Testing transparency

An international movement to boost transparency in clinical trials is gathering momentum. Iain Chalmers, who has championed these issues for many years, talks to Fiona Fleck.

Courtesy of Iain Chalmers

Iain Chalmers

For over four decades, Sir Iain Chalmers has worked to improve methods for gathering evidence on the effects of health-care interventions, and to promote public understanding of these methods. He is a co-author of *Testing Treatments: better research for better healthcare* and editor of *Testing Treatments interactive* in English. He also edits the James Lind Library, a multilingual collection of historical and other material about fair tests. In 1992, he established the Cochrane Centre in Oxford, United Kingdom, which convened the meeting the following year at which the international Cochrane Collaboration was inaugurated. During the 14 years before that, Chalmers directed the National Perinatal Epidemiology Unit in Oxford, which coordinated systematic reviews of the literature, randomized trials, and other research. After qualifying in medicine at the University of London in 1966, he worked as a clinician for seven years in the UK's National Health Service and with the United Nations Relief and Works Agency (UNRWA) in the Gaza Strip.

Q: How did you develop such a strong personal interest in transparency and other issues surrounding clinical trials?

A: When I worked in a refugee camp in Gaza in 1969 and 1970, I knew that measles – a viral infection – sometimes had superimposed bacterial infection. But I had been taught at medical school never to treat a viral disease with antibiotics, so I withheld antibiotics unless I felt that bacterial superinfection had definitely occurred. Because I didn't give children with early measles antibiotics, I believe many of them suffered unnecessarily and some may have died. I learned subsequently that six controlled trials assessing the effects of prophylactic antibiotics in measles patients had been published before I even went to Gaza. If you looked at them all together, i.e. if you did a systematic review of them, they showed that prophylactic antibiotics reduced pneumonia and other complications. I wish I had had such information when I was in Gaza. Everything I've done since then has been to try to make it more likely that clinicians and their patients have ready access to reliable information about the findings of relevant research.

Q: Why is the registration and reporting of trials so important for this?

A: Clinical trial transparency is important for moral, scientific and economic reasons. First, many people volunteer to participate in trials to help increase knowledge, so the failure to report trials is a betrayal of their trust. Second, failing to report trials fully results in biased estimates of treatment effects and leads other researchers up blind alleys. Third, precious time and resources are wasted.

Q: How did the idea of registering trials prospectively and fully reporting their results start?

A: People who conduct systematic reviews need to find as much of the relevant evidence as possible. That means not just looking at what is published in journals, but also scanning conference abstracts and unpublished sources. In the late 1970s and 1980s, with support from the World Health Organization (WHO), my colleagues and I were developing a register of perinatal controlled trials. We were concerned that we might be missing important studies that had not been reported at all, so we wrote to over 40 000 clinicians to try to flush out this information. We concluded that the yield from the retrospective approach we had used was inadequate and that the way forward was through registering all trials when they began.

Q: Were you alone in that view?

A: No. In 1986, an Australian researcher, John Simes, published systematic reviews comparing the results of trials that had and had not been prospectively registered. He showed that the review of prospectively registered trials – both published and unpublished – gave different, less optimistic results compared with a review based solely on published reports.

Q: What was the outcome?

A: An important legislative step came 10 years later with the Food and Drug Administration Modernization Act, which called for the establishment of a clinical trials registry (www.clinicaltrials.gov) and mandated registration of trials testing treatments for serious or life-threatening diseases. The International Standard Randomized Controlled Trial Number register was also established in the mid-1990s. Compliance with registration wasn't particularly good until the attorney general of New York State, Eliot Spitzer, took GlaxoSmithKline to court for suppressing information about an antidepressant which seemed to prompt suicidal ideation in teenagers. The case led to a long overdue decision by members of the International Committee of Medical Journal Editors (the Vancouver Group) to not publish the reports of trials that had not been registered at inception. WHO has also played an important role by creating the International Clinical Trials Registry Platform (in 2005), a meta-register which draws data from a growing number of international, national and regional registers.

Q: Has trial registration been a success?

A: To some extent. However, journals continue to publish reports of trials that have not been registered prospectively and no one has received exemplary fines for failing to comply with the FDA legislation. Still, there has been a gradual acceptance that prospective trial registration and full reporting are essential, for the reasons mentioned. The Cochrane Collaboration developed its register of reports of clinical trials with support from two European Union grants so that trial reports in languages other than English could be identified and added. The National Library of Medicine added

codes to reports that had been indexed in Medline but which had not been identified as controlled trials.

Q: Is support growing to make clinical trials more transparent?

A: Yes. Ben Goldacre's book *Bad Pharma* and the "all-trials" campaign (www.alltrials.net) conducted by Sense about Science, a United Kingdom charity, have caused a sea change, not only in the United Kingdom but internationally. The campaign slogan is "all trials registered, all trials reported." The campaign has already been supported by over 60 000 individuals and endorsed by many organizations, ranging from patient groups to pharmaceutical companies, including GlaxoSmithKline. Dartmouth University in the United States is campaigning to persuade academic organizations involved in clinical research to sign up to it.

Q: Who is targeted by the campaign?

A: Both industry and academia, which is as much to blame as industry for not publishing the results of some clinical trials. For example, despite the implications for global health policies, there was a delay of many years in reporting the results of a study involving nearly two million school children in Uttar Pradesh in India, which suggested that the effects of community deworming policies and vitamin A supplementation had been overestimated in previous research. The reason for the delay in publication is probably that the results had upset people who had for many years promoted more optimistic estimates of treatment effects.

Q: What are governments doing to encourage the registration and reporting of clinical trials?

A: Governments are sometimes ambivalent, particularly in countries with a major pharmaceutical sector that may regard the suppression of unwelcome trial results as being economically justified. The European Medicines Agency (EMA) [an agency of the European Union (EU)] recently decided to increase transparency by making trial information available from 2014 about drugs that have received a marketing licence in the 27 EU countries. Two United States pharmaceutical companies have challenged the EMA's decision to promote transparency. I suspect that some people are trying to derail the EMA's initiative because they regard their interests as being more important than the welfare of patients.

Q: Is there support for transparency initiatives within the industry?

A: Yes. About 20 years ago, Michael Wallace came to see me when he was the head of the British subsidiary of Schering AG, a German pharmaceutical company. He said he felt that the industry was behaving unethically and unscientifically by withholding the results of trials, and he handed over information about all his company's ongoing trials for publication in the Cochrane Library. He got a lot of stick from his colleagues in other companies, but I think he's a hero for having taken the stand that he did, which he still takes today. He is disappointed that the industry hasn't moved faster in living up to its moral responsibilities.

> "We need a reconsideration of the logic of current proscriptions and prescriptions by research ethics committees."

Q: Are governments willing to take the necessary steps to make science more honest? What is stopping them?

A: About 20 years ago, the Spanish government passed a law requiring prospective registration of all clinical trials in Spain. Few countries have gone this far. When the National Institute for Health and Care Excellence (NICE) issued one of its first judgements on a new drug in the United Kingdom, the company that produced it threatened to take its operations offshore. There appears to be a constant tension between scientific and ethical imperatives on the one hand, and economic considerations on the other, despite the in-built inefficiency in drug discovery that results from hiding relevant evidence. Research ethics committees should take a stand and insist on the registration and reporting of trials.

Q: Is that why you have criticized ethics review?

A: It is one of the reasons. Ethics committees could have done much more to ensure that trials are registered at inception and reported after completion.

Q. What are your other criticisms?

A: The other big scandal is that ethics committees are not requiring researchers to show, by referring to systematic reviews of the existing evidence, that a proposed new study is needed, or, if it is needed, that it has taken account of the results of previous studies. People participating in research and patients more generally have suffered and died unnecessarily because research ethics committees have not held researchers to account in this respect. Ethics committees should also distinguish more clearly between non-therapeutic research and research on drugs or other interventions that have never been used in humans. For example, a few years ago I was involved in trials conducted in Australia, the United Kingdom and the United States to find out how much oxygen should be given to extremely premature babies to minimize the competing risks of blindness, brain damage or death. That question has been around for 60 years. It should not require the same approach to regulation as that for a drug that has never been used in humans.

Q: Why not?

A: You have a double standard by which you are expected to provide very detailed information about a treatment if you are trying to find out whether it does more good than harm, but not if you are using it routinely. Once that double standard is pointed out, most people see straight away that it's completely crazy.

Q: What's the solution?

A: We need a reconsideration of the logic of current proscriptions and prescriptions by research ethics committees. Their ethics review needs to be proportionate to plausible risks, and empirical research is required to assess the circumstances in which ethics review does more harm than good. For example, a requirement for proxy consent given on behalf of someone who is unconscious or unable to give consent because of injury delays the start of treatment and this sometimes results in avoidable deaths. Ethics committees are also responsible for interventions intended to protect the interests of the public. They should be more ready to recognize their capacity for doing harm and ensure that their decisions are made in full recognition of the relevant evidence. ■