Are research ethics committees behaving unethically? Some suggestions for improving performance and accountability

Julian Savulescu, Iain Chalmers, Jennifer Blunt

The results of recent empirical investigations in research synthesis imply that research ethics committees are behaving unethically by endorsing new research which is unnecessary and by acquiescing in biased under-reporting of research which they have approved. The performance and accountability of research ethics committees would be improved if they required those proposing research to present systematic reviews of relevant previous research in support of their applications; to summarise the results of these reviews in the information prepared for potential participants; to register new controlled trials at inception; and to ensure that the results of these trials are made publicly available within a reasonable period of time after completion of data collection.

Properly designed, conducted, and reported research is essential to distinguish useful from useless or harmful forms of health care.[1] Research ethics committees exist to ensure, firstly, that proposed research will not expose participants to unacceptable risks and practices; and, secondly, that the potential participants can evaluate the expected consequences of their involvement and decide for themselves whether to participate.[2,3] Research ethics committees have a wider responsibility to promote the public interest by helping to ensure that relevant research is done.[3] In this article we suggest that the results of recent research in a new and rapidly expanding sphere of empirical investigation—research synthesis[4]—has important implications for the work of research ethics committees.

Research synthesis is the aggregation and integration of the results of related primary studies with the purpose of drawing conclusions from the totality of the relevant evidence. As the body of primary research evidence expands, research synthesis has become essential; but there is an emerging recognition that the quality of most research syntheses leaves much to be desired.[5,6] Research syntheses of poor quality can lead to beneficial effects of treatments being overlooked, as well as to promotion of treatments that are either ineffective or actually harmful.[6-8] It is against this background that the importance of improving the quality of research synthesis has been recognised, not only within the research community,[9] but increasingly by bodies responsible for funding scientific research and accrediting academic institutions.[10]

Reliable syntheses of the results of primary research require the adoption of methods that will reduce systematic and random errors (see box),[11] and empirical investigation to avoid such errors is a rapidly growing field of scientific inquiry.[4] In at least two important ways the results of this empirical research are relevant to research ethics committees.

Are research ethics committees satisfied that proposals for research have taken proper account of the results of existing research?

In 1981 Baum and his colleagues reported the results of a systematic review of controlled trials assessing the effects of prophylactic antibiotics on wound infection and mortality after colon surgery.[12] Cumulative synthesis of the results of these trials showed that strong evidence of the effectiveness of antibiotic prophylaxis in reducing morbidity and mortality existed by the mid-1970s. However, when Baum and his colleagues published their systematic review five years later researchers were continuing to invite patients to participate in such trials, and reports of trials involving comparison groups given no active treatment continued to appear throughout the 1980s (fig 1).[13] Research addressing previously answered questions either denies participants effective treatment or places them at risk for no benefit, or both.[14]

Nearly a decade ago Freedman noted that participants in research must not be denied access to effective care.[15] Over the past five years an increasing number of cumulative syntheses of the results of successive clinical trials (sometimes referred to as cumulative meta-analyses)[13,16] have called into question decisions made by research ethics committees to endorse proposals for new placebo controlled research when existing evidence shows that an active form of care is better than placebo. Rothman and Michels, for example, have called attention to recent trials of new secondary treatments for rheumatoid arthritis, new antidepressants, new antiemetics, new antihypertensives and new drugs for congestive cardiac failure in which they suggest that the results of previous research made the use of placebos unethical.[17]

Further research, including placebo controlled trials, may be warranted when all the relevant outcomes of an intervention (including side effects) have not been sufficiently evaluated. The justifications for such further research involve value judgements about the degree of certainty necessary for evidence to be convincing, what constitutes a relevant outcome, the place of research in changing clinical practice, and the entitlements of patients to treatment when resources are limited.

In cases in which further research is deemed to be justified, however, potential participants should still be adequately informed of the existing results of earlier

Sources of bias and methods of protecting against bias[11]

- Problem formulation
- Is the research clearly focused?
- Study identification

Is the search for relevant studies thorough?

- Study selection

Are the inclusion criteria appropriate?

- Appraisal of studies

Is the validity of included studies adequately assessed?

- Data collection

Is missing information obtained from investigators?

- Data synthesis

How sensitive are the results to changes in the way the review is done?

- Interpretation of results

Do the conclusions flow from the evidence that is reviewed?
Are recommendations linked to the strength of the evidence?
Are judgments about preferences (values) explicit?
If there is "no evidence of effect" is caution taken not to interpret this as "evidence of no effect."
Are subgroup analyses interpreted cautiously?

Clinical Ethics Project, Oxford Radcliffe Hospitals, Oxford OX3 9RP
Julian Savulescu, *Sir Robert Menzies medical scholar*

NHS Research and Development Programme, Oxford OX2 7LG
Iain Chalmers, *director, UK Cochrane Centre*

Salford and Trafford Health Authority, Eccles M30 0NJ
Jennifer Blunt, *former chair, Salford research ethics committee*

BMJ 1996;313:1390–3

research. In 1992 researchers invited women to participate in a placebo controlled trial of prophylactic antibiotics at the time of caesarean section. After endorsement by the research ethics committee the following information was presented by the investigators to potential participants: "Some *preliminary* studies suggest that giving an antibiotic at the time of caesarean section *may* reduce the chances of having an infection"[18] (our emphases). In fact, strong evidence had existed since the mid-1970s that prophylactic antibiotics at the time of caesarean section do reduce the rate of serious postoperative infection and this evidence had been presented in systematic reviews of over 60 relevant trials in 1989 and 1991.[19 20] Potential participants could and should have been provided with a proper synthesis of this "preliminary" evidence.

At present, US Food and Drug Administration regulations require that trials of new treatments use placebo controls, even when effective treatments exist. The administration has also acknowledged that there are some important deficiencies in the quality of informed consent in clinical trials.[21 22] A deficiency which the administration may not have highlighted, however, is that patients are unaware that they are being denied effective forms of care solely to comply with its policies. These coercive requirements are in contravention of international ethical guidelines,[2 23 24] and the scientific justification is in many cases dubious.[25 26] Many placebo controlled trials could and should be using treated controls.[27]

Are research ethics committees satisfied that the results of research they have endorsed are being made publicly accessible?

Over the past 10 years evidence has accumulated showing that the results of a significant proportion of controlled trials are never made properly accessible and that research which has yielded disappointing results tends to be under-reported.[28] Studies which have yielded relatively dramatic estimates of beneficial effects are more likely to be submitted for publication,[28] more likely to be reported in print,[28] more likely to be published as full reports,[29] more likely to be published in journals that are widely read,[30 31] and more likely to be cited in reports of subsequent, related trials.[32]

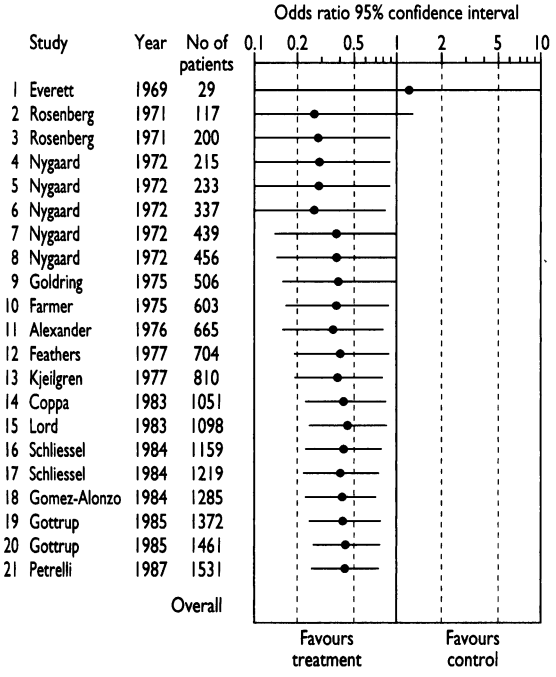

Fig 1—*Reduction of perioperative deaths by antibiotic prophylaxis for colorectal surgery.*[19]

The fate of scientific data is no idle issue. Reliable research syntheses depend on ensuring that as much as possible of the potentially relevant evidence is taken into account in systematic reviews. Simes first drew attention to the way that biased under-reporting of research can lead to misleading conclusions about the value of treatments,[30] and Egger and Davey Smith have recently suggested that this phenomenon may explain the discrepancy between the results of a review of small, early trials of magnesium administration in the acute treatment of myocardial infarction and the results of a trial involving nearly 60 000 patients which was designed to test the promising hypothesis derived from the review.[33]

Contrary to a widely held assumption, it is investigators and some research funders—and not necessarily journal editors—who are primarily responsible for under-reporting of research,[28] and there is evidence[34] that some investigators are unconcerned about this.[35 36] Prevention of this form of scientific misconduct must therefore involve the bodies to which investigators are answerable, in particular research ethics committees and research funding organisations, both public and private[37-40] as well as professional bodies.[41]

The consequences of under-reporting of research are that patients are being expected to accept the harmful side effects of ineffective forms of care; accept advice about the effects of health care which is based on evidence that is less complete than it should be; participate in research which has been conceptualised and designed on the basis of unnecessarily incomplete information; and contribute to research (both as indirect funders and as patients) which may not be published if the results come as a disappointment or an embarrassment to the investigators or sponsors.[42]

Five tasks for research ethics committees

To protect the interests of participants in research and promote the public interest in general, research ethics committees must play their part in reducing unnecessary, sometimes harmful, research and in ensuring that the results of necessary, well conducted research are made publicly available.[43] What might they do to reduce the problems we have discussed?

(1) Require systematic reviews of existing research before approving research

Research ethics committees should insist that proposals for research to assess the effects of health care be supported by scientifically defensible reviews of the results of relevant existing research.[4] Applications for ethical approval should include a section entitled "Systematic review of relevant existing research." This should show that the proposed research is necessary to address relevant uncertainty about the effects of one or more forms of health care; that it properly incorporates lessons from previous research; and that it would not entail withholding from some participants forms of care which are known to be effective. These steps would complement those which have already been taken by some national drug licensing organisations.[27 44]

While we do not propose that research ethics committees should conduct the kind of systematic reviews which we have described, we do suggest that committee members should have the capacity to evaluate systematic reviews submitted in support of applications for research. An appropriate starting place is Oxman's checklist (see box)[11] and the growing literature on this topic.[4 45 46] These skills are not beyond the reach of lay people, as shown by the encouraging experience with lay participants in training workshops organised by the critical appraisal skills programme (S Oliver, R Milne, unpublished report to the King's Fund Development Centre, November 1995).[47]

(2) Require that a summary of relevant systematic reviews be made available to potential participants

Participants in research have a right to know why research is being performed and its potential significance, as well as its potential harm. This requires that the information presented to patients includes a summary of the results of existing research, indicating not only the possible risks but also the possible benefits.

(3) Require registration of clinical trials at inception as a condition of approval

Research ethics committees should support moves to require prospective registration of controlled trials at inception.[38 48 49] Not only would such registration make it easier to identify irregularities in trial design, analysis, reporting, and publication or non-publication, but it should also help to prevent unknowing duplication of efforts within the research community. Within the United Kingdom research ethics committees should require registration of all clinical trials in the national research register.[50]

(4) Require a commitment to ensure that research results are made publicly accessible as a condition of approval

Research ethics committees should restrict approval of proposals for research to studies in which the principal investigators confirm in writing that adequate reports of the research will be made publicly accessible within a reasonable period of time (say 12 months) after the completion of data collection. Researchers who will not make this commitment should be required to make it explicit in the information and consent form inviting participation that the results of the research in which participation is invited may not be made publicly available.

Calls are increasing for the results of research to be made more accessible.[51 52] Indeed, the Council for International Organisations of Medical Sciences has stated that researchers have an obligation to inform participants of the results of research when those results have implications for their health.[53] Furthermore, some consumer groups are being actively encouraged to seek reports of the research to which their members have contributed.[54]

(5) Audit the reporting of results of research previously approved

In several countries acceptance is growing for the idea that research ethics committees have responsibilities that continue after approval of research.[39 55-61] Whatever the arguments for and against some of these proposed responsibilities, we believe that one of these responsibilities should be regular audit of the reporting of the results of research which research ethics committees have approved. Indeed, some research ethics committees do already regard this as their responsibility.[62]

Since the resources of research ethics committees are limited[57 60] audit of reporting could be selective, using a random sample of approved research projects to assess whether the results of research had been made publicly accessible. If researchers had failed to produce a publicly accessible account of the results of their research ethics committees might consider withholding approval of future research by the investigator(s) concerned until the results of the unreported research had been made available.

Conclusions

Research ethics committees are uniquely important institutions for at least two reasons. Firstly, they are the only regulatory point through which all proposed clinical research is likely to pass. Secondly, unlike other players who influence the research industry, they are unlikely to have strong vested interests in seeing particular results from research.

Summary of recommendations

Research ethics committees should:

(1) Require systematic reviews of existing research before approving research

(2) Require that a summary of relevant systematic reviews be made available to potential participants

(3) Require registration of clinical trials at inception as a condition of approval

(4) Require a commitment by investigators to make the results publicly accessible as a condition of approval

(5) Audit the reporting of results of research previously approved by them

There have been calls now for over 15 years for greater accountability of research ethics committees to justify their decisions,[63-68] and especially their decisions actively to thwart what has subsequently turned out to be well designed, beneficial research.[63 69] In medical ethics debate continues about whether there is a morally relevant difference between acts and omissions, or between what people do and what people allow to happen.[70-74]

As the most independent bodies regulating the practice of research, we believe that research ethics committees should be held accountable if, in the light of present understanding of the importance and principles of research synthesis, they continue to allow two forms of scientific malpractice to occur: the execution of unnecessary, sometimes harmful, research and the failure to ensure that the results of research are publicly accessible. Although our proposals have some resource and training implications, they are morally required. Indeed, unless research ethics committees can meet these requirements, we find it difficult to understand how their continued existence can be justified.

We are grateful to Doug Altman, Peter Davey, Claire Foster, Peter Gøtzsche, David Henry, Suzanne Hill, Les Irwig, Geir Jacobsen, Eric Meslin, Michael Minton, David Moher, John Pearn, Fiona Smaill, Alastair Watson, and an anonymous referee for helpful comments on earlier drafts.

Funding: JS is supported by the Sir Robert Menzies Foundation and the Oxford Radcliffe Hospital Trust; IC is supported by the NHS Research and Development Programme.

Conflict of interest: None.

1 Koopmans PP. Registration of drugs for treating cancer and HIV infection: a plea to carry out phase 3 trials before admission to the market. *BMJ* 1995;310:1305-6.
2 Council for International Organizations of Medical Sciences (CIOMS). *International ethical guidelines for biomedical research involving human subjects.* Geneva:CIOMS, 1993.
3 Medical Research Council. *Responsibility in investigations on human participants and material and on personal information.* London: MRC, 1992.
4 Chalmers I, Altman DG, eds. *Systematic reviews.* London: BMJ Publishing, 1995.
5 Mulrow CD. The medical review article: state of the science. *Ann Intern Med* 1987;104:485-8.
6 Antman EM, Lau J, Kupelnick B, Mosteller F, Chalmers TC. A comparison of results of meta-analyses of randomized control trials and recommendations of clinical experts. *JAMA* 1992;268:240-8.
7 Oxman AD, Guyatt GD. The science of reviewing research. *Ann NY Acad Sci* 1993;703:125-34.
8 Assendelft WJJ, Koes BW, Knipschild PG, Bouter LM. The relationship between methodological quality and conclusions in reviews of spinal manipulation. *JAMA* 1995;274:1942-8.
9 Moher D, Olkin I. Meta-analysis of controlled trials: a concern for standards. *JAMA* 1995;274:1962-4.
10 Higher Education Funding Council for England, Scottish Higher Education Funding Council, Higher Education Funding Council for Wales, Department of Education, Northern Ireland. *1996 Research assessment exercise: criteria for assessment.* London: HEFC, 1995 (Ref RAE96 3/95).
11 Oxman A. Checklists for review articles. In: Chalmers I, Altman DG, eds. *Systematic reviews.* London: BMJ Publishing, 1995:75-85.

12 Baum ML, Anish DS, Chalmers TC, Sacks HS, Smith H, Fagerstrom RM. A survey of clinical trials of antibiotic prophylaxis in colon surgery: evidence against further use of no-treatment controls. *N Engl J Med* 1981;305:795-9.
13 Lau J, Schmid CH, Chalmers TC. Cumulative meta-analysis of clinical trials builds evidence for exemplary medical care. *J Clin Epidemiol* 1995;48:45-57.
14 Freedman B. Scientific value and validity as ethical requirements for research. *IRB: A Review of Human Subjects Research* 1987;9:7-10.
15 Freedman B. Equipoise and the ethics of clinical research. *New Engl J Med* 1987;371:141-5.
16 Lau J, Antman EM, Jimenez-Silva J, Kupelnick B, Mosteller F, Chalmers TC. Cumulative meta-analysis of therapeutic trials for myocardial infarction. *N Engl J Med* 1992;327:248-54.
17 Rothman KJ, Michels KB. The continuing unethical use of placebo controls. *N Engl J Med* 1994;331:384-398.
18 Chalmers I, Herxheimer A. Drug costs and the scientific basis of therapy. In: Collier J, Bonn D, eds. *Drug costs and treatment choices.* London: Consumers' Association, 1993: 14-8.
19 Enkin M, Enkin E, Chalmers I, Hemminki E. Prophylactic antibiotics in association with caesarean section. In: Chalmers I, Enkin M, Keirse MJNC, eds. *Effective care in pregnancy and childbirth.* Oxford: Oxford University Press, 1989:1246-69.
20 Chalmers I. Improving the quality and dissemination of reviews of clinical research. In: Lock S, ed. *The future of medical journals: in commemoration of 150 years of the British Medical Journal.* London: BMJ Publishing, 1991:127-46.
21 Shapiro MF, Charrow RP. Scientific misconduct in investigational drug trials. *N Engl J Med* 1985;312:731-6.
22 Shapiro MF, Charrow RP. The role of data audits in detecting scientific misconduct. *JAMA* 1989;261:2505-11.
23 Denny WF. Use of placebo controls. *N Engl J Med* 1995;332:61-2.
24 World Medical Association. *Declaration of Helsinki.* September 1989: section II.3.
25 Freedman B. Placebo-controlled trials and the logic of clinical purpose. *IRB: A Review of Human Subjects Research* 1990;12:1-6.
26 Weijer C, Elliott C. Down with placebolatry. *New Scientist* 1996;149:47.
27 Henry D, Hill S. Comparing treatments: comparison should be against active treatments rather than placebos. *BMJ* 1995;310:1279.
28 Dickersin K, Min YI. NIH clinical trials and publication bias. *Online J Curr Clin Trials* [serial online] 1993; Apr 28: Doc No 50.
29 Scherer RW, Dickersin K, Langenberg P. Full publication of results initially presented in abstracts. *JAMA* 1994;272:158-62.
30 Simes J. Publication bias: the case for an international registry of clinical trials. *J Clin Oncol* 1986;4:1529-41.
31 Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. *Lancet* 1991;337:867-72.
32 Gøtzsche PC. Reference bias in reports of drug trials. *BMJ* 1987;295: 654-6.
33 Egger M, Davey Smith G. Misleading meta-analysis. *BMJ* 1995;310:752-4.
34 Jacobsen G, Hals A. Medical investigators' views about ethics and fraud in medical research. *J Roy Coll Phys Lond* 1995;29:405-9.
35 de Melker HE, Rosendaal FR, Vandenbroucke JP. Is publication bias a medical problem? *Lancet* 1993;342:621.
36 Vandenbroucke JP. De Cochrane Collaboration en "evidence-based medicine." *Ned Tijdschr Geneeskd* 1995;139:1476-7.
37 Chalmers I. Underreporting research is scientific misconduct. *JAMA* 1990;263:1405-8.
38 Moher D. Publication bias. *Lancet* 1993;342:1116.
39 Pearn J. Publication: an ethical imperative. *BMJ* 1995;310:1313-5.
40 Pearn J, Chalmers I. Publish and be applauded. *New Scientist* 1996; Jan 6:40.
41 Roberts J, Smith R. Publishing research sponsored by the tobacco industry. *BMJ* 1996;312:133-4.
42 Chalmers I. Publication bias. *Lancet* 1993;342:1116.
43 Herxheimer A. Clinical trials: two neglected ethical issues. *J Med Ethics* 1993;19:211, 218.
44 *Guidelines for the pharmaceutical industry on preparation of submissions to the Pharmaceutical Benefits Advisory Committee.* Canberra, Australia: Commonwealth Department of Human Services, 1995.
45 Oxman A, Sackett DL, Guyatt GH. Users' guide to the medical literature. *JAMA* 1993;270:2093-5.
46 Milne R, Chambers L. Assessing the scientific quality of review articles. *J Epidemiol Commun Health* 1993;47:169-70.
47 Milne R, Donald A, Chambers L. Piloting short workshops on the critical appraisal of reviews. *Health Trends* 1995;27:120-3.
48 Dickersin K. Why register clinical trials? Revisited. *Controlled Clin Trials* 1992;13:170-7.
49 Harlan W. Creating an NIH Clinical Trials Registry: a user-friendly approach to health care. *JAMA* 1994;271:1729.
50 Chalmers I, Gray JAM, Sheldon T. Handling scientific fraud: prospective registration of health care research would help. *BMJ* 1995;311:262.
51 Davey Smith G. Increasing the accessibility of data. *BMJ* 1996;312:1285-7.
52 Delamothe T. Whose data are they anyway? *BMJ* 1996;312:1241-2.
53 Council for International Organisations of Medical Sciences. *International guidelines for ethical review of epidemiological studies.* Geneva:CIOMS, 1991.
54 Simpson J. Collecting the trial evidence. *CF News* 1996; Summer:13.
55 Department of Health. *Local research ethics committees.* London: Department of Health, 1991 (HSG(91)5).
56 Bendall C. *Standard operating procedures for local research ethics committees.* London: McKenna and Co, 1994.
57 Weijer C, Shapiro S, Fuks A, Glass KC, Strutkowska M. Monitoring clinical research: an obligation unfulfilled. *Can Med Assoc J* 1995;152:1973-80.
58 National Council on Bioethics in Human Research. Protecting and promoting the human research subject: a review of the function of research ethics boards in Canadian facilities of medicine. *NCBHR Communiqué* 1995;6:3-32.
59 McNeill PM. *The ethics and politics of human experimentation.* Cambridge: Cambridge University Press, 1993.
60 Medical Research Council of Canada. *Guidelines on research involving human subjects.* Ottawa: Ministry of Supply and Services, 1987:49.
61 DeMets DL, Meinert CL. Data integrity. *Controlled Clin Trials* 1991;127:53-60.
62 Riordan FAI, Thompson APJ. How to get patients' consent to enter clinical trials. *BMJ* 1996;312:185-6.
63 Vitamins, neural tube defects, and ethics committees. *Lancet* 1980;i:1061-2.
64 Gilbert C, Fulford KWM, Parker C. Diversity of practice of district ethics committees. *BMJ* 1989;299:1437-9.
65 Alberti KGMM. Local research ethics committees. *BMJ* 1995;311:639-40.
66 Middle C, Johnson A, Petty T, Sims L, Macfarlane A. Ethics approval for a national postal survey: recent experience. *BMJ* 1995;311:659-60.
67 Garfield P. Cross district comparison of applications of research ethics committees. *BMJ* 1995;311:660-1.
68 While A. Ethics committees: impediments to research or guardians of ethical standards? *BMJ* 1995;311:661.
69 Chalmers I, Grant A. Salutary lessons from the Collaborative Eclampsia Trial. *Evidence-Based Medicine.* 1996; Jan/Feb:39-40.
70 Rachels J. Active and passive euthanasia. *N Engl J Med* 1975;292:78-80.
71 Beauchamp TL. A reply to Rachels on active and passive euthanasia. In: Beauchamp TL, Perlin S, eds. *Ethical issues in death and dying.* Englewood Cliffs, NJ: Prentice Hall, 1978: 246-58.
72 Beauchamp TL, Childress JF. *Principles of biomedical ethics.* New York: Oxford University Press 1994:196-200.
73 Steinbock B, ed. *Killing and letting die.* Englewood Cliffs, NJ: Prentice Hall, 1980.
74 House of Lords. *Report of the select committee on medical ethics.* London: HMSO, 1994:19-20.

(Accepted 19 September 1996)

Contraceptive implants: long acting and provider dependent contraception raises concerns about freedom of choice

M S Thompson

This is a response to an editorial about contraceptive implants by David Bromham

David Bromham's editorial on contraceptive implants ignores the wider issues to voice concern that trial by media could limit contraceptive choice by jeopardising research into new methods. However, it is more beneficial to the public for points of conflict to be debated openly. Furthermore, the impetus for research into new contraceptive technology is driven by profit and political motives and is only marginally affected by the media. Implanted contraceptives may increase the choice of contraceptive methods, but they put control of fertility increasingly into the hands of the medical profession. Herein lies their greatest problem: their potential to increase providers' control over clients' choice. There is the danger that certain groups of women may be targeted for their use: in the United States the coercive use of Norplant for mothers receiving welfare benefit has been suggested. Long acting contraceptives are a contraceptive of choice only when they are available without pressure, as part of a wider menu; when instant removal on request is guaranteed; and when there is an open and free flow of information and opinions between users, health professionals, and special interest groups.

Apartado Postal 38, 29200 San Cristobal de las Casas, Chiapas, Mexico
M S Thompson, *anthropology research student, Durham University*

BMJ 1996;313:1393–5

On 22 June the *BMJ* published an editorial by David Bromham about contraceptive implants.[1] While the article seems non-controversial, by dealing purely with the biomedical aspects of these contraceptives, David Bromham ignores the complex debate over contraceptive implants and long acting systemic contraceptives in general. The main point of his article is that women should not have their choice of different contraceptive methods limited by spurious concerns over biologically implausible, newly discovered side effects—and he accused the television programme *Horizon* of raising