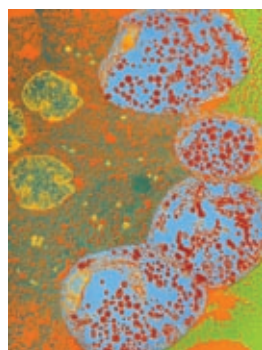


## Partner notification for the control of STIs

Assisting patients in disclosing their diagnosis to partners is the biggest priority



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### RESEARCH p 354

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In 2005 about 340 million people globally acquired new infections of the four most common curable sexually transmitted infections (gonorrhoea, chlamydia, syphilis, and trichomoniasis) and 4.1 million acquired HIV.<sup>1,2</sup> Partner notification is essential to prevent reinfection of index patients, decrease the pool of infectious people, and prevent the transmission of HIV.<sup>3,4</sup>

Provider referral, where health service personnel trace and notify partners, is practised in parts of the developed world. Patient referral, where index patients are encouraged to inform their partners of the need for treatment, is universal practice in the developing world, where provider referral is neither feasible nor affordable.

In this week's *BMJ*, Trelle and colleagues report a systematic review of strategies to improve patient referral,<sup>5</sup> as observational studies and randomised controlled trials indicate that current patient referral practices fail to reach many partners of people with sexually transmitted diseases in both developed and developing countries.<sup>6-8</sup> Fourteen randomised controlled trials, four of which were conducted in countries with low average incomes, were reviewed. The trials evaluated two novel patient referral strategies: patient delivered partner therapy, where the index patient is given drugs or a prescription for their partner(s); and home sampling, where index patients with chlamydia give partners kits for collecting urine specimens, which are posted to a laboratory for testing. Meta-analysis of five trials (four conducted in the United States and one in Uganda) showed that supplementing patient referral with patient delivered partner therapy slightly reduced persistent or recurrent infection with gonorrhoea and chlamydia in index patients (risk ratio 0.73; 95% confidence interval 0.57 to 0.93) and increased the proportion of partners treated. Two Danish studies showed that home sampling increased the proportion of partners' specimens being tested.

Patient delivered partner therapy and home sampling are attractive strategies to increase partners' access to treatment or testing, because they are quick and simple for clinicians to implement. Increasingly, patient delivered partner therapy is being used in developed<sup>8</sup> and developing countries.<sup>9</sup> However, the current review shows that patient delivered partner therapy forms only one part of an effective patient referral strategy. The beneficial effects were modest, and they were susceptible to selection bias and measurement bias (in 23-70% of index patients a measurement of the primary outcome could not be obtained). The review also shows that patient delivered partner

therapy can be substituted by patient delivered partner information (a booklet of tear out cards with treatment guidelines) with equal effect.

A home sampling strategy holds some promise in developed countries, but it needs more research as Trelle and colleagues' review could not determine whether increases in specimen testing translated into increases in the treatment of infected partners. In most developing countries, diagnostic testing of sexually transmitted infections is neither affordable nor feasible, and a syndrome based approach to their diagnosis and treatment has been adopted.<sup>7</sup> This avoids the need for diagnostic testing for most curable sexually transmitted infections, and renders a home sampling approach of little value.

Neither of these two novel interventions tackles the fundamental barrier to patient referral strategies: the difficulty people have telling their partners that they have a sexually transmitted infection. In contrast, counselling and educational interventions can be tailored to deal with the barriers patients experience in relation to disclosure, and they can begin to tackle the gender inequities that influence whether and how partners communicate about sexually transmitted infections.

The review by Trelle and colleagues included two African randomised controlled trials evaluating one to one counselling and education for index patients; it found that more partners were notified or treated than with simple patient referral. Unfortunately, the trials did not measure infection rates in index patients. Novel strategies that aim to increase partner access to treatment might produce bigger effects if used in combination with counselling and education interventions for index patients. One of the two African trials used lay counsellors.

Current evidence leaves important questions unanswered. In developing countries where the syndromic approach is used, diagnostic specificity is lacking, especially in women with vaginal discharge. This leads to the unnecessary notification of partners and potential harms, including violence against women,<sup>7</sup> about which little is known. Trelle and colleagues found no trials that investigated improving patient referral for HIV. Observational research in people with HIV suggests that continuous rather than one-off counselling services are best for tackling the difficulties index patients have in disclosing to their partners.<sup>10</sup>

While patient delivered partner therapy and home sampling alone improve patient referral to some extent, strategies that promote and assist disclosure to partners are urgently needed as part of a comprehensive approach to patient referral.

# Reducing the carbon footprint of medical conferences

## Doctors must lead by example

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The fourth assessment report of the Intergovernmental Panel on Climate Change (IPCC), published earlier this month, leaves no room for complacency.<sup>1</sup> It makes clear that warming of the climate system is unequivocal and that the increase in globally averaged temperatures since the mid-20th century is most likely due to increased human induced greenhouse gas emissions. It also states that warming and resultant sea level rises will continue for centuries even if emissions are stabilised. When scientific consensus reads like this, we are in trouble. The time to act is now.

The threat to human health from climate change—through malnutrition, disease, and flooding—is substantial, and in some parts of the world, immediate.<sup>2</sup> Most of the health burden of climate change is borne by children in developing countries.<sup>2</sup> It is ironic that doctors, for whom protecting health is a primary responsibility, contribute to global warming through unnecessary attendances at international conferences.

Lord Kelvin, physicist and past president of the Royal Society, said, “if you cannot measure it, you cannot improve it,” and it is encouraging that doctors are measuring the carbon footprint of their conference activities. Kelvin also said, “heavier-than-air flying machines are impossible,” but he was wrong. Last year, many doctors used such a machine to attend the European Respiratory Society annual congress in Munich. Julian Crane estimated that the 17 000 delegates generated about 4000 tonnes of carbon dioxide from travel alone.<sup>3</sup> Earlier this month, Callister and Griffiths reported the carbon footprint of the American Thoracic Society meeting in San Diego. The meeting was attended by about 15 000 delegates who generated an estimated 10 779 tonnes of carbon dioxide from air travel.<sup>4</sup>

Although probably serious underestimates, these are big numbers.<sup>5</sup> How do we put them in context? The yearly per capita carbon dioxide emission in the United States is about 20 tonnes, so the 11 000 tonnes from the American Thoracic Society meeting is equivalent to that produced by around 550 US citizens in one year. But the US, the most energy hungry nation on earth, is not the best comparator—11 000 tonnes of carbon dioxide is equivalent to that produced in one year by 11 000 people in India and 110 000 people in Chad. The last is arguably the most appropriate comparison as climate change has probably contributed to the disappearance of Lake Chad, formerly the sixth largest lake in the world; sand dunes now encroach on its drying bed, imperilling the lives of thousands.<sup>6</sup>

The IPCC report also makes clear that climate change will affect us all. Sea levels will rise, increas-

ing the risk of coastal flooding, and tropical cyclones and storms will become more severe.<sup>1</sup> River floods, such as those in central Europe that left more than 200 000 people homeless and about 100 dead, will become more common, as will heat waves like the one in Europe that claimed 35 000 lives in August 2003.<sup>7</sup>

Fortunately, opinions on conferences are changing. Two years ago one of us was invited to a world congress in Australia. It was the classic free lunch—registration, hotel, and air travel paid by the organisers and all for a 15 minute presentation. They did not offer to pay the environmental cost of the journey—6-10 tonnes of carbon dioxide equivalents pumped into the upper atmosphere, where they would warm the world for a century. A request on environmental grounds to make a video presentation elicited this response, “The reason for your wish to not attend seems, to say the least, unusual. We are not prepared to do video conferences.” And then after pulling out, “we have many emergency matters to deal with and whilst a number of speakers have had a very genuine reason for pulling out, we were astounded at this email.” Already such attitudes seem surprising and Trisha Greenhalgh wrote recently in the *BMJ* about her more positive experience of asking to lecture by video link.<sup>8</sup>

The Cochrane Collaboration is an example of an international medical organisation taking action to reduce the carbon footprint of its conferences. With over 15 000 members in 100 countries most of its work is done electronically. However, its annual conference involves substantial amounts of travel. The most recent was in Dublin in 2006, with 820 delegates from 40 countries. However, the organisers piloted electronic ways of enabling people to “attend” the conference on the internet, and a plenary session used video conferencing to “bring” keynote speakers from Papua New Guinea, Tunisia, and Uganda. This is a step in the right direction. The *BMJ*/IHI annual International Forum on Quality and Safety in Health Care is taking similar measures. At the meeting in Barcelona in April, videos of the four main plenaries and the subsequent panel discussions will be available on *bmj.com* in both Spanish and English.

High quality medical education is essential for patient care, and the educational benefits of conference attendance must also be considered. But Crane is sceptical — “let’s be honest, when did you last learn anything really important at a large meeting?” His view is consistent with research findings. Evidence that attending conference lectures improves practice is scant, and other methods are more effective.<sup>9 10</sup> Online



EUROPEAN COMMISSION

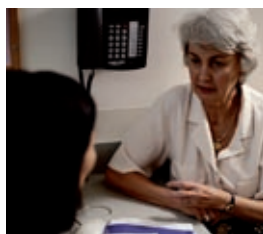
distance learning deserves more attention. But even if conferences were effective, who should decide if the benefits are worth the costs—a doctor from Colorado or a fisherman from Chad?

Air travel is not the biggest contributor to greenhouse gas emissions, but it is one of the fastest growing. In 2001 the IPCC estimated that aviation caused 3.5% of human induced global warming, which could rise to 15% by 2050. Air travel is also one of the easier aspects of our high carbon lives to change. Scope exists for

ingenuity and experimentation, as well as investment in new technologies to overcome distance. A more local focus may also have hidden benefits. Reducing travel is just part of how we must tackle global warming in the next 20 years. Other aspects of our lives must also change, and we must lobby governments to implement the laws and conventions needed to ensure that we ration our carbon use within sustainable limits.<sup>5 11</sup> Climate change is a major threat to global public health and doctors must lead by example.

## Reassuring patients about normal test results

Face to face communication strategies are effective



### RESEARCH p 352

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Every practising doctor recognises that normal test results can fail to reassure patients. One possible cause is that suboptimal reassurance strategies leave some patients distressed about their symptoms.<sup>1</sup> Uncertainty about the meaning or accuracy of normal test results may contribute to making symptoms worse and lead to additional costly and unnecessary medical visits and diagnostic procedures. Despite this, the medical literature provides little guidance about how to discuss normal findings with patients.

The study by Petrie and colleagues in this week's *BMJ* is one of the few to examine ways of providing reassurance about normal test results.<sup>2</sup> The findings of this randomised controlled trial show that patients with chest pain who received an intervention comprising an information pamphlet plus a brief pretest discussion with a health psychologist about the implications of "normal" results of an exercise stress test were more reassured by normal findings than patients who received the pamphlet alone or who received "standard information." All patients in the reassurance intervention group reported obtaining and maintaining a high level of reassurance. Moreover, relative to usual care, fewer patients who received the reassurance intervention reported continuing chest pain one month after the stress test.

At its simplest level, this study demonstrates the common sense and empirically supported observation that communication can influence health outcomes.<sup>3-5</sup> It is not particularly surprising that a face to face discussion with a healthcare provider yields better results than communicating the same message with printed materials alone. What is noteworthy, however, is the nature of the intervention and the size of its effect. The intervention was not tailored to each patient's individual circumstances, yet its health effects were substantial, reliable, and enduring. This underscores the important benefits that can be achieved with a relatively modest effort.

Carefully explaining the meaning of normal test results before testing prepared patients to be reassured if test results were normal, strengthening the value of the results. Unfortunately, the study did not investigate whether a similar explanation after test-

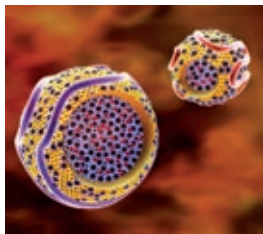
ing would have an additive effect. Normal test results might have been even more reassuring if individually tailored messages that included alternative explanations for medically unexplained symptoms were delivered after testing.<sup>5</sup> Understandably, without such explanations some patients with no objective findings remain worried about undetected medical problems if their symptoms recur.<sup>6</sup>

Although generic reassurance strategies may be useful, the results of this study show that the need for reassurance and optimal methods of providing such reassurance vary in different patients.<sup>7</sup> For example, some patients within the "standard information" group reported their reassurance level as 0 (not reassured at all), whereas others reported it as 10 (completely reassured). Individual differences known to influence the extent of reassurance include the chronicity of symptoms, the accuracy of patients' medical knowledge, and psychiatric comorbidities.<sup>8-10</sup> One study found that patients who had persistent chest pain despite negative results on exercise testing were significantly more anxious and depressed than patients who had become pain free.<sup>9</sup> Another study found that patients with gastrointestinal symptoms initially reported being greatly reassured when advised that gastroscopy revealed "nothing seriously wrong," but patients with "high health anxiety" experienced resurgence in their worry and illness beliefs as early as 24 hours later.<sup>10</sup> A "one size fits all" method is unlikely to be the best way to reassure patients about normal test results, but it seems to be better than the current system.<sup>7 11</sup>

Diagnostic testing is sometimes undertaken mainly to convince patients that their symptoms are benign. Yet this simple well intentioned act can have unintended negative consequences, as many patients are not reassured by negative findings, and merely prescribing diagnostic testing may inadvertently validate and reinforce convictions that the symptoms are serious. The potential for iatrogenesis is increased when test findings are inconclusive and is especially high if further testing is necessary to investigate a false positive result. The eventually negative results of such extended testing may be difficult for the patient to believe.<sup>8 11 12</sup>

## Early termination of drug trials

What are the ramifications for drug companies and drug safety monitoring boards?



HYBRID MEDICAL ANIMATION/SPL

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In December 2006 a randomised controlled trial of torcetrapib (a cholesteryl ester transfer protein inhibitor aimed at increasing high density lipoprotein cholesterol) was stopped after an unexpected increase in mortality in people taking the drug.<sup>1</sup> The implications are widespread, ranging from the future direction of cardiovascular prevention, the willingness of drug companies to develop new drugs in the face of massive financial risk, to the role of data and safety monitoring boards.

More than 12% of global mortality is caused by coronary heart disease.<sup>2</sup> Reduction of low density lipoprotein cholesterol with statins has been successful in primary and secondary prevention of such disease, although mortality rates remain high. Because high density lipoprotein cholesterol is inversely associated with risk of cardiovascular disease, much investment has gone into newer drugs that increase concentrations of high density lipoprotein cholesterol (such as torcetrapib).

Phase II trials found that torcetrapib increases high density lipoprotein cholesterol in a dose dependent manner when given with<sup>3</sup> and without statins, and smaller trials found no significant increase in adverse events.<sup>3 4</sup> High density lipoprotein increases by 46% with 120 mg torcetrapib daily ( $P < 0.001$ ) and 106% with 120 mg twice daily ( $P < 0.001$ ).<sup>5</sup>

Despite these promising results, improvements in surrogate endpoints do not always translate to lower mortality. For example, it was thought that controlling ventricular extrasystole would reduce death in patients with coronary heart disease. However, the CAST trial found that although several anti-arrhythmic drugs did reduce ventricular extrasystole, mortality was also increased.<sup>6</sup> A similar unexpected increase in mortality was seen for cyclo-oxygenase-2 inhibitors<sup>7</sup> and clarithromycin.<sup>8</sup>

After successfully completing earlier phase trials, torcetrapib was tested in a randomised controlled phase III trial. The ILLUMINATOR trial, sponsored by Pfizer, planned to recruit 15 000 patients to be randomised to take torcetrapib combined with atorvastatin or atorvastatin alone. Follow-up was planned to continue until 2009, but on 3 December 2006 the trial was stopped prematurely, on the advice of the data and safety monitoring board, because of significant excess mortality in patients taking torcetrapib and atorvastatin compared with those taking atorvastatin alone (82 compared with 51 deaths).<sup>1</sup> The cause of the increased mortality was not known.

The outcome illustrates, among other things, the importance of data and safety monitoring boards in monitoring the progress of trials. It is simplistic to say that the trial caused 31 unnecessary deaths because even though the difference between treatments groups was statistically significant, this difference could still be a chance finding. As results accumulate over time, outcomes often differ between treatment groups. The challenge for the safety monitoring board is to judge whether such differences are statistically and clinically

convincing. Only when a sufficient number of deaths have occurred can there be any confidence in the validity of the observation.

The data and safety monitoring board reviews these differences according to a predefined plan as the results unfold. Such boards often establish their own guidelines to indicate when the steering committee should be advised to discontinue a trial on the grounds of benefit or harm from a new treatment. Typically, a data and safety monitoring board will use "asymmetric" guidelines, so that less certainty is needed to advise stopping the trial on the grounds of harm than when the treatment under investigation seems to be beneficial.

Data and safety monitoring boards walk a narrow line; patients volunteering to be in trials should not be exposed to undue risks from drugs, yet if a trial is stopped without compelling evidence of harm or benefit many other patients may be denied potential treatments. In the ILLUMINATOR trial, no indication or hypothesis suggested that inhibition of cholesteryl ester transfer protein had serious adverse effects, and the data and safety monitoring board was correct to allow the trial to continue until harm had been shown with a reasonable degree of confidence. The potential benefit of the new treatment cannot be underestimated.

Should data and safety monitoring boards have the responsibility of observing excess deaths yet allowing treatment to continue? Although these boards face many problems,<sup>9</sup> no alternative exists; if the hypothesis on which the trial was based is convincing it can only be tested by a large phase III trial. Also, the role of data and safety monitoring boards in such trials is mandatory according to binding international guidelines.<sup>10</sup>

Bearing in mind their crucial role how can the functioning of these boards be optimised? They should comprise clinicians and statisticians who thoroughly understand the clinical area of the trial, who are experienced in the vagaries of trials, and who have no financial or other competing interest in the outcome of the trial. They should be small, at the most five members, to allow rapid communication among members. Because of the size of many clinical trials, information delays are inevitable. Much attention should be given to the speedy production and transmission of data from the trial organisation to the board, so that decisions can be made in a timely manner. These boards carry heavy responsibilities, and the scientific merits of being a member of one should be recognised as equivalent to coauthorship.

The impact on drug companies of such an event cannot be underestimated. Pfizer's action of withdrawing the drug seems proper, yet the decision to terminate the ILLUMINATOR trial must have been hard. The financial costs to the company are substantial, but keeping the drug alive might have been more costly, as seen with the Vioxx tragedy.<sup>11</sup> It must be hoped that the drug industry does not lose the will to develop innovative drugs, for which phase III trials remain essential.