Quality of randomised controlled trials in head injury. Trials in head injury are more complex than review suggests

Citation for published version:
Murray, GD & Teasdale, GM 2000, 'Quality of randomised controlled trials in head injury. Trials in head injury are more complex than review suggests' BMJ, vol 321, no. 7270, pp. 1223. DOI: 10.1136/bmj.321.7270.1223

Digital Object Identifier (DOI):
10.1136/bmj.321.7270.1223

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Publisher's PDF, also known as Version of record

Published In:
BMJ

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Letters

GMC's proposals for revalidation would not be accurate, economical, or fair

Editor—To anyone involved in assessing medical competence, the General Medical Council's proposal for revalidation is potentially unfair and inaccurate, and very expensive.1

The proposal has two parts. The first—the form of appraisal—is uncontroversial; it can be helpful.2 The second is a summative assessment every five years, aggregating the appraisals, which is reviewed by two doctors from the appraisee's field and a lay person; collectively they determine whether to recommend revalidation. This does not lead to de-registration: it acts as a sieve, seeking to identify potentially inadequate doctors, who would then undergo further assessment under the performance procedures devised by Southgate et al.3 It is the sieve that is inappropriate.

One difficulty in assessment is making it fair between candidates. In examinations, this requires minimisation of inter-examinee variables—for example, the same assessors judge the same attributes of all candidates—and thorough training of assessors. The General Medical Council proposes an individual group of assessors for each doctor's review. The levels of judgment of the assessors will differ considerably, each group being different. Serious training for all assessors for the thousands of candidates assessed annually (extraordinarily, the council cannot indicate numbers) seems improbable: an assessment of osteopaths' portfolios required up to three days' training for assessors (B Jolly, personal communication).

Portfolio assessment has good face validity and may be useful when used formatively.4 Few evaluations have been conducted of it; research in the medical field suggests that it is subject to assessor bias and is unreliable and inaccurate.5 Estimates of the time needed for the review (involving three assessors examining five-year portfolios and interviewing the appraisee; say five days for each professional to consider the submission, interview, and report and five days' preparation for the appraisee) suggest a cost of at least £50m a year, or an opportunity cost of around 1% of clinicians' time. This is an enormous expense to identify, inaccurately, those doctors to subject to further assessment.

Peer associate ratings, used in the United States,6 could be quicker and more accurate but might be inappropriate for some groups—for example, singlehanded general practitioners. But one could readily devise a paper based assessment exercise of a maximum one day's duration as a sieve towards the performance procedures. Though not directly assessing performance, it would tap measures of clinical competence best predicting clinical performance, assessing ethical and communication issues, as well as knowledge and problem solving. It would allow the appraisals to remain formative. And it would be accurate, economical of time and money, and fair.

Anyone for testing?

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BMA approves acupuncture

BMA report is wrong

Editor—The BMA report on acupuncture is regrettable. It suggests, among other things, that acupuncture is effective for back pain, dental pain, and migraine. Three recent systematic reviews show the importance of basing judgments on high quality information.

For back pain, four randomised and blind studies showed no benefit; five open studies showed benefit.1 The BMA's conclusion that acupuncture was effective in back pain was based on all nine studies.

For dental pain, a review of 16 studies concluded that it was effective.2 Many of these were not randomised, were not blind, or had major flaws. Only three small studies were adequate, and these showed no convincing benefit.3

For migraine, trials showing a significant benefit from acupuncture were inadequately randomised or not blind.2 The reviewers themselves were highly circumspect about ascribing any clinical significance to acupuncture.

The BMA report concluded that results for acupuncture are inconclusive in other conditions. These are weasel words. For smoking cessation the 12 month cessation rate with acupuncture was 14% (95% confidence interval 11% to 17%), which was no different from the placebo response with nicotine gum of 12% (11% to 13%).

Trials of acupuncture suffer problems of poor quality, which leads to bias. Reviews with poor quality studies overestimate treatment effects. Original reports may come to the wrong conclusion from their own data, a fact true of two of 13 studies of acupuncture in neck and back pain.4

For those areas where the BMA report thought there was evidence of effectiveness of acupuncture, either there was none or what quality evidence there was indicated lack of effectiveness. For those areas where the BMA thought the results inconclusive, there was either no useful information or acupuncture was shown to be ineffective. Doctors should beware. There is no useful evidence showing that acupuncture helps; there is evidence that it harms. Perhaps the important point is that we

Advice to authors

We prefer to receive all responses electronically, sent either directly to our website or to the editorial office as email or on a disk. Processing your letter will be delayed unless it arrives in an electronic form.

We are now posting all direct submissions to our website within 24 hours of receipt and our intention is to post all other electronic submissions there as well. All responses will be eligible for publication in the paper journal.

Responses should be under 400 words and relate to articles published in the preceding month. They should include ≤ 5 references, in the Vancouver style, including one to the BMJ article to which they relate. We welcome illustrations. Please supply each author's current appointment and full address, a phone or fax number or email address for the corresponding author. We ask authors to declare any competing interest. Please send a stamped addressed envelope if you would like to know whether your letter has been accepted or rejected. Letters will be edited and may be shortened.

Website: bmj.com
Email: letters@bmj.com
should not deceive ourselves, or people who trust our recommendations. There is no gold standard evidence that acupuncture improves pain or anything else. The BMA report is quite simply wrong.

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Is approval of acupuncture for back pain really evidence based?

Errone–The BMA has concluded that acupuncture should be made more widely available to British people through the NHS and that general practitioners should receive training in it.1 The association seems to base its conclusion on three things: evidence showing that “acupuncture is more effective than control interventions for back pain, nausea and vomiting, migraine and dental pain”2; the fact that 47% of general practitioners have arranged for their patients to receive acupuncture; and the wish of 46% of those professionals to receive training in acupuncture in order to treat their patients.3

The evidence on the effectiveness of acupuncture in the treatment of back pain seems to have been misinterpreted. The Cochrane Collaboration Back Review Group has published a major systematic review of the effectiveness of acupuncture in low back pain.4 This review followed a rigorous methodology and an exhaustive search for information. Its results indicated poor research methods and contradictory results from studies of acupuncture in low back pain. The review was therefore incoherent and could not serve as a basis for recommending acupuncture. This was consistent with the results of past systematic reviews5 and with a randomised trial that compared the effectiveness of acupuncture with that of massage and self care education.6 D C Cherkin et al, fourth international forum for primary care research on low back pain, Elat, Israel, 2000.

Although scientific evidence in this respect has not changed much in several years, public and medical opinion does seem to have changed. The establishment of a double standard for the approval of a treatment technique, bowing to the pressure of public opinion and not taking into account evidence based recommendations, is harmful to the public’s health and to the economy of the NHS. In time it could also be harmful to the treatment approved with the lower standard and to the credibility of its practitioners and the institutions that recommend it.

Clinical practice is not always based on scientific evidence and the search for an efficient use of resources. Many years ago patients were convinced of the effectiveness of leeches for the treatment of infectious diseases, doctors prescribed them, and apothecaries sold them. Nevertheless, despite public demand and medical interest, evidence of the efficacy, safety, and cost effectiveness of the treatment was lacking. This lesson from the past should be kept in mind.

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1 Silver M. Acupuncture wins BMA approval. BMJ 2000; 321:11.(1 July)

Lung cancer and passive smoking

Turning over the wrong stone

Errone–In their reanalysis of the epidemiological evidence on lung cancer and smoking Copas and Shi6 assert that after allowing for publication bias the apparent average excess risk of lung cancer from passive smoking7 would drop from 24% to 15%. Despite the lack of supporting data,8 we are asked to believe solely on the basis of statistical inference that such data must be hiding under a stone. They are, however, turning over the wrong stone.

More important than publication bias is the underestimation of risk that occurs when these studies assess exposure solely on the basis of whether non-smokers either lived or did not live with a smoker,9 when other exposure exists.

Where other exposure is common—for example, in childhood, in social situations, or in the workplace—the risk of lung cancer may be seriously underestimated. Spouses of non-smokers exposed in other circumstances will be misclassified as non-exposed, contaminating the referent group, and attenuating the risk estimate. For example, Hackshaw et al estimate that the odds ratio would have been 1.42 (95% confidence interval 1.21 to 1.66) if those with spousal exposure alone were compared with those who were truly unexposed.10 By comparison, in a recent meta-analysis of risk associated with workplace exposure, Wells found an estimated relative risk of 1.39 (1.15 to 1.68) for the five studies meeting basic study quality standards.11 Repace and Lowrey found that when both workplace exposure and an unexposed referent group were taken into account in the American Cancer Society study of passive smoking and lung cancer, a population relative risk of 1.2 increased to 1.7.12

Repace and Lowrey modelled the risk of workplace exposure, estimating the average relative risk at 2.0 for office workers in the United States in the 1980s. This result is consistent with a value reported by Reynolds et al for women with 30 or more years of workplace exposure—namely, at ages at which lung cancer mortality begins to become significant.13

Moreover, all of these analyses focus on average risk. Repace et al estimated that individuals at the 95th centile—for example, those experiencing high smoker density and low air exchange—have an exposure, and a risk, much as four times as high as those at the median. This result is commensurate with observations of dose14 and risk.15 Turning over stones may indeed alter the estimated risk, but turning over the right stone indicates that in the original meta-analysis, the actual passive smoking-lung cancer risk is underestimated, not overestimated.

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Competing interests: None declared.


Increased risk is not disputed

Errone–In their paper on lung cancer and passive smoking,1 Copas and Shi say that in our review of passive smoking and lung cancer there is clear evidence of publication bias and that allowing for this substantially lowers the estimate of relative risk (which we reported as 1.24 before correction for other biases and confounding and 1.26 after correction).12 Neither is correct.

It is proposed that large studies will tend to be published regardless of their result but small studies published only if they are positive (publication bias). As Copas and Shi point out, studies with a large standard error (indicating a small study) tend to be
associated with a large relative risk (correlation coefficient 0.35, P = 0.05), implying that there may be some unpublished small negative studies. An indication of the size of the effect can be obtained by restricting the analysis to those studies with smaller standard errors which are less susceptible to increase publication bias. If the six studies with the largest standard errors (> 0.5) are excluded there is no evidence for an association between standard error and relative risk (correlation coefficient 0.13, P = 0.48) and the estimate of risk is 1.22; even if the 12 studies with the largest standard errors (> 0.4) are excluded the estimate is 1.23; neither is materially different from the estimate based on all 37 studies (1.24). This indicates that the effect of unpublished studies is likely to be negligible.

There is further evidence against material publication bias in that 32 of the 39 studies reported non-significant results and in 16 (41%) the authors had either concluded that there was no effect (15) or that the evidence was inconclusive (3), suggesting that the passive smoking literature is one with a strong tendency for positive results to be published while negative results remain unpublished.

Even if one accepts the calculations of Copas and Shi, their relative risk estimate, which assumes that as many as 20% of all studies are unpublished, is 1.15, not substantially different from our own estimate (1.26) and well within the confidence interval on our result (1.06 to 1.47). Even under the extreme assumption that 40% of studies were not published their estimate (1.11) would still be consistent with ours.

Copas and Shi do not dispute that there is an increased risk of lung cancer due to passive smoking nor do they seriously challenge our estimates of its magnitude.

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Competing interests: None declared.

Nothing new was said

Editor—My reaction to this paper is a big yawn. Copas and Shi think that there is evidence of publication bias against small studies that reach the negative conclusion that second hand smoke causes lung cancer. This is nothing new, nor is the analysis they present (based on something called a funnel plot).

Copas and Shi agree that a meta-analysis of the published studies on passive smoking and lung cancer shows a significant increase in risk of 1.24. They compute that if only 60% of the studies that have ever been done were published and that the remaining 40% of studies that were done but never published—and that no one has ever heard of—were all negative, then the increase in risk would only be 1.11 and not significant. There is no evidence that these studies were ever done. Our investigation suggests that there is no publication bias.

Copas and Shi also point out that if only 70% of the studies were published, and all the unpublished studies showed no elevation in risk, then the pooled risk would be 1.13 and significant (P = 0.052).

So, you could argue that they proved that, while failure to publish negative studies would lower the true risk of lung cancer associated with passive smoking, under any reasonable guess at how much "unpublished" research there was, there would still be an increase in risk. But despite the fact that many people have tried to find these unpublished studies, no one has been able to find them. The tobacco industry would make sure we knew about them.

What Copas and Shi say is that if several people did studies that found no effect of passive smoking and lung cancer and found no increase in risk, and we suddenly knew about these papers, then our estimate of how much the risk was increased would be smaller. But the risk would still be increased.

The real killer from second hand smoke is heart disease, not lung cancer. Heart disease kills about 10 times more people than lung cancer. Not even the tobacco industry has contested the evidence on asthma.

So … what's the big deal?

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Competing interests: None declared.

Scales for visual test of publication bias are unfair

Editor—Funnel plots can be useful to detect publication and related bias. The funnel plot in the review of the epidemiological studies of passive smoking and lung cancer by Copas and Shi is, however, biased. In the absence of publication bias the plot can be assumed to be symmetrical only if relative risks are plotted on a logarithmic scale. The scale used by Copas and Shi is not logarithmic and will give the visual impression of publication bias even when there is none. Studies indicating that exposure to passive smoking increases the risk of lung cancer will spread out on the graph because the relative risk may range from 1.0 to infinity; in contrast studies showing a reduction in risk will be compressed in the range of 1.0 to zero. Visual interpretation of the data is therefore not possible by using the scale presented.

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Authors' reply

Editor—We thank the respondents for their comments on our paper. We agree with Johnson and Repace that the truth will be hiding under stones. Some of these stones (causes of bias) were considered in the earlier review by Hackshaw et al. They found that some papers give an increase in risk, others a decrease, and that on aggregate they tend to cancel out. What we have done is to add one more stone (publication bias) and use it to redo their calculation of the overall risk. It is not the wrong stone, just one of several stones.

Johnson and Repace start their letter by asserting that we claim that the excess risk decreases from 24% to 15%. We have not come up with a single best estimate. This is impossible without making assumptions that cannot be proved about how many unpublished studies there are. Our conclusion is that at least some publication bias is needed to explain the trend in the funnel plot, and that allowing for even a small amount of study selection can give a substantially lower figure.

The paper by Bero et al, which we did refer to in our paper, suggests that there is no publication bias. We would emphasise the word "suggest"—neither their arguments nor the fact that no unpublished papers have been found mean that none exists. Our analysis does not dispute that the risk is increased; the question is by how much. Neither do we claim that the unpublished papers were all negative. We can say nothing at all about them, just that there may be a pool of studies from which the ones in the review are a selection. Our method lets the funnel plot tell us how much bias there may have been in this selection.

Just because more people die of heart disease than of lung cancer does not necessarily mean that there are more deaths attributable to passive smoking. A rather similar review by He et al, who are looking at studies of passive smoking and heart disease, comes up with a relative risk of 1.28. Thus, in relative terms, the elevation of risk is fairly similar.

In their letter, Hackshaw et al point out that most of the range of estimates we discuss is within their confidence band. Publication bias is another source of statistical uncertainty but, unlike ordinary sampling variability, acts in the downward direction only. Whatever confidence range is given, it tends to be just the single figure which is remembered. If there is good reason to think this is an overestimate, then surely this needs to be pointed out.

Finally, Cates is right in pointing out that we did not use logarithmic scales in our funnel plot. We decided to plot the raw figures so they could be compared more easily with the various values of relative risk discussed in the earlier article by Hackshaw et al. But this is
just the presentation. Our analysis was in fact based on log relative risks. To keep our paper as simple as possible we omitted all such statistical technicalities. A complete description of our method, including graphs on logarithmic scales, will appear later this year in the new statistical journal Biostatistics.

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Competing interests: None declared.


Quality of randomised controlled trials in head injury

Trials in head injury are more complex than review suggests

Editor—The review by Dickinson and colleagues1 shows a remarkably narrow view of research in head injury and virtually ignores the need to match the design to the research question. Historically, many clinical trials have been underpowered, but the authors’ premise that the main aim of head injury trials should be to detect changes of “a few percentage points” in the rate of death or disability does not apply, for example, to phase II/II trials in the acute stage or the later interventions used in many of their reviewed trials. The authors might find it useful to reread the article “Why do we need some large, simple randomized trials?” by Yusuf et al (note the word “some” in the title).2

Several factors influence the relevant effect size and hence the size of the trial. Some potentially powerful interventions in severe head injury are not widely practicable and are likely to be expensive, and therefore evidence of a substantial effect is required if budget holders are to be persuaded to support them. The focus on a 10% benefit has reflected a perception that funding could be obtained for a treatment that benefits 1 person in 10. However, even this may be optimistic. Despite the 13% benefit obtained from nimodipine treatment in subarachnoid haemorrhage,3 corresponding to a number needed to treat of eight, clinicians have had difficulties in gaining funding for the routine use of this drug. The effectiveness in individual patients is also relevant.

Dickinson and colleagues say that unfamiliarity among ethics committees and investigators with the idea of randomisation without consent obstructs recruitment. This is erroneous and displays a dangerously superficial attitude towards a complex area. What urgently needs to be clarified is the legal framework in which research in incompetent adults takes place. Recent legislation in the Scottish parliament contains no provision for an exception to the requirement to obtain informed consent. Equally it is not clear that any legal framework exists to allow research without consent in the rest of the United Kingdom.

The authors highlighted inadequate funding as one obstacle that has prevented large randomised controlled trials of widely practicable treatments for head injuries. The corresponding author is an applicant to the Medical Research Council for substantial funding for developing the CRASH study4 into a full scale trial, a study that is in part supported by the manufacturer of the agent under trial. In view of this, and his apparently strong position on this issue, it may be found surprising that no competing interests were declared.

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Competing interests: As director of a charitable organisation, the European Brain Injury Consortium, Professor Murray has been active in providing statistical advice to several pharmaceutical companies on the design, conduct, and analysis of clinical trials in head injury—namely, Bayer, Cambridge Neuroscience, Novartis, Pharmos, SmithKlineBeecham, and Synthelabo. In addition to extensive declared interests in head injury (BMJ 2000;250:1631-3), Professor Teasdale was a co-applicant to the Medical Research Council and a member of the steering committee for the pilot phase of the CRASH study but is not an applicant for funding for the full phase and has withdrawn from the steering committee.


Authors’ reply

Editor—We are pleased that Murray and Teasdale agree that clinical trials in head injury have been too small and that some large simple randomised controlled trials are needed. To date, there have been no such studies in head injury.

We are grateful to Professors Murray and Teasdale for identifying yet another obstacle to conducting large trials in head injury, the idea that to obtain funding a treatment must benefit at least 1 person in 10. There is no rational basis for the use of such a decision rule. Many factors impact on the decision to provide a treatment but considerations of efficiency require that priority is given to treatments that provide the greatest benefit per unit of cost. Even expensive treatments that benefit fewer than 1 person in 10 might be worth funding if the intervention offers an overall net welfare gain. In head injury, with high rates of long term disability, such a situation might easily occur.

When the effect size is large even small trials may be able to detect it. However, Murray and Teasdale fail to appreciate that both the size and the precision of the estimated treatment effect must be taken into account in therapeutic decision making. Large trials, with larger numbers of outcome events, provide more precise estimates of treatment effect, and the true treatment effect is likely to be close to what has been observed. Imprecise estimates of even large treatment effects from poor quality trials make clinical and funding decisions difficult.

We agree that the legal framework in which research in incompetent adults takes place needs to be clarified. Given that such senior investigators as Murray and Teasdale are unclear on this issue, we hope that we might be forgiven for suggesting that less experienced investigators also find this issue problematic.

In our paper we openly and publicly make the scientific argument for some large simple randomised trials in head injury. We openly and publicly acknowledge that the same scientific argument underpins the Medical Research Council’s CRASH trial (corticosteroid randomisation after significant head injury), the first large simple randomised controlled trial in head injury. Open scientific argument in the pages of a medical journal does not constitute a conflict of interest and we are surprised that Murray and Teasdale think otherwise.

Finally, we would point out that the CRASH trial is sponsored by the Medical Research Council and not the manufacturers of the agent under trial. The manufacturers have donated the drug for the trial to the Medical Research Council, but the design, management, and finance of the trial are entirely independent of them.

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Competing interests: None declared.

If in doubt, declare competing interests

Editor—Five years ago it was unusual for contributors to medical journals to declare competing interests even though they often had them. Now, increasingly, contributors do declare them, but there continues to be confusion over when to declare.

The BMJ started its campaign on competing interests by asking authors to declare any sort of competing interest, be it personal, political, religious, or whatever. Now we concentrate on financial competing interests because they are easier to define and there is stronger evidence that they matter.

Dr Roberts and others chose not to declare that they had applied to the Medical
Research Council for a grant for a large trial of the treatment of head injury. The BMJ's guidance to contributors says: "A competing interest exists when professional judgment concerning a primary interest (such as patients' welfare or the validity of research) may be influenced by a secondary interest (such as financial gain or personal rivalry)." It seems entirely plausible that the view of Dr Roberts and others on the desirability of a large trial of treatment of head injury may be influenced by the Medical Research Council's being more likely to award them a grant if that view becomes widely accepted. In my judgment, they would thus have been wiser to declare their competing interest.

There is nothing wrong with having competing interests, and my advice to contributors is: "If in doubt, declare."

Richard Smith editor, BMJ

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Use of steroids for acute spinal cord injury must be reassessed

Editor—Yates and Roberts's editorial on corticosteroids in head injury caused me considerable concern in so far as it portrayed the situation for treating acute spinal cord injury. Intravenous high dose methylprednisolone given within eight hours of injury has been promoted since the second American national acute spinal cord injury study. The positive benefit of this is based on conclusions derived from a selected post hoc subgroup analysis in one clinical trial. Current recommendations regarding evidence of clinical efficacy consistently advise caution in applying results from such non-randomised groups of patients.'

The evidence produced by a systematic review that colleagues and I recently carried out supports the use of high dose methylprednisolone in acute spinal cord injury to improve neurological recovery.' We also concluded that "a deleterious effect on early mortality and morbidity cannot be excluded by this evidence." In terms of experimental acute spinal cord injury, the functional neurological results extracted from non-rodent animal studies using high doses of either methylprednisolone or dexamethasone "constituted a body of evidence which cannot endorse a beneficial effect." A trend to increased mortality in cat models of high spinal cord lesions was of concern.

On the basis of information available to them, clinicians in Canada' and the United States' also consider it inappropriate to advise treatment with methylprednisolone in this context.

An independent assessment of the evidence available, particularly information from the American national acute spinal cord injury studies, is long overdue.

Deborah Short consultant in spinal cord injuries and rehabilitation medicine

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Out of hours demand is higher in Wales than in England and Scotland

Editor—Contact rates for out of hours services are greater in Wales than in England and Scotland. Statistics gathered by two south Wales cooperatives based in Gwent and Neath Port Talbot show that the workload is considerably higher than that indicated by Salisbury et al.'

The Gwent cooperative covers a population of 116 040 patients and 56 doctors and the Neath cooperative 95 000 patients and 32 doctors. The number of patient contacts/1000 patients/year in 1999 was 294 in Gwent and 346.5 in Neath. This compares with the reported rates for those English and Scottish cooperatives that included bank holiday cover (both Welsh organisations provide this) of 145 and 221. The table compares the figures for the Gwent and Neath cooperatives with those for England and Scotland given by Salisbury et al. Although statistics have been collected in different ways, reasonably accurate comparisons can be made.

The Neath area does not attract high deprivation payments; my practice of 6150 patients, which is typical of the area, receives band 1 deprivation payments. In Neath, the number of calls having been between 32 000 and 33 000 for the past three years. Considerable seasonal variation occurs, with a much higher demand in December and January. Figures for December 1999 and January 2000 were 4206 and 3750 respectively.

Details of patient contacts with two cooperatives in Wales, 1999, compared with figures given in study done in England and Scotland' (statistics have been collected in slightly different ways). Figures for England and Scotland are numbers (percentages); those for Gwent and Neath are percentages alone.

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<td>408 407 (45.4)</td>
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<td>Given home visit</td>
<td>312 550 (23.8)</td>
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<td>8.9</td>
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1 Salisbury C, Treliva M, Bruce S. Demand for and supply of out of hours care from general practitioners in England and Scotland: observational study based on routinely collected data. BMJ 1999;320:618-21. (4 March.)

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Treatment for intestinal helminth infection

Contrary to authors' comments, meta-analysis supports global helminth control initiatives

Editor—Dickson et al's meta-analysis of the effects of treatment for intestinal helminth infection on growth and cognitive performance in children has produced two important findings, only one of which has been discussed by the authors.

The meta-analysis has helped highlight the poor quality of many of the trials carried out so far. The more important result (not remarked on) is the extraordinary finding that, despite the many systematic differences observed between the studies used in the meta-analysis, treatment unfaithfully has a positive average effect on both the outcomes studied (table 3). In addition, the fact that many systematic differences were observed between the studies in the meta-analysis seriously questions the value of trying to derive global summary results for any of the comparisons on both statistical and biological grounds.

The result of the meta-analysis supports an important principle for judging causality from the results of clinical trials—that if different trials address related questions
then differences are more likely to occur in the size of any effects than in their direction. When interpreted in this light it is clear that the present results provide quite firm support for the conclusions of the better designed individual trials that anthelmintic treatment may indeed significantly improve child growth and cognitive function; this is in direct contrast to the authors' own pessimistic conclusion. Thus rather than undermining the global helmint control initiatives promoted by the World Bank and World Health Organization, the present review has actually produced evidence in their support.

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Conclusions should have been based on broader considerations

En territory—in their systematic review on the effects of treatment for intestinal helmint infections on growth and cognitive performance in children, Dickson et al note numerous shortcomings in the design of previous studies. The authors themselves, however, conclude misleadingly that developing countries should not invest in mass treatment of children against helmint infections.

Firstly, no studies have apparently been designed to disentangle the effects of helmint infections on cognitive function from the effects of other sicknesses. Using a dynamic multivariate random effects framework, children's cognitive test scores, I found that an index of morbidity was significantly associated with lower scores but that hookworm egg count per gram of stool was not a significant predictor of cognitive scores. The data were not sufficiently detailed to shed light on the hypothesis that helmint infections may be negatively associated with cognitive test scores because they increase the duration and intensity of sicknesses.

Secondly, some psychologists have suggested that helmint infections may occasionally be beneficial for cognitive function. This would seem counter intuitive, and is perhaps a fallacy arising from a failure to recognize the magnitude of within subject data. It is, for example, well known that nutrient intakes exhibit day to day variation. At the other extreme, psychological tests such as the Brazelton neonatal behavioural assessment scale are subject to high within subject variation that often renders them useless unless babies have neurological defects. The magnitude of within subject variability in schoolchildren's cognitive scores is lower than that for scores on the neonatal behavioural assessment scale, but this factor should be incorporated when trials for assessing the effects of anthelmintic treatment on cognitive function are being designed. For example, the children could be tested several times before and after the treatment.

Finally, parasitic infections probably exacerbate iron deficiency anaemia in children growing up in unhygienic environments; bioavailability of iron from cereal based diets is low. Iron deficiency anaemia, in turn, is associated with poor learning. Anthelmintic treatment in most studies has been of short duration, and reinfection rates are typically high. It would therefore seem premature for Dickson et al to conclude that mass anthelmintic treatment may not be cost effective. Rather, cost benefit analysis of extended anthelmintic treatment, including the development of vaccines against certain types of infection, merit closer attention. It would be far sighted to approach anthelmintic treatment from a broad long term perspective in developing countries.

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Studies of short term treatment cannot assess long term benefits of regular treatment

En territory—The Cochrane review of anthelmintic trials chiefly shows that studies of short term treatment cannot assess the long term benefits of regular treatment.

When the World Health Organization, Unicef, Unesco, and the World Bank included deworming as one component of their efforts to focus resources on effective school health (the “FRESH start” partnership) they intended that infrequent but regular treatment from an early age would ensure that children avoided heavy infection throughout the vulnerable years of growth and development. A review of trials that have not evaluated such a strategy is not an appropriate basis for policy recommendations, especially since the review omitted, for example, the benefits of avoiding hookworm anaemia and Trichuris collitis.

The remarkable cost effectiveness of deworming derives not from some easily measured and immediate clinical benefit of a single intervention but from the longer term preventive value of an annual investment of less 7p.

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Message does not follow from systematic review's findings

Environmental—The number of parasites per host in persistent parasitic infections such as the helmintiases is characteristically dispersed in a frequency distribution that is extremely skewed compared with Gaussian or even Poisson distributions. From this follow a couple of points that are relevant to a meta-analysis such as that by Dickson et al.

Firstly, heterogeneity in parasite burdens is of special importance, exceeding that of age and drug type, which the authors had hoped to take into account but could not do from the primary trials. Secondly, attempting to allow for this heterogeneity by generating a random effects model may be inappropriate since this is done by introducing an error term with an assumption of Gaussian distribution of the error.

More generally—and this point is also related to the extremely skewed and over-dispersed worm distributions—achieving endpoints of growth and cognitive development in trials of the treatment of populations, even where the prevalence of infections is high, needs thinking about. The difference between having no worms and having a few worms is probably much less clinically important than the difference between having some worms and having an enormous burden of worms (having an enormous burden is always relatively rare).

This is like the difference between carriage of Neisseria meningitidis (high percentage of the population) and invasive meningococcal disease (a few thousand cases a year in the British Isles). Currently in the United Kingdom we are vaccinating about 15 million people to prevent 1,500 cases of type C meningococcal disease and 150 deaths a year. But we shall not be assessing our effectiveness by changes in the total morbidity or mortality of the 15 million population, which would be lost in the dilution, or by any measure such as numbers needed to vaccinate to prevent a case of meningococcal disease: we will count the individuals with type C meningococcal disease.

In a similar way the greatest effect of anthelmintic treatment on growth and development of children will be concentrated in those with the heaviest parasite burdens. This effect occurred in one of the trials reviewed and was considerable when only intense, severely symptomatic
trichuriasis was treated, in a study where placebo control would have been unethical. The systematic review is useful, but the message in the “What this study adds” panel that “There is little evidence to support the use of routine anthelmintic treatment to improve growth and cognitive performance in children in developing countries” does not follow from its findings.

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5 Callender B, Grantham-McGregor S, Walker SP. “There is little evidence to support the use of routine anthelmintic treatment to improve growth and cognitive performance in children in developing countries” does not follow from its findings. BMJ 2000;320:1697-701. (24 June)

Authors’ reply

Ennour—Michael points out that the weight changes favour the intervention. But the differences in weight gain between the groups are often small. Michael is incorrect in saying that the evidence presented provides firm support that anthelmintic treatment significantly improves cognitive function. It is certainly not the case, as he implies, that treated children invariably do better in cognitive and academic tests than control children. Control children taking placebo have shown greater gains in some tests than treated children, and in some cases this difference has been significant. On this topic, Bhargava seems to imply that the failure to find an effect may be due to the unreliability of the tests. But most tests used have had adequate to good reliability.

Bundy and Peto comment that our review does not evaluate infrequent but regular treatment from an early age. We sought trials that repeated treatments, and this was defined in our protocol. But there were few such trials, and the data were limited. The current large cluster randomised trial in Lucknow will help provide some answers to the effectiveness of these strategies.

Cooper notes that the random effects estimate may be inaccurate because of the skewed dispersion of worms in a population. His argument suggests that the uncertainty around effect estimates is increased. In our protocol we sought to conduct subgroup analyses by intensity of worm burden, but no trials provided the data necessary for us to do this.

The letter from the World Health Organization with 13 authors states that they disagree with how we interpreted the data, but again they do not provide substantive evidence to support their past and current recommendations. Savioli and Albonico provided helpful input to the protocol development for this review. We did not intend to imply that they had agreed with the results of the review, only to acknowledge their valuable input in the review process; we will make this explicit in the Cochran review.

Several authors comment on the fact that the review was not able to draw conclusions about the effects of long term treatments. We were unable to find any randomised controlled trials that evaluated long term benefit, and the evidence of short term benefit was not, for us, convincing. We therefore stand by our conclusion that it was premature to recommend this widely, and for countries to borrow money from the World Bank to routinely implement national population based policies of routine repeated treatment. We believe that the introductory statement to a World Health Organization publication—that “regular chemotherapy of infected populations reduces morbidity and morbidity in pre-school children, improves nutritional status and school performance of school children”—is not based on current available evidence.
Routine treatment with anthelmintics could well be an exciting and important intervention. But we need the results of larger, well-designed trials, such as the current trial in India, before lending money to already poor countries to invest in an intervention where there are doubts about its wholesale benefit.

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### Adjuvant irradiation for breast cancer

**Treatment plans need to be made with better anatomical information**

**Editor—**Kunkler’s editorial on adjuvant irradiation for breast cancer addressed an important problem. More and more patients of all age groups with potentially highly curable disease are being treated with both adjuvant chemotherapy and radiation. It is therefore most important that the treatment should be given in the safest possible manner while maintaining its therapeutic advantage. Increasingly, people recognise that radiotherapy can improve survival in breast cancer, and practitioners are becoming aware not just of the cardiac morbidity that occurs but also of the cardiac mortality.

To investigate the magnitude of these problems we have undertaken a series of magnetic resonance scans on patients before radiotherapy planning and treatment. The advent of magnetic resonance imaging has allowed us to quantify the accuracy with which radiotherapy treatments are being delivered in breast cancer. The architecture of our magnetic resonance scanner is open and allows patients to be scanned in the treatment position. Magnetic resonance images have the advantage over other imaging techniques in that they clearly show tumour, tumour bed, and lymph nodes.

Because of the limited resource, patients were chosen if they were to have radiotherapy on the left side or if they were to have extensive radiotherapy, including of the nodes, to the right side. We have now scanned 600 patients; preliminary analysis on the first 200 clearly shows that, in at least 30% of cases, conventionally planned treatments would have been suboptimal. As far as the heart is concerned, more than 80% of the left sided treatments would have irradiated a considerable fraction of cardiac tissue, quite often in the territory of the left anterior descending coronary artery.

A finding of potentially greater importance was that the tumour bed was frequently missed. In the first 200 patients more than 30% would have had complete or partial treatment failure. In over 90% of the patients requiring adjacent nodal irradiation the entire cervicoaxillary chain below the clavicle failed to be encompassed. Despite the lack of precision of conventional treatment planning that we have shown, radiotherapy does improve survival. It is therefore reasonable to expect that if future treatment plans were made with the benefit of adequate anatomical information, its efficacy would be greatly enhanced. In addition, cardiac morbidity and mortality would be reduced.

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**Author’s reply**

Errone—the Whipp and Candiﬁsh provide pertinent data on the extent of cardiac irradiation in patients with left sided tumours or undergoing extensive adjuvant locoregional radiotherapy. Their observations strongly support the case for more sophisticated imaging during the planning of breast radiotherapy than is available in most centres in the United Kingdom. As they point out, accuracy in treatment delivery is important; two large randomised trials showed a 9-10% survival advantage from the addition of locoregional radiotherapy to systemic treatment in high risk women.

The recent update of the Oxford overview of randomised trials of breast radiotherapy identiﬁed an increase in risk of death from vascular causes (death rate ratio 1.30 (SE 0.09)). The overview does not provide any subgroup analysis of vascular causes of death (for example, heart or great vessels) by volume of irradiation of these structures or laterality of tumour. An analysis of vascular mortality by laterality is planned in the next overview. Much less information is available on cardiac morbidity; this is not included in the overview.

Long term follow up of patients included in the Danish Breast Cooperative Group’s trials of postmastectomy irradiation in high risk women receiving adjuvant systemic treatment suggests that there is no difference in cardiac morbidity or mortality between irradiated and non-irradiated groups. In these trials, electrons with limited penetration beyond the chest wall would have minimised dosage to the heart and great vessels.

Most centres in the United Kingdom, however, use a different treatment technique from that adopted in the Danish trials. Using electronic portal imaging of patients during adjuvant irradiation with tangential megavoltage beams for left sided breast tumours, Magee et al in Manchester showed that the cardiac apex was irradiated in 9% of cases. Cardiac morbidity and mortality therefore need to be assessed in long term prospective studies of adjuvant locoregional irradiation.

At present, open magnetic resonance facilities are not available in most departments. Currently, wide aperture (90 cm) computed tomography simulators, adequate to accommodate patients in the treatment position adopted in many radiotherapy departments, are not commercially available.

An urgent dialogue is needed between clinical oncologists to decide whether, to minimise cardiac exposure, computed tomography should be adopted for all women undergoing irradiation for left sided tumours. Until long term data on cardiac morbidity and mortality from prospective studies are available the avoidance of unnecessary cardiac irradiation seems a sensible approach. The development of computed tomography simulators with wider apertures than are currently available is an important priority.

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**Comparing survival rates between different registries can be difficult**

**Errone—**The paper by Stotter et al is an important reminder of the need for caution when comparing incidence and survival rates between different populations. At the Thames Cancer Registry we have developed a method of estimating completeness of ascertainment as a function of time since diagnosis. As part of this procedure, Kaplan-Meier estimates of survival are calculated, and we have included cases registered solely on the basis of information from their death certificates, assuming that their
Survival will be the same as that of cases in whom the initial registration was made from the death certificate but subsequent tracing of records has led to further information and a “proper” date of diagnosis.

Using data on all registered cancer cases with a date of diagnosis (or date of death for those cases registered on the basis of death certificates only) in 1992, and calculating survival with and without inclusion of these cases by the above method, gives an estimate of five year survival rate of 37% when the cases registered on the basis of their death certificate only are omitted and 30% when they are included (figure). This is in line with the findings of Berrino et al,6,7 who showed that the percentage reduction in estimated survival resulting from the inclusion of such cases is generally of the same order as the proportion of such cases in the sample. The rate of cases registered on the basis of their death certificate only in the Thames Cancer Registry in 1992 was 19%.

A large rate of cases in whom the initial registration was made from the death certificate but additional information used to gain further information and the date of diagnosis—which implies that many cases become known to the registry only when they die—tends to bias survival estimates downwards, as it leads to less complete registration in young patients and those with cancers associated with good long term survival. This effect can be seen when comparing completeness estimates in patients with lung cancer (94% complete two years after diagnosis) and melanoma (64%),7,8 It is important to know the rates of types of registrations when comparing survival rates between different registries.

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Support for studies in paediatric medicine is needed

Editor—The paper by Aynsley-Green et al highlighted the apparent lack of political clout among those delivering medical services for children.1 We have experienced the effect of this in our efforts to pilot the use of morphine-6-glucuronide as a sedative in newborn babies who were given artificial ventilation.

We wish to highlight the difficulties we had in researching this drug, to give a better understanding of why 90% of babies in neonatal units continue to receive unlicensed or off-label drugs.2

Opiates are used frequently in neonatal medicine, and morphine is the most widely used. Studies have examined their metabolism and pharmacokinetics, but the knowledge about pharmacodynamics is limited.

We studied the effects on respiratory drive in 14 babies being given ventilation who were treated with standard doses of morphine.3 This showed a reduction in respiratory rate, which was delayed by up to 12 hours and did not occur until measurable amounts of morphine-6-glucuronide were found in the plasma. We proposed that morphine-6-glucuronide may provide a more reliable and faster acting means of sedation.

We approached a small pharmaceutical company, which was able to supply morphine-6-glucuronide free of charge for our proposed pilot study. We also shared the protocol with a professor of paediatric pharmacology, who believed that it was an appropriate study to undertake.

The local research ethics committee considered our application and consulted external expert assessors, whose names were provided by the Royal College of Paediatrics and Child Health. Approval was given, subject to clarification about non-negligent indemnification. The drug company would not apply for an exemption certificate for clinical trials, although it was doing so for a study including adults, but there was no financial incentive to support our study. We therefore considered an exemption certificate for doctors and dentists. The matter of non-negligent indemnification went to the hospital trust, and legal advice was sought about the likely financial exposure the study would entail.

Although we have a sound basis for our study, supported by our own research, the current literature, and external assessors, to date we have not been able to proceed. In addition to setting up such a study, there are important issues regarding obtaining consent from parents in today’s climate. These seem like insurmountable hurdles. Without a change in support for such studies, how will we address the real problem of giving unlicensed medicines to many children under our care or proceeding with research into new treatments?

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