmaceutical industries seeking cheap research subjects, he fails to provide a description of the difference between exploiting the economic, social and political status of developing countries and adjusting study designs to allow for these conditions.

Lie argues that even a trial with ACTG076 as control might be unethical³⁰ if it is carried out only because the available treatment is too expensive. A shorter regime than ACTG076 might have the benefit of reducing the risk of drug resistance, while still offering protection. A trial of short treatment versus ACTG076 could therefore be carried out in USA. If, as advocated by Lurie and Wolf, these trials are run in developing countries, the result would be useful to the sponsoring country (USA). However, at '80 bucks a pop',⁵⁰ the results are unlikely to be useful to host countries, hence such trials exploit developing countries. Thus, Lie argues that ACTG076-controlled trials are ethically worse than placebo-controlled trials. A general obligation to attempt to improve unacceptable social conditions is recognized by Lie: he sees this as the failing of Tuskegee study.

A clear statement of ethical problems with the vertical HIV transmission trials is given by Schüklenk, who has the integrity to admit he was wrong in his earlier support of ACTG076-controlled trials.⁴² He suggests that the quality of the review of the ethics of the HIV transmission trials, and the adequacy of information given to participants has not been seriously considered, although without any comparison with whatever is normal practice in developed countries. Schüklenk notes that although Resnick relies on *principles*, he justifies placebo-controlled trials in terms of the *consequences* for trial participants and other women in developing countries.

The economic justification of the trials is evaluated by Schüklenk in terms of the objective of developing an affordable regimen, and whether concentrating on AZT was the most cost-effective strategy for African or other countries. The utilitarian argument is that it is fair to expose some participants to substandard care if a larger number of people will subsequently benefit from affordable care. Schüklenk first asks whether the HIV trials have resulted in affordable care. No guarantees have been given of affordable access to AZT for people in countries where trials have been carried out. Even with 'discounts' offered by Glaxo-Wellcome, the manufacturer of AZT, the drug will not be affordable in many countries, and those who can afford it are likely to add substantially to the manufacturer's profits.⁴²

Secondly, Schüklenk considers whether similar results might have been achieved by alternative means. Although there is a relation between general health and vertical HIV transmission rates, with 60–90% of infants unaffected, western sponsors have not given much support to research into alternatives to pharmaceutical treatment. It is thus not possible to say whether alternatives would be as effective.

Finally, the choice between spending funds on preventing vertical HIV transmission versus other modes of transmission is considered. The management of sexually transmitted diseases in adults is a more cost-effective way to reduce HIV incidence.¹⁹ All societies have to choose how to allocate their health care budgets, and choices are more critical with a restricted budget. Most of the discussion of these HIV trials focuses only on the cost of one drug.

The weakness of ethics and scientific committees in developing countries is mentioned by Thomas, who also points out that neither patients nor researchers in developing countries are generally aware of the market implications of research.⁴⁶ The contractual arrangements between sponsoring and host nations are usually short term, but HIV is a life-long disease. Ethical debate has focused on the minimal requirements over the time-span of a trial. A short course of AZT might prevent transmission of HIV, but if the baby's mother dies (from AIDS or other causes), the baby has little chance of living. The agenda for HIV research has not systematically included investigating how to enhance traditional health care. A single company has the patent right to AZT, so pharmaceutical companies in developing countries are prevented by global trade policies from producing cheaper AZT.

A fuller view of ethics considers not only access to treatment, but also issues of human rights, equity, relations between health and social care, and education. The trade policies of developed countries include the use of sanctions to express disapproval of human rights violations. Access to health care is deemed to be a

national issue, without reference to international trade policies. There is a single Universal Declaration of Human Rights, and it is appropriate to have a single standard for research ethics.⁴⁶

Even in developed nations, newly developed and approved drugs are not always available at prices which the communities which provided research participants can afford.⁴⁰

In response to the above comments, Resnick recognizes the importance of the question 'what should researchers be trying to prove?', and the possibility of changing the price rather than the treatment.³⁸

4 Proposed changes to the Declaration of Helsinki

In 1999 a draft of revisions to the DH was published in response to the urgent need to curb HIV infection.²¹ Part of the proposal is to change from

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (CLINICAL RESEARCH)

3. In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method.

to

18. *Access to health care*: In any biomedical research protocol, every patient-subject, including those of a control group, if any, should be assured that he or she will not be denied access to the best proven diagnostic, prophylactic or therapeutic method that would otherwise be available to him or her ... [a placebo can be used whenever it is] justified by a scientifically and ethically sound research proposal.

19. *Controlled clinical trials*: ... When the outcome measures are neither death nor disability, placebo or other no-treatment controls may be justified on the basis of their efficiency.

Greco presents four objections to the arguments of cost and absence of treatment in developing countries used to support the revisions.²¹ First, to be worried about scaring industry by insisting that drugs are provided to newly infective volunteers is paternalistic and protectionist. No serious effort has been made to consider sharing finances or to assess the financial impact. The urgency for many countries is for a vaccine, not for trials. It is possible to adjust treatment comparisons to allow for providing AZT to the controls. Finally, using placebo adds insult to injury through the emotional and sophistic claim that anything is better than nothing. Greco concludes that 'the pressure for change is a matter of timing and economics and not of ethical or scientific conduct'.

An evaluation by an international, multidisciplinary group of experts of the American Medical Association sponsored revisions of DH aimed to extend debate beyond the WMA.³⁵ The evaluation considered the DH in the context of other international guidelines and bodies. The DH is highly valued, and any revisions should be subject to full and open debate. Concern was expressed about whether the requirement not to publish unethical research was being met (DH.I.8).

Brennan raises the question of whether the proposed revisions will weaken the ethical principles underlying research.¹³ The proposed new DH.18 & 19 allow placebos to be justified by 'efficiency', indicating the economic motivation of the revision. He is concerned about a shift from a commitment to the research subject,

with just allocation of benefits and burdens, to an efficiency-based utilitarian standard. The shift is partly due to the growth in research sponsored by ‘for-profit’ organizations. Ethics committees of businesses increasingly review protocols, rather than university-based review boards. The logical implications of the proposed revisions are an increase in research in developing countries intended to benefit developed countries. A circular argument for placebo is included – they are allowed if ‘ethically sound’. The prohibition against publishing unethical research is lessened by allowing investigators an opportunity for special pleading.

Brennan questions whether vertical HIV transmission trials should be allowed to drive revisions. He notes that the rhetoric of efficiency has not often been supported by detailed calculations. If studies are only appropriate if the research population can benefit from the results, why is it also reasonable to set the standard of care by local poverty? Emphasizing efficiency belies the claim to benefit local participants. Utilitarian justifications can strengthen distributive justice or moral duty arguments, but not replace them. The proposed revisions are only concerned with overall benefit, and do not emphasise local benefit of research. Duty to research participants is an expression of justice and virtue, but is not a feature of the market place. Brennan warns that changes to ethical principles will affect all research. Even if the advocates of revision do not intend to promote for-profit research in the developing countries, the reality of greed remains.¹³

Levine argues that DH must be revised, because it is defective in two aspects,²⁹ and therefore frequently ignored. His first claim is that the distinction between therapeutic and nontherapeutic research is impossible to maintain. The DH provisions for ‘therapeutic’ research (DH.II.6) are very different from those for ‘nontherapeutic’ research (DH.III.2). Levine argues that these principles make research into the causes of disease impossible, and are therefore absurd, and must be changed. He asserts that if there are ‘minimal risks’ to subjects, consent is unnecessary. Levine states that the requirements that a control group must have the ‘best proven therapy rules out the development of all new treatments’ for any disease where a treatment exists. He makes use of essentially the distinction between therapeutic and nontherapeutic research, which he scorned previously, to justify placebo trials, and also invokes efficiency. He claims that DH is not intended to cover research experiments, i.e. controlled trials, (despite the DH reference to ‘experimental protocols’, DH.I.2), and that it is paternalistic in its protection of patients because it was drafted in the early 1950s. With regard to trials in developing countries, the various arguments above about costs of treatment, the existence of health care infrastructure, and different priorities for practices such as breast feeding are used by Levine to justify replacing the ‘best proven therapy’ with the ‘highest attainable and sustainable therapy’. ‘Attainable’ refers to the conditions of the trial, ‘sustainable’ to implementation in the host country after the trial. Levine acknowledges ‘with regret that there are great imbalances in the distribution of wealth among the nations ...’.

With regard to Levine’s claim that failure to respect DH means that it must be revised, statisticians should note that departure from an ethical framework should be carefully debated, not based on ignorance.²⁷ In contrast, the revisions of DH are intended to remove principles which demand thought. The distinction between therapeutic and nontherapeutic research was not made in the Nuremberg Code, which

required the same standard for all human experiments. Research into the causes of disease were a major part of the work condemned in the Nuremberg doctors trial.⁴³ Nontherapeutic research must avoid exploitation, so benefits to society should not be used to pressurize people into volunteering. Of course, people can have various reasons for taking part in research. Schüklenk and Ashcroft point out that the DH principles encourage people to evaluate each project thoroughly: careful assessment of therapeutic and nontherapeutic interventions is essential.⁴³ Even if it is not always easy to distinguish, the separation of benefit for a patient from that for society must be retained. Consent should not be waived for 'nontherapeutic research', even if someone estimates the risks to be low. Woodward discusses who should assess of these risks.⁵² A basic DH principle states that the importance of the objective should be in proportion to the risk to the participants (DH.I.4). In contrast, the ISI commentary on protecting the interests of subjects considers not only immediate risks, but requires statisticians to protect subjects from potential future harm (ISI.4.4).

Contrary to Levine's claim, the DH provision on control groups does not rule out the use of placebos. His argument equates 'best proven' with 'any known'. If one give serious consideration to the criteria for 'best', there might be criteria on which a new treatment will be better than the current treatment. What constitutes proof is also sometimes open to debate.²⁴ A standard treatment might have negative as well as positive effects. In this case, depending on the illness, a placebo might be better than the standard treatment in one dimension, and worse in another. If the risks associated with a condition are low, a patient accepting a placebo accepts a (usually temporary) loss of benefit for the good of providing information for society, and herself. Notice, however, even when there are high risks, such as with cancer, proven treatments can have side effects severe enough for patients to prefer not to be treated. Furthermore, patients can be given a best proven treatment, and then also receive either a new treatment or a placebo. The new treatment is therefore compared with placebo. This is the usual practice for epilepsy.

If experiment is Levine's real concern, he should advocate the Nuremberg Code, which explicitly refers to experiments. His claim that DH is paternalistic is incoherent in the light of the DH principles on informed, freely given consent, and the careful emphasis on types of research. The need to protect patients from the medical profession was still clear in 1953; forgetting history is not a moral advance.

In discussing what health care can be attained or sustained, Levine fails to consider time scales. He does not consider the impact that debt relief might have, although the Jubilee 2000 campaign for remission of debts of very poor nations was active when he published. He also ignores the role of profit for multinational companies, and of Structural Adjustment Policies, which require developing countries to reduce spending on health care and education in order to increase payments to developed nations, in determining what health care is affordable.

A useful critical overview of the debate is given by Schüklenk and Ashcroft.⁴³ They point out that it is doubtful that an identifiable local standard of care exists, because the standard of care in, say, Ivory Coast, depends on prices set by western manufacturers of drugs and equipment. A government in a developing country which attempts to use compulsory licenses to reduce costs is likely to face a trade war. Discussion of local standards implicitly includes disagreement about the moral

responsibility of one nation to another. The UK Nuffield Council inserts the word 'available' into DH.II.3,³⁶ but Schüklenk and Ashcroft express the concern shared by many people in developing countries that this qualification 'available' completely changes the meaning of the sentence.

5 Counter-examples

The Nuremberg Code remains relevant, even if it is inconvenient and hence ignored. The debate on vertical HIV-transmission trials is dominated by USA writers, and the standard USA example of dreadful abuse of research subjects, Tuskegee, is used. It is worth reflecting on the standard European example, 'Nazi medicine'. It is helpful to consider whether suggested modifications to principles could be interpreted such that some of the Nazi experiments which gave rise to the Nuremberg Code would be permissible. Although there is general agreement that the various Nazi experiments were unethical, specifying exactly what was wrong is not simple.¹¹ The experiments were conducted against a background belief that eugenics was a valuable science, a belief which was widespread in the western world, and is not without present-day adherents.

In developed countries, new AEDs are tested in combination with standard AEDs, as it is regarded as unacceptable not to treat epilepsy.³² However, in trials which compare established AEDs, not inconsiderable proportions of people are 'instantly' cured, in that they do not have any seizures after randomization, and achieve one of the clinically defined endpoints.⁴⁷ As there are risks associated with AEDs, and people with epilepsy may take AEDs for the rest of their lives, it could be of benefit to establish whether a subgroup of people who will not require AEDs can be identified. It might be possible to convince an ethics committee in a developed country that a controlled trial of a standard AED against placebo was legitimate. However, if one accepts the proposed DH revisions, then one could simply, and efficiently, run such a trial in a very poor country, such as Malawi. This could be of future benefit to Malawi, as targeting of inadequate health care resources could be refined. It would also be of benefit to developed countries, but would potentially lead to a loss of market, and hence profits, for pharmaceutical companies. However, the new freedom to run such trials in poor countries if 'availability' and 'sustainability' criteria are allowed looks remarkably like exploiting poverty.

Bacterial resistance to antibiotics is increasingly a matter of concern, and possible limits on prescribing would be worth knowing. It would be useful to know whether careful nursing of people with mild or moderate bacterial infections would suffice, without antibiotics. Consider a community which has no access to antibiotics. Under the DH revisions, or the Nuffield Council's insertion of 'available' in DH.II.3, one could carry out a placebo-controlled trial of antibiotics for moderately serious infections, with participants receiving normally available care. Two communities in which an efficient study could theoretically be conducted are Afghan women, and inmates of stables or concentration camps. If one takes the narrow view, that one regrets 'that there are great imbalances in the distribution of wealth ...'²⁹ and access to resources, but that, given these imbalances, one can invoke local standards of care,

there is no more reason to object to these theoretical trials than to those of vertical transmission of HIV. If one allows ‘the abominable state of health care’²⁹ to justify studies, one would agree to use women in Afghanistan to investigate marginal effects of well-known drugs, as these women are currently denied health care. However, if one acknowledges the importance of basic human rights (RSS.2) and obligations to a wider community (ISI.1) then the important question ‘How did these Jews come to be in concentration camps?’ arises. The USA and other European nations were responsible for the incarceration of some Jews, because when these people had the opportunity to emigrate in the 1930s, they were prevented from immigrating. In the USA, the misuse of statistics and of IQ tests were part of the procedures used to deny entry to many east European would-be immigrants.²⁰ Those who put people in harm’s way are not innocent, even if they can usually act with impunity.

It is noticeable that the debate about feasible treatments for developing countries has largely ignored endemic diseases which cause considerable morbidity and mortality. Consider now a disease endemic to developing nations, such as malaria, sleeping sickness or river blindness (leaving aside concern for tourists). Some treatments for illness and methods for control of the insect vectors exist for these parasitic afflictions. However, economic and infrastructure limitations (and occasionally, environmental concerns) restrict the availability of these interventions. If a poor country wishes to investigate the efficacy of a traditional medicine, should any controlled trial be placebo controlled or chemically controlled? Does the ethical legitimacy of a study depend on the source of funding and nationality of initiating investigators? German doctors treated German Jews. The source of funding can influence the nature of the trial, and concern about exploitation will address the power and influence of investigators. And what does informed consent look like in these circumstances (CIOMS.16 &17), where chemicals might be sprayed from the air?²⁵

Would the revised DH provide adequate safeguards in these general situations, or has it been driven too much by vertical HIV-transmission trials? I believe these examples indicate that the proposed revisions are not only unnecessary, but are unwise. It is safer to retain high standards and require careful justification from anyone who wishes to depart from these principles.

6 Informed consent

Although most of the debate on vertical HIV transmission trials addresses placebos and availability of treatment, consent was also discussed. Resnick’s remarks on informed consent are not well informed: he claims that telling subjects they are free not to participate is an added precaution, but it is a basic requirement (N1, DH.I.9). It is true that some subjects in Africa have a limited understanding of trials, and there are cultural and linguistic differences, but these factors also apply in developed nations.⁷

The difficulty of accepting that a poor person can give voluntary, informed consent, when a trial might be their only means of getting treatment, is raised by Annas and Grodin.⁵ They cite a single instance of a woman in Ivory Coast who perhaps did not fully understand the trial in which she participated. Despite their assertion, a woman

might volunteer for a study which brought no benefit to her community, as she might recognize possible benefit for herself: I would. However, as Annas and Grodin do not compare this instance with levels of understanding in developed nations, their concern could, unkindly, be interpreted as racism. Although I agree with the principle of benefiting a community, I do not think that awareness of the potential pressures on poor people justifies researchers' presuming that such people cannot give valid consent.

Rural communities are singled out by CIOMS.14 and 15, which I find offensive, as the assumption that rural people in developing countries are less able to give informed consent is not justified by my experience. It has been obvious in many conversations I have had that there are urban professionals, including medical professionals, in developed countries who are not familiar with the ideas and methods of experimental medicine. The quality of some published medical work² supplements direct evidence of lack of familiarity.¹⁷ It can be valuable to use local knowledge to ensure informed consent, but the ISI.4.2 and Nuremberg principles, that responsibility for obtaining consent cannot be delegated, must not be forgotten: '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' (N.2).³⁷ A review of the ethics of clinical trials, and the sociocultural contexts, found no evidence of cultural objections or obstacles to voluntary consent.⁸

Another context in which it is suggested that informed consent might not be feasible is that of community interventions (CIOMS.16 &17). Cluster designs require careful application of existing principles,²⁵ and as these designs become more widely used, statisticians should reflect on the ethical issues.

In contrast to DH.I.9 & 10, which require freely given informed consent, obtained by a physician who has no conflict of interest, the revised DH.23 allows consent to be waived if an ethics committee decides the risks associated with the research are slight, or that the procedures are used in practice without consent. The first condition (slight risks) denies the fundamental principle of individual informed consent. The defence of acting in the best interests of a community has been shown to be invalid. Nazi medicine and Tuskegee have demonstrated that voluntary consent is essential. The second condition (routine use) involves addressing the double standards in research and routine care by lowering research standards.¹⁵

Schüklenk and Ashcroft raise the difficult question of whether one can voluntarily refuse a chance to get treatment in a placebo-controlled trial when one has a terminal illness, if refusal will mean no treatment.⁴³ By implication, one would be even less likely to refuse a trial which guarantees some treatment. The view that such trials are unethical relies on a common, but unjustified, belief that new treatments are better than old or no treatment of a terminal illness. Confusion of hopes for treatment with assured prediction of benefit is not restricted to developing countries.

Two systematic reviews of reasoning⁷ and empirical data¹⁸ on patients' understanding of informed consent noted that there are difficulties in developed countries. Despite these difficulties, the authors recommend that informed consent remains essential⁷ or that '... the spirit of informed consent' be retained and seriously attempted, with ethics committees for further protection.¹⁸ These recommendations are

fully compatible with those of the ISI Declaration (ISI.4.2 & 4.3). Although some patients and professionals have expressed concern about the beneficial or detrimental effect on the patient of asking for her consent, alternative forms of consent require restrictions on patients' knowledge, personal responsibility and freedom of choice.²⁶

It is valuable to realise that there are various aspects and interpretations of informed consent.¹ Guidance such as ISI or DH usually focuses on consent as involving delivery of information in a manner which respects the rights of the person. At one extreme, this is viewed as a polite ceremony which is not essential, as doctors always have their patient's best interests to the fore. Consent is convenient because it transfers responsibility from the doctor or researcher to the patient or subject. The other extreme views consent as necessary protection against useless, dangerous or unwelcome interventions imposed by a powerful profession. Consent changes patients from research objects to research subjects.⁵² Recognising that informed consent is partly a process of acknowledging illness and gaining some understanding of available interventions helps us to appreciate that it is not necessary to view consent given by poor people as inferior.

7 Conclusion

In the debate over the HIV trials, the arguments about the ethical factors to be considered depend substantially on the question the researchers choose to address and their view of evidence. The scope of many of the issues raised about the ethics of medical research is determined by how narrowly or broadly the research question is phrased. The choice of question will relate to the primary motive for doing the particular study, which might be patient or community benefit, career advancement or profit. The last of these is important to plans for delivery of interventions, where one can contrast changing the choice of treatment with changing the price of the treatment. It will not always be possible to determine the primary motivation of a study. Pharmaceutical companies can cite studies by independent investigators in submissions to regulatory bodies for licences.

Statisticians have various opportunities, and therefore responsibility, to contribute to ethical medical research in the developing nations. Initially, a sound summary of existing evidence is required (DH.I.1, N2 & N3). Clarifying the research question, and providing good design is essential before a study begins. The presence of statisticians on ethics committees in host and sponsoring countries would be ideal, especially if transparency about statistical methods and their choice, plus mutual support and education, as recommended by the statistical codes is achieved. As referees or editors, statisticians can help to prevent publication of unethical research, thus lessening the incentive to take short cuts with a view to career enhancement. Recent concern in the statistical community about fraud reminds us of the contribution of statisticians to standards of publication.¹⁴ Finally, statisticians on regulatory bodies such as the Committee for Safety of Medicines in the UK could raise objections to evidence gained by exploitation of people. Formal regulations for licensing medical interventions could discourage such practices.

The debate, and the counter examples discussed demonstrate that there is no need to change the Declaration of Helsinki. It is essential to be vigilant about conditions of research, and informed consent remains a very important part of the protection of people who take part in biomedical studies.

Statisticians are expected to act at a very high standard, avoiding any breach of human rights (RSS.2) and seeking to benefit the widest possible community (ISI.1) with awareness of the consequences of research (ISI.4.4). In the end, wherever we live, we each have to answer the question: 'Am I my sister's keeper?'.

Acknowledgements

I thank all those who participated in the International Centre for Theoretical Physics 'School on Modern Statistical Methods in Medical Research' for stimulating discussions. In particular, I thank David Harrington for drawing the articles by Brennan and Levine to my attention.

References

- 1 Alderson P, Goodey C. Theories of consent. *British Medical Journal* 1998; **317**: 1313–15.
- 2 Altman DG, Bland JM. Improving doctors' understanding of statistics [with discussion]. *Journal Royal Statistical Society A* 1991; **154**: 223–67.
- 3 American Statistical Association Committee on Professional Ethics. *Ethical guidelines for statistical practice*. American Statistical Association, Alexandria, 1983.
- 4 Angell M. The ethics of clinical research in the third world. *New England Journal of Medicine* 1997; **337**: 847–49.
- 5 Annas GJ, Grodin MA. Human rights and maternal–fetal HIV transmission prevention trials in Africa. *American Journal of Public Health* 1998; **88**: 560–63.
- 6 Ashcroft RE. Giving medicine a fair trial. *British Medical Journal* 2000; **320**: 1686.
- 7 Ashcroft RE, Chadwick DW, Clark SRL, Edwards RHT, Frith L, Hutton JL. Implication of socio-cultural contexts for the ethics of clinical trials. *Health Technology Assessment* 1997 **1**(9): iv–65.
- 8 Ashcroft RE, Chadwick DW, Clark SRL, Edwards RHT, Frith L, Hutton JL. Implication of socio-cultural contexts for the ethics of clinical trials. In: Black N, Brazier J, Fitzpatrick R, Reeves B eds. *Health services research methods: a guide to best practice*. London: BMJ Books, 1998: 108–16.
- 9 Bayer R. The debate over maternal–fetal HIV transmission prevention trials in Africa, Asia, and the Caribbean: racist exploitation or exploitation of racism? *American Journal of Public Health* 1998; **88**: 567–70.
- 10 Benatar SR. Global disparities in health and human rights: a critical commentary. *American Journal of Public Health* 1998; **88**: 295–300.
- 11 Biagioli M. Science, modernity and the 'Final Solution'. In: Friedlander S ed. *Probing the limit of representation: Nazism and the 'Final Solution'*. Cambridge, MA: Harvard University Press, 1992: 185–205, 371–77.
- 12 Brazier M. *Medicine, patients and the law*, second edition. Harmondsworth: Penguin, 1992.
- 13 Brennan TA. Proposed revisions to the Declaration of Helsinki – will they weaken the ethical principles underlying human research? *New England Journal of Medicine* 1999; **341**: 527–31.
- 14 Buyse M, George SL, Evans S *et al*. The role of biostatistics in the prevention, detection and treatment of fraud in clinical trials. *Statistics in Medicine* 1999; **18**: 3435–51.
- 15 Chalmers I, Lindley R. Double standards on informed consent to treatment: ignored for a quarter of a century by most professional medical ethicists. In: Doyal L, Tobias JS eds. *Informed consent: respecting patients' rights in research, teaching and practice*. London: BMJ Books, in press.
- 16 Council of the International Organisation of Medical Sciences. *International guidelines for biomedical research involving human subjects*. 1993: guidelines 1–3.

- 17 Edwards SJL, Braunholtz DA, Lilford RJ, Stevens AJ. Ethical issues in the design and conduct of cluster randomised controlled trials. *British Medical Journal* 1999; **318**: 1407–409.
- 18 Edwards SJL, Lilford RJ, Braunholtz DA, Jackson J, Hewison J, Thornton J. Ethical issues in the design and conduct of randomised controlled trials. *Health Technology Assessment* 1998; **2(15)**: vi–128.
- 19 Gilson L, Mkanje R, Grosskurth H *et al.* Cost-effectiveness of improved treatment services for sexually transmitted diseases in preventing HIV-1 infection in Mwanza Region, Tanzania. *Lancet* 1997; 350.
- 20 Gould SJ. *The mismeasurement of man*. New York: Penguin, 1981.
- 21 Greco DB. Clinical trials in ‘developing’ countries: the fallacy of urgency or ethics vs. economics. *Bulletin of Medical Ethics* 1999; **150**: 33–34.
- 22 Howard-Jones N. Human experimentation in historical and ethical perspectives. *Social Science and Medicine* 1981; **16**: 1429–48.
- 23 Hutton JL. Statistics is essential for professional ethics. *Journal of Applied Philosophy* 1995; **12**: 253–61.
- 24 Hutton JL. The ethics of randomised controlled trials: a matter of statistical belief. *Health Care Analysis* 1996; **4**: 95–102.
- 25 Hutton JL. Are distinctive ethical principles required for cluster randomised controlled trials? *Statistics in Medicine* (in press), 2001.
- 26 Hutton JL, Ashcroft RE. Some popular versions of uninformed consent. *Health Care Analysis* 2000; **8**: 41–52.
- 27 International Statistical Institute. *Declaration of professional ethics*. Voorburg: International Statistical Institute, 1985. (<http://www.cbs.nl/isi/ethics.htm>).
- 28 Karim SSA. Placebo controls in HIV perinatal transmission trials: a South African viewpoint. *American Journal of Public Health* 1998; **88**: 564–66.
- 29 Levine RJ. The need to revise the Declaration of Helsinki. *New England Journal of Medicine* 1999; **341**: 531–34.
- 30 Lie RK. Ethics of placebo-controlled trials in developing countries. *Bioethics* 1998; **12**: 307–11.
- 31 Lurie P, Wolfe SM. Unethical trials of interventions to reduce perinatal transmission of the human immunodeficiency virus in developing countries. *New England Journal of Medicine* 1997; **337**: 853–56.
- 32 Marson AG, Kadir ZA, Hutton JL, Chadwick DW. The new anti-epileptic drugs: a systematic review of their efficacy and tolerability. *Epilepsia* 1997; **38**: 859–80.
- 33 Matchaba P. Are African governments allocating sufficient resources to fight AIDS? *British Medical Journal* 1999; **318**: 1351.
- 34 Msamanga GI, Fawzi WW. The double burden of HIV infection and tuberculosis in sub-saharan africa. *New England Journal of Medicine* 1997; **337**: 849–51.
- 35 Nicholson R, Crawley FP. Revising the Declaration of Helsinki: a fresh start. *Bulletin of Medical Ethics* 1999; **151**: 13–17.
- 36 Nuffield Workshop. *The ethics of clinical research in developing countries*. Nuffield Council on Bioethics, London, 1999.
- 37 Nuremberg Code (1947). *British Medical Journal* 1996; **313**: 1449.
- 38 Resnik DB. The ethics of HIV research in developing nations. *Bioethics* 1998; **12**: 286–306.
- 39 Resnik DB. Replies to commentaries. *Bioethics* 1998; **12**: 331–33.
- 40 Rio CD. Is ethical research feasible in developed and developing countries? *Bioethics* 1998; **12**: 328–30.
- 41 Royal Statistical Society. *Code of Conduct*. London: Royal Statistical Society, 1993.
- 42 Schüklenk U. Unethical perinatal HIV transmission trials establish bad precedent. *Bioethics* 1998; **12**: 312–19.
- 43 Schüklenk U, Ashcroft RE. International research ethics. *Bioethics* 2000; **14**: 158–72.
- 44 Semba RD, Miotti PG, Chiphangwi JD *et al.* Maternal vitamin A deficiency and mother-to-child transmission of HIV-1. *Lancet* 1994; **343**: 1593–97.
- 45 Smith AFM. Mad cows and ecstasy: Chance and choice in an evidence-based society [the address of the president]. *Journal Royal Statistical Society A* 1996; **159**: 367–83.
- 46 Thomas J. Ethical challenges of HIV clinical trials in developing countries. *Bioethics* 1998; **12**: 320–27.
- 47 Tudur C, Marson AG, Williamson PR, Hutton JL, Chadwick DW. Carbamazepine vs phenobarbitone monotherapy for epilepsy (protocol for a Cochrane Review). In *The Cochrane Library*. Oxford: Update Software, 1999: Issue 1.
- 48 Varmus H, Satcher D. Ethical complexities of conducting research in developing countries. *New England Journal of Medicine* 1997; **337**: 1003–1005.

- 49 Vollmann J, Winau R. Informed consent in human experimentation before the Nuremberg code. *British Medical Journal* 1996; **313**: 1445–50.
- 50 Wilkinson D, Karim SSA, Coovadia HM. Short course antiretroviral regimens to reduce maternal transmission of HIV. *British Medical Journal* 1999; **318**: 479–80.
- 51 Williamson PR, Hutton JL, Bliss J, Blunt J, Campbell MJ, Nicholson R. Statistical review by research ethics committees. *Journal Royal Statistical Society A* 2000; **163**: 5–13.
- 52 Woodward B. Challenges to human subject protections in US medical research. *Journal American Medical Association* 1999; **282**: 1947–52.
- 53 World Medical Association. Declaration of Helsinki (1964, 1975, 1983, 1989, 1996, currently under review). *British Medical Journal* 1996; **313**: 1449–50.