Monitoring clinical trials—interim data should be publicly available

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Interim results from clinical trials are, by growing convention, scrutinised by committees, commonly called data monitoring committees or institutional review boards. This allows clear evidence of benefit or harm to be identified expeditiously. The UK Medical Research Council sponsored trial of folic acid prophylaxis against recurrence of neural tube defects[1] and a trial of antiarrhythmic medication for prophylaxis against ventricular fibrillation[2] were terminated early because of favourable and adverse interim results respectively. Current practice is to keep interim data secret, on the presumption that their release would undermine recruitment and provoke "premature" adoption of treatment. Data monitoring committees offer timely expert advice on such matters as data collection[3 4] and can stop patients being offered randomisation to treatments that would be regarded as inferior by almost any person who had understood the interim data. Knowledge accrues incrementally,[5] however, and we argue that interim results should be made publicly available, thereby enabling patients to make individual decisions on the basis of data that might rationally provoke different choices from different people. Firstly, we explain why the practice of withholding data is ethically dubious, and, secondly, we argue that making data publicly available has potential practical advantages.

Summary points

- Interim analysis in clinical trials is done in secret because authorities fear premature adoption of promising but "unproved" treatments
- Withholding, without debate and endorsement of the policy, information that patients might find useful is at best paternalistic, at worst authoritarian and arguably unnecessary
- Releasing such information might in fact increase recruitment and would make the task of data monitoring committees easier

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"Near term" and "far term" patients

Assume, for the time being, that disclosure of results leads patients to choose a particular treatment and that this leads to failure of further recruitment. Then, these "near term" patients benefit at the expense of "far term" patients (those who would gain in the long term from greater precision contingent on a policy of withholding interim results). As there are, typically, many more far term than near term patients, withholding interim results provides the greatest good for the greatest number.[6] A data monitoring committee, therefore, has to decide where, between a neutral and strongly positive result, it should act. In doing so, it trades the interests of far term and near term patients as knowledge gradually accumulates.[7 8] Although procedural guidelines exist on how data monitoring committees should operate, no consensus exists on how the interests of near term and far term patients should be traded off or on the principles that should guide this decision.[9–20] Should all potential patients (near term and far term) be weighted equally in a classic utilitarian calculus?[6] Should overwhelming weight be given to the interests of near term patients? Or is there some compromise position in which near term patients are given some—but not total—preference? The problem is that data monitoring committees make big decisions using opaque (and doubtless variable) heuristics while ignorance is perpetuated to stop potential participants voting with their feet.

Setting up a system that perpetuates ignorance violates Kant's injunction that people should not be used as a "mere" means to an end. Meanwhile, information arising separately from an index trial is not withheld, nor is publication of that information delayed, pending completion of recruitment. Recent guidelines, moreover, charge principal investigators with a duty to keep up to date with the literature and modify the information they give to patients accordingly.[21 22] So why should data arising in a trial be secret when the same data arising elsewhere would be not only published but actively disseminated? The current practice of withholding data has emerged with no public endorsement, is not based on transparent and replicable methods, and conflicts with other practices. Moreover, this practice may be unnecessary even on its own terms.

Feedback and recruitment

Making data publicly available would enable patients and doctors to take a personal view on the meaning of

the interim data. Some—depending on prior beliefs and values—may move into equipoise,[5] and others may move out. Thus feedback of data would not necessarily always reduce recruitment, and it might even increase it,[7] while generalisability would probably be enhanced by widening the base of participants. Empirical evidence on the effect of feedback on recruitment is sparse.[14] Publication of interim results of the second international study of infarct survival (ISIS 2)[23] disclosing improved survival of heart attack with clot busting drugs resulted in increased recruitment as initially sceptical clinicians moved into equipoise (R Doll, personal communication). We suspect that if feedback is not available greater public awareness and a perceived threat of censure will provoke data monitoring committees to adopt increasingly risk averse policies, terminating trials in circumstances where informed patients might still have wished to participate.

Feedback trial

In a feedback trial, results could be made available after meetings of the data monitoring committee. Clinicians would then be free to share this information with patients and discuss its limitations and its relation to data arising elsewhere. It could be argued that members of a data monitoring committee would be less likely to over-react to interim data than would the media, which might overinterpret the data. Our view is that this argument derives from a culture of secrecy and scientific imperialism and is self fulfilling: keeping clinicians, patients, and the media in the dark allows naive views to flourish. In addition, bayesian presentation of results could help to prevent overinterpretation, which can occur when data are presented in a frequentist way, since even "significant" results may look unimpressive on bayesian analysis.[24]

Some trials are concerned with long term treatments—for example, different insulin regimens—where interim data may affect the behaviour of patients receiving ongoing trial treatments, resulting in "crossovers" and dilution of any treatment effect, but we argue that there is an implicit "contract" between researcher and participant in such cases, which makes the obligation to openness all the greater.

Future action

Procedures for monitoring the progress of clinical trials involve ethical, not just statistical, considerations. The topic thus deserves wider debate than it has received hitherto. It may turn out that the public is sanguine about current arrangements or would be content with less radical measures than those we have proposed—for example, inviting patients' advocates to join data monitoring committees and/or deriving a "stopping" algorithm in which value assumptions were made explicit and endorsed by society. Indeed, the consensus might be that current procedures are appropriate in some circumstances (perhaps when study treatments are not otherwise freely available, as in pre-licensing pharmaceutical trials) but that feedback is preferable in others (for example, in very large trials of treatments that are already in widespread use). We believe that the meaning of interim data will vary from person to person, so decisions made on the basis of such data should be individual ones—they should not be collectivised.

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1 Wald N, Sneddon J, Densem J, Frost C, Stone R. Prevention of neural tube defects; results of the Medical Research Council vitamin study. *Lancet* 1991;338:131-7.
2 Preliminary report: effect of encainide and flecainide on mortality in a randomised trial of arrhythmia suppression after myocardial infarction. The Cardiac Arrhythmia Suppression Trial (CAST). *N Engl J Med* 1989;321:406-12.
3 De Pauw M. Quality control in data monitoring of clinical trials. *Acta Urologica Belgica* 1994;62:31-5.
4 Fleming TR. Data monitoring committees and capturing relevant information of high quality. *Stat Med* 1993;12:565-70.
5 Lilford RJ, Jackson JC. Equipoise and the ethics of randomisation. *J R Soc Med* 1995;88:552-9.
6 Berry DA, Wolf MC, Sack D. Public health decision making: a sequential vaccine trial. *Bayesian Statistics* 1992;4:79-96.
7 Thornton JG, Lilford RJ. Preterm breech babies and randomised trials of rare conditions. *Br J Obstet Gynaecol* 1996;103:611-3.
8 Spiegelhalter DJ, Freedman LS, Parmar MKB. Bayesian approaches to randomised trials. *J R Stat Soc* 1994;157:357-416.
9 Freedman LS, Lowe D, Macaskill P. Stopping rules for clinical trials incorporating clinical opinion. *Biometrics* 1984;40:575-86.
10 George SL, Chengchang LI, Berry DA, Green MR. Stopping a clinical trial early; frequentist and bayesian approaches applied to a CALGB trial in non-small-cell lung cancer. *Stat Med* 1994;13:1313-27.
11 Ashby D, Machin D. Stopping rules, interim analysis and data monitoring committees. *Br J Cancer* 1993;68:1047-50.
12 Baum M, Houghton J, Abrams K. Early stopping rules—clinical perspectives and ethical considerations. *Stat Med* 1994;13:1459-69.
13 Crowley J, Green S, Lui PY, Wolf M. Data monitoring committees and early stopping guidelines: the Southwest Oncology Group experience. *Stat Med* 1994;13:1391-9.
14 Green S, Fleming TR, O'Fallon JR. Policies for study monitoring and interim reporting of results. *J Clin Oncol* 1987;9:1477-84.
15 Hughes MD. Stopping guidelines for clinical trials with multiple treatments. *Stat Med* 1993;12:901-15.
16 Heitjan DF, Houts PS, Harvey HA. A decision-theoretic evaluation of early stopping rules. *Stat Med* 1992;11:673-83.
17 Lewis RJ. An introduction to the use of interim analysis in clinical trials. *Ann Emerg Med* 1993;22:1463-9.
18 Machin D. Interim analysis and ethical issues in the conduct of trials. In: Williams CJ, ed. *Introducing new treatments for cancer*. New York: Wiley, 1992.
19 Pocock SJ. Statistical and ethical issues in monitoring trials. *Stat Med* 1993;12:1459-75.
20 Pocock SJ, Hughes MD. Practical problems in interim analysis, with particular regard to estimation. *Controlled Clinical Trials* 1989;10:S209-21.
21 Medical Research Council. *MRC guidelines for good clinical practice in clinical trials*. London: MRC, 1998:22-6. (MRC Clinical Trials Series report.) www.mrc.ac.uk/clinical trials/ctg.html (accessed 8 May 2001).
22 *Guideline for good clinical practice*. International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use, 1996. www.ifpma.org/ich1.html (accessed 9 May 2001).
23 ISIS 2 Collaborative Group. Randomized trial of intravenous streptokinase, oral aspirin, both or neither among 17187 cases of acute myocardial infarction. *Lancet* 1988;ii:349-53.
24 Hughes MD. Reporting bayesian analyses of clinical trials. *Stat Med* 1993;12:1651-63.

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Endpiece

An enthusiastic man

He was a man whose enthusiasms sometimes outran his judgement, he was likely to say more things which a more discreet man would have left unsaid.

Robertson Davies (1913-95), *What's bred in the bone*, London: Penguin, 1986