Reforms to the health sector must retain vertical programmes like those for tuberculosis

Editor—Health sector reform has become the policy urged on poor countries in the developing world. Basically it entails transferring responsibility for health services and health budgets to local communities. I am sympathetic to this approach. But its uncritical application by governments has a dangerous obverse.

Vertical programmes—for instance, central coordination and monitoring of the World Health Organization’s DOTS (directly observed treatment short course) programme for control of tuberculosis—may be discouraged. The programme may be suddenly abolished. The economy of scale resulting from national bulk buying of antituberculous drugs disappears. The tuberculosis experts in the Ministry of Health, who provide leadership and coordination and who monitor the programme, are dispersed to other jobs. Suddenly there are no drugs for tuberculosis, either centrally or at the periphery, and no control programme.

I am told that this has already occurred in Zambia and Ethiopia. It almost occurred in Bangladesh. It is threatening to occur in many other countries.

With HIV infection and multidrug resistance, the World Health Organization has declared tuberculosis to be a global emergency. It is a desperate race against time to establish good national tuberculosis control programmes, especially in the 22 countries that contain four fifths of the world’s cases. National control programmes would prevent the development of multidrug resistance—always the result of bad doctoring—before the alliance of multidrug resistance with HIV infection creates an almost untreatable pandemic (tuberculosis is no respecter of frontiers).

It is essential to retain the economies of scale offered by the central purchase of drugs and basic diagnostic equipment. It is essential to retain control of central monitoring and coordination and gradually to hand over the major responsibility of the service to local communities as their skill develops. Just as in community development projects in the United Kingdom, professionals continue to be needed in the background to pick up the bits when a local administration fails.

When I raised this problem at a recent symposium on global health the representative of Save the Children supported me. He said that the child immunisation programme in Uganda had almost collapsed for the same reasons. I have just visited the School of Tropical Medicine in Liverpool and had discussions with people working on tropical disease problems in poor countries. Although sympathetic with the concept of health service reform, many are disturbed by the possibility of the sudden abolition of vertical programmes with no real provision for their effective replacement.

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Misconceptions about tuberculosis among immigrants to the United States

Editor—Charatan’s story in news extra about tuberculosis among foreign born people in the United States requires clarification. The term immigrant is not used accurately. An immigrant to the United States is a person who is admitted as a lawful permanent resident or who becomes a permanent resident while living there.

About 400 000 people qualify in each category annually; about 70 000 refugees enter annually.²

Within the Public Health Service, the Division of Quarantine of the Centers for Disease Control and Prevention writes the guidelines for the medical examination required for all immigrants and refugees and notifies receiving health departments of those who may have tuberculosis (figure).

Potential immigrants and refugees who have infectious tuberculosis must be treated until they are not infectious. They are then allowed into the country on condition that they are followed up by the local health department. Those with possible noninfectious tuberculosis are also referred to local health departments; over 90% are evaluated.³

The United States Immigration and Naturalization Service has estimated that five million people born outside the United States were living in the country unlawfully in October 1996.⁴ It has responded to this with increased screening of those who are apprehended and detained. Roughly 155 000 people were placed in Immigration and Naturalization Service detention during fiscal year 1999. The Public Health Service’s Division of Immigration Health provides healthcare support to the immigration service by screening detainees for tuberculosis.

In the last fiscal year the division screened over 32 000 detainees who were held for at least 48 hours or had symptoms of tuberculosis (G Migliaccio, personal communication, 1999). Other detainees might have been screened for tuberculosis while in correctional systems not covered by the division.

The total number of people born outside the United States who had tuberculosis in the country fell from 7 930 in 1995 to 7 591 in 1998. During the same period the rates of tuberculosis in people born in the United States and people born outside the United States fell to 4.4/100 000 and 28/100 000, respectively.⁵

The Centers for Disease Control and Prevention has made it a priority for state and local health departments to follow up and treat immigrants and refugees identified as possibly having tuberculosis and for the Division of Quarantine to continue forwarding their medical documentation to relevant health departments.⁶ The recent decline in tuberculosis among people born outside the United States probably reflects successes in tuberculosis screening and follow up. More effort is needed to address the problem of tuberculosis among the roughly five million undocumented people living in the United States to ensure that all segments of the population receive screening and treatment.

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sgc0@cdc.gov

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**Arriving immigrants and refugees with chest radiographs suggesting possible current or old healed tuberculosis, fiscal years 1995-7, United States**

<table>
<thead>
<tr>
<th>Fiscal year</th>
<th>Total/number</th>
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<tbody>
<tr>
<td>1995</td>
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</tr>
<tr>
<td>1996</td>
<td>15 000</td>
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<td>1997</td>
<td>10 000</td>
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GMC's advice in Serious Communicable Diseases

Is consent to testing necessary for tuberculosis in same way as for HIV infection?

Entror—The General Medical Council recently sent all medical practitioners in the United Kingdom its booklet Serious Communicable Diseases,1 which replaces the earlier HIV Infection and AIDS.2 In this the council broadens its earlier advice on consent to testing to include investigation of tuberculosis and hepatitis as well as HIV infection. We completely agree that tuberculosis should be regarded as a serious communicable disease, but treating it in the same way as HIV infection in the context of obtaining consent to investigation and treatment potentially presents major problems, which we wish to draw to the attention of readers of the BMJ.

Clearly, when the suspicion of tuberculosis is high it is appropriate to explain to patients the time of collecting sputum or other specimens for investigation. However, sputum is commonly tested for tuberculosis in patients being investigated for common respiratory symptoms, when the likelihood of having the disease is low. In our view, obtaining consent to specific testing for tuberculosis in such patients may create unnecessary anxiety. Alternatively, it may even mean that appropriate specimens are not examined because of the concerns this might raise. We suggest that asking for general permission to test samples to exclude infection is appropriate without necessarily specifically naming tuberculosis when the probability of the patient having the disease is comparatively low.

We have raised our concerns about this advice with the GMC but it sees no need to modify its guidance.

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Tracker trials

Introduction of resistance testing might be an inappropriate use of resources

Entror—Lilford et al argue for starting randomised studies of new health technologies as early as possible, even if the technology is in a phase of rapid development.1 They advocate that ethics committees allow for randomisation of patients with HIV infection to receive or not receive resistance testing,2 which most commonly is used for monitoring resistance to antiretroviral drugs. The basis for these recommendations is not clear: the arguments are more complex than they first seem, and the empirical evidence that resistance testing improves clinical outcome is limited.3

The most commonly used form of resistance testing entails DNA sequencing of the reverse transcriptase and protease genes. But quality assurance studies have found that current methods frequently fail to identify key mutations associated with resistance.4 Moreover, it is often difficult to decide how to use the result of the resistance assay, since the influence of viral polymorphisms on in vivo response to the many combination drug regimens available is poorly understood. It is likely that resistance testing will ultimately improve the selection of drug regimens and become cost effective as the accuracy and interpretation of assays improve. There is no certainty, however, that this point has been crossed, and the widespread introduction of resistance testing at this time could be an inappropriate use of scarce health resources.

Lilford et al propose flexible randomised trials—where duration is not predetermined and frequent interim analyses are conducted explicitly—and recognise that the effectiveness of a health intervention may change over time and they aim to monitor such changes.1 Testing for resistance of HIV may be appropriately evaluated by this type of study, although, as in other areas, convincing the medical community of the merits of this approach and securing funding may be problematic.5

A randomised trial would collect the information required for analyses to elucidate the clinical significance of viral mutations. These analyses could be performed during the trial without compromising the main comparison of resistance testing versus no testing. In principle, the findings from these analyses could influence the interpretation of resistance assays performed later in the study. This would be a strength, not a weakness.

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Janet Darbyshire director
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Competing interests: The MRC Clinical Trials Unit is currently coordinating a (conventional) randomised controlled trial of HIV resistance testing.

Continuous process of trial and review is needed

Editor—With reference to the paper by Lilford et al, successful implementation of tracker trials would require development of a more flexible approach to research not only by the medical profession but also by prospective participants and the commercial sector. The public could well be attracted to the proposition of methodically evaluated introduction of new technologies as well as skill in their use, particularly during the learning curve, following growing awareness of such problems through media coverage of, for example, the Bristol case cited by Lilford et al.

This proposal for overlap of audit and trial may be an ideal opportunity not just for flexible research but for flexible consent procedures where the current notion of trial participants being guinea pigs could be turned on its head. The public is coming to appreciate that it is those patients who are the subject of poorly monitored interventions who, in retrospect, are the guinea pigs. The medical profession acknowledges that patients in trials do do better—for whatever reasons. A rigorous, standard continuous process of trial and review, discarding the inferior intervention and identifying the poor performer, would be a demonstration of the constant striving for improvement through research (rather than “breakthroughs”) that would surely serve to create a new attitude and a more positive general understanding of the striving for clinical excellence.

If any notion of imposition is to be avoided it is essential to involve potential participants, namely the general public, in consideration of this new approach at an early stage. As stakeholders in the NHS, patients have a vested interest in such methods that weed out ineffective treatments by continuous evaluation. Their contribution as active partners on steering committees providing the users’ viewpoint is essential in the constant iterative learning process that a tracker trial would constitute.

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Are generalists still needed in a specialised world?

Role of accident and emergency doctors should be expanded

Editor—Turnberg in his article on the survival of the general physician rightly highlights the potential problems posed when an undifferentiated emergency patient is cared for by medical subspecialists. Four models of care cited proposed as possible solutions, including the development of specialised emergency physicians, calling for a new breed of doctor and a specific training programme, although its success would depend on having enough doctors who are sufficiently motivated to take on this type of work.

The specialty of emergency medicine already exists, but its potential for contributing to a solution to the problem remains unfulfilled because of historical, cultural, and resource factors as well as perhaps the stubborn retention of the UK-specific name “accident and emergency medicine.”

Turnberg alludes to the difficulties medical subspecialists have in maintaining their general skills and knowledge. Accident and emergency physicians now undergo a five-year specialist training programme whose exit examination requires the demonstration of knowledge and skills in all aspects of clinical emergency medicine as well as evidence based critical appraisal and management skills. No such objective final assessment exists for trainees in general (internal) medicine. An expansion in the numbers of accident and emergency consultants, combined with a sociopolitical climate in which senior doctors’ participation in all aspects of patient care will be demanded, suggests that the time is right to expand the role of accident and emergency doctors.

I therefore propose a fifth model: the undifferentiated emergency patient is cared for on an admissions or observation unit integral to the hospital’s emergency department, under the supervision of the accident and emergency consultant on duty. Medical subspecialists provide advice and ongoing care when indicated. Patients no longer acutely ill who require further investigation and diagnostic expertise are referred to the general (internal) medicine specialists. This way acutely ill patients remain under the care of physicians motivated and trained to provide that care. The current system of separate medical assessment units and emergency departments, with its consequent duplication of precious resources, would end, and a single point of hospital entrance would exist for emergency patients regardless of whether they dialled 999 or were referred by their general practitioner.

To create a new emergency specialty would perpetuate this duplication and thinning of resources for the patients who most need them. Far better to invest in those specialties we already have, since Turmberg’s “new breed” is already breeding.

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Additional issues need to be addressed

Editor—Turnberg covers many of the issues surrounding general and specialty medicine. There are, however, other factors that should be considered.

Specialism is not without problems. Increased specialism goes hand in hand with decreased flexibility in bed use. “General” patients can usually be admitted to any of a number of wards, even after taking into account their sex (and sometimes age). A bed is likely to be available sooner from this larger pool than if the patient can go only to the ward of one specialist (and therefore staff) are required in a specialist system than in a general system to avoid longer trolley waits. Specialism must therefore be justified not only on grounds of clinical benefit but also on grounds of cost effectiveness.

“Speciality systems” must bring patients and the appropriate specialty together. Delayed access to specialty care is likely to reduce its benefits. Sometimes it may be impossible to get to the ward of the “correct” specialty. A system based on patients’ needs as well as their geographical location is required. The patient being looked after by the “wrong” specialist is likely to be more disadvantaged the greater the degree of specialisation within the system; staff will see fewer patients from “alien” specialties and run the risk of atrophied generalist expertise. It would be wrong to rely on trainees to protect patients in these circumstances.

It is not always possible to identify the relevant specialty straight away (in general practice or in accident and emergency). Some facility is therefore needed for patients whose problem cannot immediately be categorised. This facility must contain not
only beds but also clinicians whose area of expertise (and interest) lies in the initial care of patients admitted as emergency cases. Unless every specialty can maintain a service for 24 hours a day, staff are needed who are able to deal with acute problems arising from any system. We have specialties based on systems and age of patients.

There will be a need for a specialty defined in terms of the stage of patients’ illnesses rather than system(s) affected (“acutism”) if generalism is to go.

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Qualitative research in health care

Good communication is essential part of educational process

Editor—The first Education and debate section of the new millennium was very educational in a way that was almost certainly not anticipated or intended by either the staff of the journal (unless they were being very mischievous) or the authors of the papers concerned. 1 2 In the paper by Lilford et al 3 the study under discussion was clearly defined, but unfortunately in the paper by Mays et al 4 I was not able, after reading the paper three times, to find a definition of the type of research being discussed anywhere.

The style of the paper by Lilford et al allowed an easy understanding of the thesis being developed, but the same could not be said of the paper by Mays et al, which seemed to lack a clearly discernible logic in relation to the case being made. The paper was replete with jargon and many strangely unscientific terms, which made it difficult to read—such as “epistemological,” “extreme relativists,” “anti-realist,” “reflectivity,” “inductive inquiries,” and “subtle realism.” No such problem seemed to exist in relation to the paper by Lilford et al. As one of the “researchers from other traditions,” I was “appalled to read a research inquiry trying to ‘derive . . . unequivocal insights.’ ” I thought in my “naïve realism” that we sought facts. Should not all research “be concerned to develop theory?” The need to develop a hypothesis to be tested is surely not “arguable.” I was taught by my research mentors that the truth, rather than subtle realism, was what we were trying to attain. It would have been unthinkable to omit a clear account of the process of data collection and analysis.

In this double blind (I had no idea prior to publication of the content or style), randomised (by chance I chose to read the “unintelligible paper” first) controlled (the papers were controls for each other) trial, not intended by the journal (3), I found a significant difference (I could not even understand one of the papers) in favour of tracker studies. Perhaps this was because of my only admitted bias or conflict of interest, that of being a surgeon and an educator. I am not really sure what all of this means except that if the journal does publish papers for education and debate it follows that they should be understandable to all of the readers of the journal, including such loyal students as surgeons, and that it has to be remembered by educators that an essential part of the educational process is good communication. Quality in qualitative research is a mystery to many health services researchers, and, sadly, it is an even greater mystery to me now. I am left pondering the simple question “Who should be responsible for educating the educators?”

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Antirealism is an excuse for sloppy work

Editor—We were struck by Mays and Pope’s indulgent treatment of the antirealist position. 1 Antirealistic researchers contend that there is no “social” reality or truth that is independent of the observer. Antirealists, a species of postmodernists, scoff at those naïve enough to believe in the physical reality of social world: “what the parochial view in the social, behavioral, and service sciences has touted as ‘science’ is historical and practical myth.” Presumably “social” reality consists of the interactions of human beings—that is, spoken or written words, and all human actions that relate to other humans. Thus the antirealists apparently would contend that this letter has no reality. Antirealists thus fall headlong into self contradiction. If no utterances (presumably including their own) have reality, why should we read what they write? Furthermore, why should we pay any attention to the work of supposedly “scientific” researchers who deny the independent reality of what they research?

The antirealist view seems to be at best an excuse for sloppy work. Antirealists have argued that bias in research is good—“not something to be eliminated, but is a productive element, a foundation for formulating questions and understanding answers in the process of research.” They have asserted that the traditional notions of methodological rigour, “the classical canons of reliability, validity, and objectivity,” are irrelevant to their kind of qualitative research, to the point that a “powerful case can be made for methodological anarchy.” In retreating to ancient subjectivist attitudes, antirealists have renounced qualities that are part of the scientific attitude: rigour, self discipline, humility in the face of evidence, and willingness to risk failure and blind alleys.

Alan Sokal, the physicist whose parody of postmodernism in science received wide attention, made the point well. First he decried “a particular kind of nonsense and sloppy thinking: one that denies the existence of objective reality.” Then he wrote, “Intellec- tually, the problem with such doctrines is that they are false. There is a real world; its properties are not merely social constructions; facts and evidence do matter. What sane person would contend otherwise?”

We applaud the efforts of Pope and May to bring more rigour to the design,
Open access follow up for inflammatory bowel disease

Would have been better to use t test than Mann-Whitney U test

Editor—Williams et al undertook a randomised trial to evaluate whether follow up of patients with inflammatory bowel disease is better with open access than with routine appointments. They compared primary and secondary care resource use and costs and concluded that open access follow up saves secondary care resources. This conclusion, however, is mistaken because they used inappropriate statistical methods.

Resource use and cost data tend to have highly skewed distributions. As a result, the authors decided that standard parametric statistical methods were not appropriate and assessed significance by using a Mann-Whitney U test. Although this is consistent with conventional statistical guidelines, it does not address the question of interest in economic evaluations. As the authors themselves state, “economic analysis is mainly concerned with a comparison of means.” Use of a Mann-Whitney U test, however, makes an overall comparison of distributions in the two groups, in terms of both means and variances. This is better with open access than with routine follow up appointments of patients with inflammatory bowel disease: pragmatic randomised trial and cost effectiveness study. BMJ 2000;320:544-8. (20 February)

1 Williams JG, Cheung WY, Russell IT, Cohen DR, Longo M, Levy B. Open access follow up for inflammatory bowel disease: pragmatic randomised trial and cost effectiveness study. BMJ 2000;320:544-8. (20 February)
10 As the disease specific questionnaire was not validated, drawing any conclusion from it would not be valid. Yet the table comparing quality of life (table 1 in the paper) was interesting; although the results of all results were not significant, there was a clear trend with negative numbers predominate, indicating a “better change” in the routine follow up patients compared with the open access patients. The open question of whether the non-significance was due to lack of power of the study to pick up a true difference when one existed.

Open access greatly reduces secondary care costs. This conclusion, however, is mistaken because they used inappropriate statistical methods.

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The most appropriate simple method for comparing mean costs is the ordinary t test. Because economic analysis focuses on means we also reported these. As expected, our completed bootstrapping, to be published elsewhere, confirms the findings reported in the BMJ. In particular, open access greatly reduces secondary care costs.

We regret that Barber and Thompson, frustrated by our interim analysis, ignored the conventional statistical guidelines they cited by applying the t test to our data. The substantial differences between their findings and those achieved with the U test confirm that the data are highly skewed. Thus the findings of the t test are misleading.

We agree with Coomarasamy and Van Der Berg about the need to screen patients at high risk of developing malignancy. A gastrointestinal nurse practitioner could do this screening. As we do not yet have such a

Mean (SD) costs (£) per patient in hospitals over 24 months

<table>
<thead>
<tr>
<th>Cost of investigations</th>
<th>Open access (n=77)</th>
<th>Routine visit (n=78)</th>
<th>P value from Mann-Whitney U test</th>
<th>P value from t test</th>
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<td>0.002</td>
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</table>

Total 656 (860) 699 (516) 0.011 0.71

1 William JG, Cheung WY, Russell IT, Cohen DR, Longo M, Levy B. Open access follow up for inflammatory bowel disease: pragmatic randomised trial and cost effectiveness study. BMJ 2000;320:544-8. (20 February)
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Given these weaknesses, we do not think that an open access strategy should be recommended other than in a more powerful and longer study to answer these important issues.

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1 Williams JG, Cheung WY, Russell IT, Cohen DR, Longo M, Levy B. Open access follow up for inflammatory bowel disease: pragmatic randomised trial and cost effectiveness study. BMJ 2000;320:544-8. (20 February)

Authors’ reply

Enntor—We agree with Barber and Thompson that highly skewed cost data are best analysed by non-parametric bootstrapping. However, the BMJ set a deadline for papers submitted for its issue on managing chronic diseases. As our bootstrapping was not complete we followed conventional statistical guidelines and used the Mann-Whitney U test. Because economic analysis focuses on means we also reported these. As expected, our completed bootstrapping, to be published elsewhere, confirms the findings reported in the BMJ. In particular, open access greatly reduces secondary care costs.

We regret that Barber and Thompson, frustrated by our interim analysis, ignored the conventional statistical guidelines they cited by applying the t test to our data. The substantial differences between their findings and those achieved with the U test confirm that the data are highly skewed. Thus the findings of the t test are misleading.

We agree with Coomarasamy and Van Der Berg about the need to screen patients at high risk of developing malignancy. A gastrointestinal nurse practitioner could do this screening. As we do not yet have such a
post it was not appropriate to include the costs in our study. We intend to evaluate this role in a further randomised trial.

General practitioners who were familiar with the principles of open access follow up but independent of the service at both hospitals undertook the semistructured interviews with study practitioners. Since the study practitioners had patients in both arms of the trial, however, the suggestion that the interviewers should have been blind is meaningless.

Although there was no disease specific quality of life questionnaire valid for the United Kingdom when the trial was designed, we have since developed and validated such a questionnaire. The trend towards a greater improvement in quality of life with routine care was balanced by a trend towards greater improvements in other variables with open access. It would indeed have required a very large sample to classify as significant differences as small as those observed. Furthermore, we judge that they are not clinically significant.

In short, we believe that our published conclusions stand in the face of the comments from the authors of these letters.

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I T Russell professor of health sciences
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Comments from the authors of these letters.


Burns after photodynamic therapy

Drug point gives misleading impression of incidence of burns with temoporfin (Foscan)

Editor—We were not suggesting that the true incidence of burns with temoporfin (Foscan) is 43%—this was just the incidence in the group of patients referred to us. As Bryce reports, the correct figure is probably around 2%. What we were trying to highlight was that photodynamic agents can cause serious burns and that these may be more severe than conventional burns. This is an unusual occurrence and we state that, to our knowledge, this is the first group of patients given photodynamic therapy ever reported to have burns after exposure to environmental light.

We agree that the incidence of complications in this group was particularly high. This may well have been due to a problem during the administration of the drug. We discussed this directly with Bryce at the time, during Scotia’s initial collaboration on the paper. However, this was not a pure extravasation injury. The burns occurred only after prolonged exposure to sunlight and photoactivation, two weeks after the drug was given. In addition, other body areas away from the infusion site were also affected, though less severely. This implies that the patients were generally photosensitive because of Foscan. We suspect that there was some leaking out of the drug on administration, leading to high tissue concentrations around the infusion site. On photoactivation the most severe reaction occurred here, resulting in the worst burns.

Irrespective of whether there was some problem with the administration of the drug, these patients had serious burns and we believe that the causative agent was Foscan. This is a rare but serious complication that the medical community needs to be aware of. It is important for clinicians using photostimulizers to know that complications can occur and for burns surgeons to know that burns induced by photodynamic therapy may behave differently from conventional thermal injuries.

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John Clarke consultant plastic and reconstructive surgeon
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Competing interests: Mr Clarke has provided medical reports on the injuries and the initial management of the six patients reported on in the drug point. No fee was charged.

Incidence of burns associated with temoporfin (Foscan)

<table>
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<th>Phase 1 pharmacokinetic study</th>
<th>Current Foscan safety database</th>
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<tr>
<td>Volunteers (n=14)</td>
<td>Patients with cancer (n=23)</td>
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<tr>
<td>No of burns</td>
<td>6</td>
</tr>
<tr>
<td>Incidence</td>
<td>43%</td>
</tr>
</tbody>
</table>
Authors’ reply (Täubel and Besa)

Editor—We have until now been cautious to enter into the debate which has arisen concerning the article of 6 May.1 In view, however, of the legitimate interest doctors and the public have in the issues raised, and in view of the criticism of ourselves and Charterhouse Clinical Research Unit which has arisen as a result of the contents and comments on the BMJ article, it is important that we now set out the facts and answer some of the criticisms that have been made.

Notwithstanding that we were named as coauthors, the final form of the article published in the BMJ had not been approved or seen by us. Amendments which we had made were apparently rejected at some stage and an addition was made which was simply incorrect—namely, that the volunteers had signed disclaimers and were therefore not entitled to compensation. In fact, no fault compensation insurance was put in place by both ourselves and the drug company in accordance with our standard practice.

The formulation of Foscan (temoporfin) used in the trial reported in the BMJ article of 6 May were given to understand by the drug company, different from that used in previous trials. Specifically, a new solvent was added to the drug so that it would be more soluble and less painful to administer. This factor is relevant to an evaluation of the results of the trial and any comparison of the results with those in previous trials.

While seven of the volunteers were treated by Mr Clarke at Chelsea and Westminster Hospital Burns Unit, they were the only volunteers it was appropriate to refer for specialist treatment. In fact, of the 14 volunteers on whom the new formulation of the drug was tested, all 14 suffered some form of burn on the forearm into which the drug was infused. In 13 cases the burn tracked the vein into which the drug was injected and was long and oval in shape, starting close to the site of infusion and extending along the forearm (although in one instance this was obscured by the extent of the burns to the forearm). In the other case, although there was a burn which appeared to follow the infusion vein, the burn only started to occur towards the elbow, away from the site of injection.

Charterhouse was especially careful to ensure that the drug was correctly injected into the vein of each volunteer. None of the infusions was given perivenally, and no drug was split on the skin as suggested in one press article. Charterhouse is very experienced at carrying out infusions which demand that there is no accidental injection into surrounding tissues and performs them on a regular basis. We applied an appropriate standard technique of administering the drug into a vein of the forearm. We did not attempt to inject into veins in the antecubital fossa as they are best avoided because of the risk of interarterial injection (aberrant ulnar artery) and the possibility of median nerve damage, particularly as the drug had the potential to cause local damage. Numerous safeguards in our routine procedures prevent us from accidentally injecting any drug into surrounding tissue. These include (a) injecting into superficial veins in the forearm to provide a visual control as to whether or not the canula is correctly placed; (b) the use of pumps with an inbuilt pressure sensor that immediately stops the pump if there is an increase in pressure, which would occur if a canula slipped out of a vein and into the surrounding tissue (which would cause increased resistance); (c) the flushing of canulas with water for injection before starting the infusion to provide a visual and visual check as to whether there is any resistance as a result of either a blood clot forming at the tip of the canula or the tip being displaced into tissue; and (d) personal supervision of each infusion by staff with the requisite expertise and experience.

Each safeguard detailed above was followed in respect of every injection given in the Foscan trial reported in the BMJ. Each infusion was personally supervised by one of us. In each and every case, there was no evidence or indication that the drug was administered perivenally to any of the 14 volunteers. If a perivenal injection had been given, one would expect the resultant burn to be approximately circular in shape around the site of infusion and not a long oval burn tracking the line of the vein.

We considered that the most probable cause of the burn to the infusion forearm suffered by each of the volunteers was that the drug, having being injected into the vein, then leaked from the vein by an unknown mechanism (a hypothesis supported by the number of volunteers on whom the burn was observed). We do not know whether there is any connection between the leakage and the new solvent used in the trial we performed, but so far as we are aware the characteristic shape of the burns we recorded were not recorded in previous trials of the drug.

It is unfortunate that the BMJ did not send us a copy of its standard form on competing interests and published their answers, Mr Clarke and Drs Täubel and Besa have now declared their competing interests. Although many journals ask authors to declare competing interests, our own experience is that virtually nobody volunteers a competing interest unless presented with a set of explicit questions. That is why we now have a form that includes explicit questions on financial competing interests (available at http://www.bmj.com/advice/5.html), and our experience is that authors do respond to this form. I am sorry that we failed to send the form to the authors on this occasion.

The letter from Drs Täubel and Besa is considerably longer than we normally allow. We apologise to readers for this, but we wanted to publish these letters and explain our part in the story promptly. When it became clear that the authors had not been communicating well among themselves we postponed publication to allow Drs Täubel and Besa to respond separately. Their letter arrived, via their lawyers, at this length at the last possible moment for inclusion in this week’s journal, allowing no time for negotiation over editing. We thought that it was better to publish their letter at this length together with the other letters than to publish it separately next week.

Richard Smith  editor, BMJ

Rapid responses

Correspondence submitted electronically is available on our website