Saturday 13 September 1997

BMJ

Meta-analysis and the meta-epidemiology of clinical research

Meta-analysis is an important contribution to research and practice but it's not a panacea

This week's *BMJ* contains a pot-pourri of materials that deal with the research methodology of meta-analysis. Meta-analysis in clinical research is based on simple principles: systematically searching out, and, when possible, quantitatively combining the results of all studies that have addressed a similar research question. Given the information explosion in clinical research, the logic of basing research reviews on systematic searching and careful quantitative compilation of study results is incontrovertible. However, one aspect of meta-analysis as applied to randomised trials has always been controversial[1 2]—combining data from multiple studies into single estimates of treatment effect.

In theory, aggregation of data from multiple trials should enhance the precision and accuracy of any pooled result. But combining data requires a leap of faith: it presumes that the differences among studies are primarily due to chance. In fact, differences in the direction or size of treatment effects may be caused by other factors, including subtle differences in treatments, populations, outcome measures, study design, and study quality.[3] Thus meta-analyses may generate misleading results by ignoring meaningful heterogeneity among studies, entrenching the biases in individual studies, and introducing further biases through the process of finding studies and selecting results to be pooled.

Our understanding of these limits of meta-analysis has arisen partly because a generation of investigators has stepped back from the unthinking pooling of data and begun researching clinical research itself. Those interested in the science of systematic reviews focus on trials as the unit of analysis; and along the way they have usefully shifted the goalposts for reporting on clinical research.

Publication bias

Among the surprising challenges in any systematic review is finding all the studies that have addressed the question(s) of interest. Many studies have documented publication bias favouring clinical trials that show a significant treatment effect. Stern and Simes extend these findings in their "cohort study" of a range of experimental and observational protocols submitted to a research ethics committee at an Australian teaching hospital (p 640).[4] Studies with statistically significant outcomes were more likely to be published than non-significant studies, including a threefold difference for randomised trials. They also showed that, even after adjustment for other factors that influenced publication, the negative studies took significantly longer to appear in print.

If trials with positive results are published more often and faster any meta-analysis based only on published trials will inevitably generate an inflated and unduly precise estimate of a given treatment's effectiveness. As Stern and Simes argue, the most practical solution is mandatory registration of all randomised trials at the time of ethics review or other regulatory approval.[4] This policy assures patients who agree to be randomised that their contribution to the betterment of medical care will not be lost.

What is a negative trial?

A step along the path to registration is the "medical editors trial amnesty" that also appears in this week's *BMJ* (p 622).[5] Over 100 medical journals world wide are inviting readers to submit information on unpublished trials, including those published only as abstracts. Will this do the trick? I suspect not. The journal editors are offering registration, not publication, and the pay off from registration is obscure.

What is missing, moreover, is a clear definition of a negative trial. A negative trial is best defined as one in which a clinically significant effect on predefined end points was ruled out. This requires post hoc examination of the confidence intervals around the treatment effect size estimate in the trial. Editors could help their cause by reminding authors that they welcome submission of such negative studies for possible publication.

In contrast, an inconclusive trial is one in which uncertainty remains about the treatment's effectiveness owing to wide confidence intervals around the point estimate of the treatment effect size. Such inconclusive studies are most at risk of homelessness. Perhaps journal editors should annually invite researchers to submit these inconclusive trials for publication in a special electronic supplement. If, after peer review, the reason for an inconclusive result is indeed lack of statistical power rather than some other flaw, the

authors could at least glean some publication credit for their troubles.

As meta-analysts seek unpublished trials and unpublished data from published trials they are often led into conversations with trialists. Such transactions are colourfully described by Roberts and Schierhout in what may be seen as qualitative research to complement the new meta-epidemiology of randomised trials (p 686).[6] The reluctance of many investigators to provide even aggregate unpublished data makes it more remarkable that some meta-analysts have regularly succeeded in gathering individual patient data for re-analysis from trialists. Methodologists continue to debate the importance of gathering individual patient data for meta-analysis, but it does have advantages. Firstly, if errors in the results as published arise from basic programming or statistical mistakes, these can be rectified. Secondly, there can be greater standardisation, for example, in patient subgroups, follow up times, or use of an intention to treat analysis. Dilemmas over data access for meta-analysis emphasise the need for the research community to debate the conditions under which data from randomised trials should be shared.

Data excess

At times the problem for meta-analysts may not be data access but data excess. Huston and Moher have noted that a single trial of risperidone for chronic schizophrenia was reported in seven different publications with different authorship.[7] Tramèr et al provide a striking example of how duplicate data can affect a meta-analysis in this week's issue (p 635).[8] In a systematic review of the effects of ondansetron on postoperative emesis they found that data from nine trials appeared in 23 separate publications, including four pairs of almost identical reports with completely different authors. Only one paper openly acknowledged the prior publication of the same data. The greatest duplication occurred in placebo controlled trials of a single 4 mg intravenous dose of prophylactic ondansetron. When the overlapping publications were weeded out 6.4 patients (95% confidence interval 5.3 to 7.9) had to be treated for every episode of postoperative emesis avoided. When they were not weeded out, the number needed to treat fell to 4.9 (4.4 to 5.6). This is the flip side of publication bias. Just as negative trials are less likely to be published, so positive trials are more likely to be published more than once. The consequences for meta-analysis are similar in both cases: excessively precise and inflated effect size estimates. But, on the positive side, it is the science of systematic reviews that has highlighted this phenomenon of covert duplicate publication.

Given these potential biases, the question remains: how often does meta-analysis mislead rather than guide therapeutic decision making? What can be done to detect misleading meta-analyses? *BMJ* readers will find this issue illuminating, but perhaps not reassuring.

For example, more and more meta-analyses with conflicting conclusions are dotting the literature. Petticrew and Kennedy invoke Sherlock Holmes to make sense of over 20 systematic reviews that have addressed surgical thromboprophylaxis, many with apparently disparate results (p 665).[9] Holmes's bottom line is that surgeons should use mechanical methods rather than heparins, aspirin, or warfarin. Unfortunately, the process whereby the great detective reaches this conclusion is not particularly transparent.

The correspondence columns this week will also reinforce readers' wariness of meta-analysis, as six letters[10] criticise the results of a meta-analysis that purported to show an absence of cardioprotective effect from hormone replacement therapy in postmenopausal and perimenopausal women (p 676).[11] For one, I shall continue to tell my patients that hormone replacement therapy is likely to help prevent coronary disease.

So, how often are meta-analyses wrong? Villar et al examined 30 meta-analyses in perinatal medicine, comparing the results of a meta-analysis of several small trials with a single large trial addressing the same topic.[12] Directionally, 80% of meta-analyses agreed with the results from the larger trial, although concordance for statistically significant findings was much less. Cappelleri et al reviewed 79 meta-analyses and also found about 80% directional agreement.[13]

Very recently LeLorier et al arrived at a more pessimistic assessment.[14] Comparing 12 definitive randomised trials to 19 previous meta-analyses, they claimed the meta-analyses would have led to the adoption of an ineffective treatment in 32% of cases and rejection of a useful treatment in 33%. However, their definition of positive and negative trials was simplistically based on the presence or absence of a statistically significant treatment effect. Directional congruence of point estimates of effectiveness occurred for 80% of the outcomes assessed in the trials and meta-analyses—a result similar to those of the previous studies. The credibility of this work is also undermined by oversights. The authors cite apparent discordance between the 1993 results of the EMERAS trial [15] and a 1985 meta-analysis of thrombolysis for acute myocardial infarction.[16] But they ignore both the findings of ISIS-2,[17] which constituted a more definitive test of the hypotheses generated by the 1985 meta-analysis, and a 1994 meta-analysis that used individual patient data from all trials of thrombolysis for acute myocardial infarction that randomised more than 1000 patients.[18] Conversely, they find concordance between the results of the LIMIT-2 trial[19] and an overview of magnesium for acute myocardial infarction by Teo et al,[20] overlooking the results of ISIS-4[21] and the controversy about magnesium and meta-analysis that has followed.[22-24]

A magic method?

Such discrepancies nevertheless lead one to ask: is there a magic method of determining when a meta-analysis is likely to be misleading? The short answer is no. But in this issue Egger et al do describe a graphical method that may help (p 629).[25] Funnel plots show sample sizes against the point estimate of treatment effectiveness generated in individual studies. A symmetrical funnel shaped plot is expected because of greater scatter in treatment effect estimates for smaller trials, with convergence among larger trials. Egger et al argue that asymmetry in the funnel plot suggests bias in a meta-analysis and propose a statistical method to measure the degree of asymmetry. In reviewing 75 meta-analyses from leading journals and the *Cochrane*

Database of Systematic Reviews, they found 19 reviews with significant funnel plot asymmetry.

This ingenious approach has limitations. For validation the authors show funnel plot asymmetry in three of four cases where meta-analyses of multiple small trials disagreed with subsequent large trials but not in four other cases where the meta-analysis and trials were concordant. That is not a statistically convincing number of test cases. Simulated data with computer intensive methods may provide a complementary approach to test this concept. Secondly, the unit of analysis is the randomised trial, not its patients; and the method's power is limited when only a few trials are included. It is probably prudent to pay more attention to the shape of the plot than to any statistical measures of asymmetry. Above all, even dramatic funnel plot asymmetry does not tell readers what type of bias (if any) is occurring. It must therefore be viewed as a non-specific and partially validated screening test for bias in meta-analysis.

In sum, meta-analysis has made and continues to make major contributions to medical research, clinical decision making, and standards of research reportage. However, it is no panacea. Readers need to examine any meta-analyses critically to see whether researchers have overlooked important sources of clinical heterogeneity among the included trials. They should demand evidence that the authors undertook a comprehensive search, avoiding covert duplicate data and unearthing unpublished trials and data. Lastly, readers and researchers alike need to appreciate that not every systematic review should lead to an actual meta-analysis of data with aggregate effect size estimates.[25] If the process of pooling data inadvertently drowns clinically important evidence from individual studies, then a meta-analysis can do more harm than good.

C David Naylor *Chief executive officer*

Institute for Clinical Evaluative Sciences, North York, Ontario M4N 3M5, Canada

1 Chalmers TC, Mattra RJ, Smith H, Kunzler AM. Evidence favouring the use of anticoagulants in the hospital phase of acute myocardial infarction. *N Engl J Med* 1977;297:1091-6.
2 Goldman L, Feinstein AR. Anticoagulants and myocardial infarction: the problems of pooling, drowning, and floating. *Ann Intern Med* 1979; 90:92-4.
3 Naylor CD. Two cheers for meta-analysis: problems and opportunities in aggregating results of clinical trials. *Can Med Assoc J* 1988;138:891-5.
4 Stern JM, Simes RJ. Publication bias: evidence of delayed publication in a cohort study of clinical research projects. *BMJ* 1997;315:640-5.
5 Smith R, Roberts I. An amnesty for unpublished trials. *BMJ* 1997;315:622.
6 Roberts I, Schierhout G. The private life of systematic reviews. *BMJ* 1997;315:686-7.
7 Huston P, Moher D. Redundancy, disaggregation, and the integrity of medical research. *Lancet* 1996;347:1024-6.
8 Tramèr MR, Reynolds DJM, Moor RA, McQuay HJ. Impact of covert duplicate publication on meta-analysis: a case study. *BMJ* 1997;315:635-40.
9 Petticrew M, Kennedy SC. Detecting the effects of thromboprophylaxis: the case of the rogue reviews. *BMJ* 1997;315:665-7.
10 Singleton S, Bailey K; Shah S, Rhodes L; Seagroatt V; Sundkvist T; Al-Azzawi F, et al; Col NF, et al; Hemminki E [letters]. Impact of postmenopausal hormone therapy on cardiovascular events and cancer. *BMJ* 1997;315:676-9.
11 Hemminki E, McPherson K. Impact of postmenopausal hormonal therapy on cardiovascular events and cancer: pooled data from clinical trials. *BMJ* 1997;315:149-53.
12 Villar J, Carroli G, Belizan JM. Predictive ability of meta-analyses of randomised controlled trials. *Lancet* 1995;345:772-6.
13 Cappelleri JC, Ioannidis JPA, Schmid CH, de Ferranti SD, Aubert M, Chalmers TC, et al. Large trials versus meta-analysis of smaller trials. How do their results compare? *JAMA* 1996;276:1332-8.
14 LeLorier J, Gregorie G, Benhaddad A, Lapierre J, Derderian F. Discrepancies betweeen meta-analyses and subsequent large randomised controlled trials. *N Engl J Med* 1997;337:536-42.
15 EMERAS (Estudio Multicentro Estreptoquinasa Republicas de America del Sur) Collaborative Group. Randomised trial of late thrombolysis in patients with suspected acute myocardial infarction. *Lancet* 1993;342:767-72.
16 Yusuf S, Collins R, Peto R, Furberg C, Stampfer MJ, Goldhaber SZ, et al. Intravenous and intracoronary fibrinolytic therapy in acute myocardial infarction: overview of results on mortality, reinfarction, and side effects from 33 randomised controlled trials. *Eur Heart J* 1985;6:556-85.
17 ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet* 1988;ii:349-60.
18 FTT Collaborative Group. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. *Lancet* 1994;343:311-22.
19 Woods KL, Fletcher S, Roffe C, Haider Y. Intravenous magnesium sulphate in suspected acute myocardial infarction: results of the second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2). *Lancet* 1992;339:1553-8.
20 Teo KK, Yusuf S, Collins R, Held PH, Peto R. Effects of intravenous magnesium in suspected acute myocardial infarction: overview of randomised trials. *BMJ* 1991;303:1499-1503.
21 ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58 050 patients with suspected acute myocardial infarction. *Lancet* 1995;345:669-85.
22 Yusuf S, Flather M. Magnesium in cute myocardial infarction. ISIS-4 provides no grounds for its routine use. *BMJ* 1995;310:751-2.
23 Egger M, Davey Smith G. Misleading meta-analysis. Lessons from "an effective, safe, simple" intervention that wasn't. *BMJ* 1995;310:752-4.
24 Collins R, Peto R. Magnesium in acute myocardial infarction. *Lancet* 1997;349:282-3.
25 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34.
26 Naylor CD. The case for failed meta-analyses. *J Eval Clin Pract* 1995;1:127-30.

Food safety: from plough to plate

Both public and industry need a food agency with clout

See p 625

The crisis over bovine spongiform encephalopathy may have been the most serious scare to hit Britain's food industry, but it was not an isolated event. It followed a stream of other concerns—about food additives, irradiation, salmonella in eggs, *Escherichia coli*, pesticides, genetically modified tomatoes, and the rising incidence of food poisoning. On each occasion ministers, producers, and retailers have struggled to restore consumer confidence. But their efforts have increasingly misfired, being seen as patronising, misleading, and stemming more from a desire to protect profits than to protect the public's health. Now at last it seems clear that the problem is not simply the public's perception that food is unsafe but real failings in the system of safeguards.

A fundamental shake up is required, in particular one that separates the conflicting responsibilities of the Ministry of Agriculture, Fisheries, and Food, currently charged with both safeguarding the public's health and promoting the interests of Britain's food industry.[1] In a report commissioned by the outgoing Conservative government and published in April, Professor Philip James of Aberdeen University proposed a new Food Standards Agency.[2] Some aspects of the proposals are

uncontroversial. But, as was evident at a meeting on food safety in London last week organised by the Transport and General Worker's Union, others still elicit fierce debate.

The new agency, as proposed by Professor James, would be independent of government but accountable to parliament, reporting to the Secretary of State for Health. Its first priority would be to protect public health. It would deal with four main aspects of food safety and quality: bacterial contamination, including bovine spongiform encephalopathy; toxicology and pesticides; genetic engineering; and nutritional quality. Modelled on the Health and Safety Commission and its executive, and on food safety bodies in other countries,[1] the agency would coordinate the currently fragmented system of food policy and safety control.

Few argue with the agency's need to be independent, free from commercial conflicts of interest, and transparent in its proceedings. But representatives of industry oppose the inclusion of nutritional standards, arguing that healthy eating is a matter of individual behaviour and is already covered by the government's strategy for health, Health of the Nation. In reply, food activists argue that the Health of the Nation targets are far from ambitious and will be met simply as a result of existing trends. In not issuing clear guidance on healthy eating, the government has, they say, bowed to pressure from industry, which fears the impact such guidance would have on its profits. Jeanette Longfield of the National Food Alliance said, "If the Food Standards Agency is just about restoring public confidence in the food supply, it doesn't need to cover nutrition. But if it's about public health, nutrition must be in there."

Other issues remain unresolved. Firstly, how will the agency fit into the complex structures that oversee the international food market? Much of the regulation controlling food safety in Britain now originates in Europe; and beyond that is the World Trade Organisation, which works to ensure that a country's food safety controls are not trade barriers in disguise. The World Trade Organisation has recently upheld the United States' view that the European Union's ban on growth hormones in meat is illegal because there is no scientific evidence to support this.

Secondly, how will the agency get enough input for agricultural experts without reinventing the conflicts of interest inherent in the existing system? Patrick Holden, director of the Soil Association, believes that Professor James' proposals don't put enough emphasis on what happens to food before it leaves the farm. This, he says, is where the major problems of food safety originate, resulting from intensive production methods. He would like to see an integrated ministry of sustainable agriculture and food standards that builds the bridge between the Food Standards Agency and the old Ministry of Agriculture, Fisheries, and Food.

Thirdly, what should be the agency's role in educating and informing the public about food safety and quality? Suggestions at the meeting ranged from getting supermarkets and other outlets to provide computerised information about individual products which could be accessed via the bar code on the label, to the more ambitious challenge of educating the public about levels of risk.

Finally, should the agency be responsible for the socioeconomic impact of food production and retail activities, such as the effects on communities of agribusiness and out of town supermarkets? Regulation of the pharmaceutical industry now covers this so called "fourth hurdle," in addition to the safety, quality, and efficacy of drugs. The food industry will resist this additional inteference, but for once the political tide may be against it.

While the agency's exact remit will need to be clarified when the government considers the responses to the James report this autumn, an impressive consensus exists over the essentials. After all, the food scares of the past few years have damaged the industry's health as much as the public's. The government should capitalise on this consensus to introduce an agency with clout which will not only restore consumer confidence but will, in the long term, bring about concrete changes in the way in which our food is produced and delivered.

Fiona Godlee *Assistant editor, BMJ*

1 McKee M, Lang T. Food for independence. *BMJ* 1997;314:459-60.
2 James P. Food Standards Agency: an interim proposal. London: Cabinet Office, 1997.

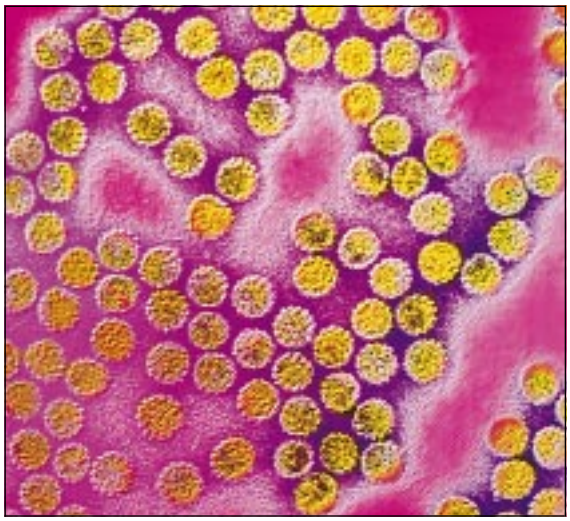
Is human papillomavirus an infectious cause of non-cervical anogenital tract cancers?

Results from a large study provide strong epidemiological evidence

"Temporality" is a central tenet in the epidemiological assessment of causality, requiring that exposure to a putative cause must precede development of the disease.[1] However, temporality has been difficult to demonstrate in the study of human papillomavirus infection as a cause of non-cervical anogenital tract tumours.

In cervical cancers human papillomavirus DNA can be detected in over 90% of lesions. Moreover, cervical human papillomavirus has been detected before the development of cervical intraepithelial neoplasia, which is well established to be a precursor of cancer.[2] In non-cervical anogenital tumours a common causal relation with human papillomavirus is suggested by the raised risk of anal, vulvar, and vaginal tumours after cervical cancer[3]; a high prevalence of penile intraepithelial neoplasia in the sexual partners of women with cervical intraepithelial neoplasia[4]; and the high prevalence of human papillomavirus DNA in non-cervical anogenital cancer tissues.[5] Infection of normal non-cervical anogenital epithelium may be as common as in the cervix.[6]

See p 646


SPL

Human papillomavirus

Thus, the anogenital tract can be considered to be a generally susceptible region for epithelial human papillomavirus infections, with each local area a potential viral reservoir and source of autoinoculations. Human papillomavirus infection of the cervical transformation zone, however, produces the major burden of anogenital cancers. Indeed, non-cervical anogenital cancers are rare, and tissue specimens from before the development of non-cervical anogenital neoplasia are not generally available from prospective studies of human papillomavirus infection. Using recently validated serological methods, Bjørge et al, in this edition of the *BMJ*, present the first major study to examine the relation of exposure to human papillomavirus to the later development of non-cervical anogenital cancers.[7]

The researchers conducted a nested case-control investigation of the seroprevalence of human papillomavirus antibodies and subsequent anogenital tumours in Finland and Norway by matching data in the cancer registries in the two countries to nearly 700 000 subjects who had provided stored blood samples at various earlier times. The pre-disease specimens were tested for IgG to virus-like particles of human papillomavirus 16, 18, and 33—three types commonly detected in specimens from anogenital tumours. They tested 81 patients with non-cervical anogenital cancer and 240 matched controls. Human papillomavirus antibodies, but not antibodies to another sexually transmitted infection—*Chlamydia trachomatis*, were more common in people who later developed anogenital cancers, including vulvar, vaginal, and penile cancers. Anal cancer, however, was not related to seroprevalence of these three types of human papillomavirus.

The findings suggest that human papillomavirus infection is associated with later diagnosis of vulvar, vaginal, and penile cancers. This inference is further reinforced by the consistency of these findings with results from prospective human papillomavirus serological studies of patients who later developed cervical cancer.[8 9] There are caveats, however. In the investigation by Bjørge et al only the results in vulvar and vaginal cancer were statistically significant, and the absence of an anti-human papillomavirus IgG association with anal cancer was not explained—although it may have been due to a chance increase in seroprevalence among the small group of matched controls. It would also have been useful to know whether the cases positive for human papillomavirus antibody developed tumours containing DNA of the same types as implicated by serology. In addition, consideration of pathological subtypes of cancers in an investigation with longer follow up is needed. For example, warty and basaloid vulvar tumours in younger women are generally associated with human papillomavirus, but not the typical keratinising carcinomas of older women.[10] Lastly, repeated observations over time, rather than a single serological result for each patient, would further confirm these causal relations. Nevertheless, given the rarity of non-cervical anogenital tumours and the general unavailability of large collections of prospectively stored specimens, it is unlikely that many other research groups could expand considerably on these results. Thus, Bjørge et al have provided an important and difficult to obtain piece of evidence demonstrating the probable relation between human papillomavirus infection and later development of non-cervical anogenital cancers.

Prospective and large population based studies like this show that human papillomavirus serology is an increasingly useful biomarker. Its sensitivity and specificity are not optimal, however. For example, only about half the women positive for cervical human papillomavirus 16 DNA are antibody positive.[11] Therefore, human papillomavirus seroassays remain primarily epidemiological research tools. Overall, the major public health importance of the findings by Bjørge et al is that a successful human papillomavirus vaccine could have benefits beyond the primary goal of preventing cervical cancer.

Howard D Strickler *Senior clinical investigator*

Viral Epidemiology Branch

Mark H Schiffman *Chief interdisciplinary studies section*

Environmental Epidemiology Branch, National Cancer Institute, Bethesda, Md 20892, USA

1 Hill AB. The environment and disease: association or causation. *Proc R Soc Med* 1965;58:295.
2 IARC Working Group. *Monographs on the evaluation of carcinogenic risks to humans.* Vol 64. *Human papillomaviruses.* Lyon: IARC, 1996.
3 Rabkin CS, Biggar RJ, Melbye M, Curtis RE. Second primary cancers following anal and cervical carcinoma: evidence of shared etiologic factors. *Am J Epidemiol* 1992;136:54-8.
4 Barrasso R, De Brux J, Croissant O, Orth G. High prevalence of papillomavirus-associated penile intraepithelial neoplasia in sexual partners of women with cervical intraepithelial neoplasia. *N Engl J Med* 1987;317:916-23.
5 Schneider A, Meinhardt G, Kirchmayr R, Schneider V. Prevalence of human papillomavirus genomes in tissues from the lower genital tract as detected by molecular in situ hybridization. *Int J Gynecol Pathol* 1991; 10:1-14.
6 Bauer HM, Ting Y, Greer CE, Chambers JC, Tashiro CJ, Chimera J, et al. Genital human papillomavirus infection in female university students as determined by a PCR-based method. *JAMA* 1991;265:472-7.
7 Bjørge T, Dillner J, Anttila T, Engeland A, Hakulinen T, Jellum E, et al. A prospective seroepidemiological study of the role of human papillomavirus in non-cervical anogenital cancers. *BMJ* 1997;315:646-9.
8 Lehtinen M, Dillner J, Knekt P, Loustarinen T, Aromaa A, Kirnbauer R, et al. Serologically diagnosed infection with human papillomavirus type 16 and risk for subsequent development of cervical cancer: nested case-control study. *BMJ* 1996;312:537-9.
9 Shah KV, Viscidi RP, Alberg AJ, Helzlsouer KJ, Comstock CW. Antibodies to human papillomavirus 16 and subsequent in situ or invasive cancer of the cervix. *Cancer Epidemiology Biomarkers and Prevention* (in press).
10 Kurman RJ, Toki T, Schiffman MH. Basaloid and warty carcinomas of the vulva. *Am J Surg Pathol* 1993;17:133-45.
11 Kirnbauer R, Hubbert NL, Wheeler CM, Becker TM, Lowy DR, Schiller JT. A virus-like particle enzyme-linked immunosorbent assay detects serum antibodies in a majority of women infected with human papillomavirus type 16. *J Natl Cancer Inst* 1994;86:494-9.

An amnesty for unpublished trials

Send us details on any unreported trials

See p 683

This month over 100 medical journals around the world are inviting readers to send information on unpublished trials. This amnesty should have important benefits for patients. Why?

Reports of properly conducted randomised controlled trials are the foundation of effective health care, but many are not submitted for publication.[1 2] This reduces the power of systematic reviews to detect moderate but clinically important treatment effects. Patients may thus be denied effective forms of health care. A second problem is that since trials that show more promising effects are more likely to be submitted, research syntheses can give misleading conclusions about effectiveness. Patients may thus be exposed to useless or even harmful treatments.[3] Finally, patients may be asked to participate in new studies designed to address questions that have already been answered.[4]

Trials go unreported for a myriad of reasons: it is well documented that trials with non-significant results are substantially less likely to be submitted for publication.[1] Sometimes recruiting participants takes longer than expected at the expense of time set aside for report writing; investigators may change jobs and work remain unfinished; or investigators may discover a recently published trial on the same topic and conclude that their own results are redundant. Editors must also take some responsibility: there is a limit to the number of reports we can publish. Many investigators regret not having published their results, and when contacted almost all are delighted to provide them.

Although amnesty means giving pardon, we hope that investigators will see this as an opportunity—namely, to make the results of previously unreported trials publicly accessible, thus having the potential to contribute to the scientific foundation of health care. We urge all investigators with unreported trial data to register their trials by returning a photocopy of the registration form shown below. We would like to register any unreported controlled trial, including trials that have only been published as an abstract.

Registration can be undertaken by anyone able to provide the registration information, even if they cannot provide the actual trial data. We expect a degree of duplicate registration. The information will be made available by listing the trial details on a web site and in other ways. If specific trial data are required, for example by those conducting systematic reviews, then the reviewer will be able to seek this information directly from the trialist. Some of the trials may be suitable for full publication, and the journal will be happy to consider these.

Medical editors are acutely aware of the trials and tribulations of research reporting. On this occasion, because of the serious implications of unreported research, we are trying to cleave the trials from the tribulations. We are confident of a good response.

Richard Smith *Editor, BMJ*
Ian Roberts *Director*

Child Health Monitoring Unit, Institute of Child Health, London WC1N 1EH

1 Dickersin K, Min YI. NIH clinical trials and publication bias. *On-line J Curr Clin Trials* [serial online] 1993; 28 Apr: Doc No 50.
2 Easterbrook PJ, Berlin JA, Gopalan R, Matthews DR. Publication bias in clinical research. *Lancet* 1991;337:867-72.
3 Egger M, Davey Smith G. Misleading meta-analysis. *BMJ* 1995;310:752-4.
4 Savulescu J, Chalmers I, Blunt J. Are research ethics committees behaving unethically? Some suggestions for improving performance and accountability. *BMJ* 1996;313:1390-3.

Unreported trial registration form

Register any controlled trial which has not been published in full, including trials that have been published only as an abstract. Registration can be undertaken by anyone able to provide registration information, even if they are unable to provide the actual trial data. Please complete one form for each trial being registered.

Contact details

Surname: _____ Forename(s): _____

Postal address: _____ Phone (with regional codes): _____

_____ Fax (with regional codes): _____

_____ Email: _____

_____

Trial details

Approximate number of participants in the trial: _____

Type of participants (eg people with head injury, women at risk of breast cancer): _____

_____

Type of intervention (eg steroids versus placebo, annual mammography versus standard practice):

_____ versus _____

Please post or fax registration forms to: Medical Editors' Trial Amnesty, BMJ Editorial Department, Tavistock Square, London WC1H 9JR. Fax: 44 (0)171 383 6418. Alternatively the information can be sent by email to: meta@ucl.ac.uk