Symposium on ethics and clinical trials

Clinical trials: two neglected ethical issues

Andrew Herxheimer UK Cochrane Centre, University of Oxford

Author's abstract

Ethical reasons are presented for requiring 1) that a proposal for a clinical trial should be accompanied by a thorough review of all previous trials that have examined the same and closely related questions, and 2) that a trial should be approved by a research ethics committee only if the investigator undertakes to register it in an appropriate register of clinical trials as soon as one exists.

Introduction

Important questions to be asked about a clinical trial include: 1) Why is the trial necessary, or worth doing? 2) Will the findings of the trial be made public? Both questions raise ethical issues, discussed below, which have implications for the work of ethics committees.

1) The need for systematic review

A trial may be necessary to answer an important unanswered question. It may be that the question has been examined in previous trials, with inconclusive or conflicting results; or it may not have been addressed before. However, if the question has been clearly answered by previous trials, the gain from doing another may be negligible, and it would not be justified. A well known example is the use of a placebo in a condition for which a treatment of proven effectiveness exists. In such a case the use of a placebo is unacceptable, unless the condition is a trivial one.

It follows that a proposal for a trial should be accompanied by a thorough review of all previous trials that have examined the same and closely related questions. Only in the light of such a review can a sound opinion be given on whether the proposal is ethical.

2) Publication of the results

It is important that the evidence generated in well performed clinical trials is published, but much of it remains inaccessible. This under-reporting of research must be regarded as a form of scientific misconduct, because it creates a distortion in the publicly available evidence. It represents not only a waste of the resources used in the unreported work (patients' co-operation, investigators' skill, health facilities, time, money), but impedes the use of effective treatment or the abandonment of ineffective treatment; it also requires otherwise avoidable subsequent research to correct the distortions. It is mainly investigators and commercial sponsors rather than referees or journal editors, who appear to be responsible for the under-reporting (1). Investigators, research ethics committees and funding agencies should all take steps to ensure that this form of scientific misconduct is minimised.

It may be unrealistic to expect all trials to be published, but their findings must be made accessible to anyone wishing to make a systematic review of the trials concerned with a particular problem. The first step towards this goal is to ensure that it is possible to obtain a complete listing of these trials, and the names and addresses of the people who have information about them. A simple way of achieving this would be to register all clinical trials at inception in a register (2). Such registers already exist for trials in some areas of medicine. However, more systematic development of such registers is needed, both in Britain and in other countries. Ethics committees have important opportunities to foster these developments and to ensure that the necessary information is assembled efficiently.

Implications for ethics committees

Ethics committees should routinely require that a proposal to undertake a clinical trial be accompanied by a systematic review of previous work concerned with the same and closely related questions, so that the proposal can be put into its proper context.

Approval by an ethics committee of a proposal to do a trial should be conditional on it being registered by

Key words

Clinical trials; systematic review of clinical trials; publication of clinical trials; registration of clinical trials.

continued on page 218

- (3) Bartlett R H *et al.* Extracorporeal membrane oxygenation (ECMO) cardiopulmonary support in infancy. *Transactions of the American Society for Artificial Internal Organs* 1976 Apr, 22: 80–93.
- (4) Neonatal ECMO registry of the extracorporeal Life Support Organization (ELSO). Ann Arbor, MI: 1992 Jul.
- (5) Stolar C J H, Snedecor S M, Bartlett R H. Extracorporeal membrane oxygenation and neonatal respiratory failure: experience of the Extracorporeal Life Support Organization. *Journal of pediatric surgery* 1991; 26: 563–571.
- (6) Bartlett R H *et al.* Extracorporeal circulation in neonatal respiratory failure: a prospective randomized study. *Pediatrics* 1985; 76: 479–487.
- (7) Wei L J, Durham S D. The randomized play-the-winner rule in medical trials. *Journal of the American Statistical Association* 1978; 73: 830–843.
- (8) O'Rourke P P *et al.* Extracorporeal membrane oxygenation and conventional medical therapy in neonates with persistent pulmonary hypertension of the newborn: a prospective randomized study. *Pediatrics* 1989; 84: 957–963.
- (9) Knox R A. A Harvard study on newborns draws fire: doctors faulted for limiting life-saving treatment. *Boston globe* 1989 Aug 7.
- (10) Wung J T *et al.* Management of infants with severe respiratory failure and persistence of the fetal circulation, without hyperventilation. *Pediatrics* 1985; 76: 488–494.
- (11) Dworetz A R *et al.* Survival of infants with persistent pulmonary hypertension without extracorporeal membrane oxygenation. *Pediatrics* 1989; 84: 1–6.
- (12) Advertisement. *America West Airlines magazine* 1990; 5, 3: 6.
- (13) Ware J H. Investigating therapies of potentially great benefit: ECMO [with discussion]. *Statistical science* 1989; 4: 298–340.
- (14) Berwick D M, Fineberg H V, Weinstein M C. When doctors meet numbers. *American journal of medicine* 1981; 71: 991–998.
- (15) Miké V. Philosophers assess randomized clinical trials: the need for dialogue. *Controlled clinical trials* 1989; 10: 244–253.
- (16) Zelen M. A new design for randomized clinical trials. *New England journal of medicine* 1979; 300: 1242–1245.
- (17) Freedman B. Equipoise and the ethics of clinical research. *New England journal of medicine* 1987; 317: 141–145.
- (18) Lantos J D, Frader J. Extracorporeal membrane oxygenation and the ethics of clinical research in pediatrics. *New England journal of medicine* 1990; 323: 409–413.
- (19) Miké V. Clinical studies in cancer: a historical perspective. In: Miké V, Stanley K E, eds. *Statistics in medical research: methods and issues, with applications in cancer research*. New York: John Wiley & Sons, 1982: 111–155.
- (20) Miké V. Understanding uncertainties in medical evidence: professional and public responsibilities. In: Mayo D G, Hollander R D, eds. *Acceptable evidence: science and values in risk management*. New York: Oxford University Press, 1991: 115–136.
- (21) Relman A S. Assessment and accountability: the third revolution in medical care. *New England journal of medicine* 1988; 319: 1220–1222.
- (22) Ellwood P M. Outcomes management: a technology of patient experience. *New England journal of medicine* 1988; 318: 1549–1556.
- (23) Pellegrino E D. The metamorphosis of medical ethics: a 30-year retrospective. *Journal of the American Medical Association* 1993; 269: 1156–1162.
- (24) Katz J. Randomized clinical trials: 'Am I my brother's keeper?' *Journal of clinical gastroenterology* 1981; 3 (suppl 2): 141–146.
- (25) Lebacqz K. Imperiled in the wilderness. *Second opinion* 1986; 2: 26–31.
- (26) Silverman W A. Epoché in retinopathy of prematurity. *Archives of disease in childhood* 1986; 61: 522–525.

continued from page 211

in an appropriate register of clinical trials as soon as one exists.

Andrew Herxheimer, FRCP, is a Consultant at the UK Cochrane Centre, Oxford, part of the international Cochrane collaboration, which prepares and maintains systematic, up-to-date reviews of randomized controlled trials of health care. UK Cochrane Centre, University of Oxford, NHS Research and Development Programme,

Summertown Pavilion, Middle Way, Oxford, OX2 7LG.

References

- (1) Chalmers I. Under-reporting research is scientific misconduct. *Journal of the American Medical Association* 1990; 263: 1405–1408.
- (2) Anonymous. Making clinical trialists register. *Lancet* 1991; 338: 244.