A clinical trials register for Europe

Stop talking and start making it happen

For more than a decade, clinical trialists and their sponsors have been saying that they want all controlled clinical trials tagged and listed somewhere while they are in progress—preferably on an international register that's simple to use, searchable, and free to anyone who wants to know who is studying what and where. No one doubts that registering ongoing controlled trials is a good idea. The Americans have made an excellent start with their publicly funded register (www.clinicaltrials.gov).[1] And the United Kingdom's Medical Research Council and the NHS Research and Development Programme have made important progress through a meta-register of controlled trials (www.controlled-trials.com), established by Current Controlled Trials, a publisher. Why has it not happened more widely in Europe? Last year the European Science Foundation, an umbrella organisation, advised all its member organisations to register controlled trials through www.controlled-trials.com and to assign each of them a unique identifier—an international standard randomised controlled trial number (ISRCTN).[2] Last month, the foundation hosted a meeting in Frankfurt to review progress, and more importantly, to urge members to stop talking and do something.

The compelling arguments that started this debate 10 years ago remain the same:[3 4] The international research effort is chaotic. It is impossible to find out, even with inside knowledge, who is studying what. This means that patients and their doctors don't know about trials they could take part in, researchers don't know if someone has already started a trial they want to do, funding bodies and governments can't easily set research strategies (because they don't know what's going on), and research that's never published disappears without a trace.

All this amounts to duplication of effort and large biases in the information doctors use to treat patients. These biases are not just inconvenient, they cost lives. The "disappearance" of unpublished data on the dangers of prophylactic antiarrythmic drugs in people with heart attack contributed to tens of thousands of avoidable deaths.[5] There is a growing consensus, voiced at this meeting, that failure to register and report controlled clinical trials somewhere public is a form of research misconduct.

To be fair, local initiatives exist in some member states, notably the United Kingdom, the Netherlands, and Germany. But the European effort adds up to little more than a proliferation of national registers, many of which are confined to trials of new drugs and closed to everyone but the national regulatory body for medicines. Information about ongoing clinical trials remains inaccessible to the people who need it most. Why?

The meeting talked about three major challenges: firstly, money. Setting up and maintaining a public register of trial activity is expensive. A heavyweight bid for funding from the European Commission failed unexpectedly in February this year, leaving existing initiatives demoralised, struggling, and dependent on a mixture of private and public finance. The web based "register of registers" run by Current Controlled Trials is simple, searchable, publicly accessible, and free to users. It contains 24 registers of trials from across the world and nearly 14 000 trials, many of which now have international standard randomised controlled trial numbers. This unique identifier helps eliminate double registering and makes it easy to trace the life-cycle of a trial from protocol to publication. Unfortunately, the European Union's decision not to support public registration until it is required by law means that to offer free access to users the company now has to charge trial sponsors for an international standard randomised controlled trial number. Worse, there are no registers from mainland Europe on the "register of registers."

Core items on www.controlled-trials.com

Title (including acronym)
Disease
Inclusion criteria for patients
Interventions
Contact details for the principle investigator
Source of funding
Name of trial sponsor

A publicly funded European database is under development. But it will be confined to trials of drugs, and completely closed. Trialists and sponsors will have access, but only to their own entry. The meeting decided that working with controlled-trials.com was the option most likely to succeed.

The second challenge is how to convince the drug industry to be more open about their ongoing trials. Glaxo Wellcome made a commitment to trial registration in 1998, but the rest of the industry has not followed Glaxo's lead.[6]

Thirdly, how do you persuade researchers to register their controlled trials? In an ideal world people would declare their trials for the greater good, to help with recruitment, and to make their work more visible. In reality, a few extra forms on top of the mountain of paper work already generated by a trial are often too much. Some countries, including the United States, use the law. The Food and Drug Administration Modernization Act 1997 says that all trials must be registered, but only if they are testing new treatments for serious or life threatening diseases.[7] The commercial sector interprets this as AIDS or cancer trials, which leaves big holes in clinicaltrials.gov and other US registers.[8]

The European Science Foundation meeting decided instead to push for registration to be linked to funding as it already is for many controlled trials in the United Kingdom, where the MRC releases funds only for trials registered on controlled-trials.com and identified by an international standard randomised controlled trial number. The idea is that funding agencies across Europe, led by members of the European Science Foundation, insist that all trials are registered somewhere—probably on a national register—then

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ensure that core items are also placed on controlled-trials.com where everyone can see them (box).

The foundation will review progress in six months and challenge the European Commission to follow through its repeated calls for trials to be registered. In the meantime, what should the rest of us be doing? Lobbying politicians. It worked in the United States where a sustained campaign by patient groups led to a change in the law. Patient groups should be urging European politicians to open up the planned European database or pay for another more accessible initiative. Ethics committees should apply pressure to researchers at the ethical review stage. Finally, editors of medical journals should ask authors to register their trials and commit to publishing a trial's international standard randomised controlled trial number alongside the published paper.

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Drug eluting coronary stents

May sound the death knell for restenosis

Percutaneous coronary revascularisation has revolutionised the treatment of ischaemic heart disease during the past two decades. Despite technical refinements, however, long term results after using standard techniques remain limited by the phenomenon of restenosis—a process whereby elastic recoil and neointimal hyperplasia occur at the site of endothelial injury, often resulting in recurrent symptoms within six months of the procedure. Although the use of coronary stents is associated with lower rates of restenosis than balloon angioplasty alone,[1] rates of up to 40% have been reported in some series, and treatment options are often unsatisfactory, with high recurrence rates after further intervention.[2]

Neointimal hyperplasia begins soon after coronary intervention as a result of platelet activation, inflammation, and proliferation of smooth muscle cells. Pharmacological inhibition of these processes by using drugs administered systemically has had little success in preventing restenosis. A platelet IIb/IIIa receptor antagonist, abciximab, has shown a modest benefit for patients with diabetes mellitus undergoing stent implantation,[3] but trials of other drugs have often failed spectacularly despite promising preliminary work in animal models. Intravascular radiation (brachytherapy) using sources emitting γ rays or β rays is an effective way of treating established restenosis,[4 5] although its use for the prevention of restenosis has been disappointing. Furthermore, several important safety issues are associated with brachytherapy, and owing to strict regulation the procedure is currently restricted to specialist centres.

Previous pharmacological trials focused on giving a systemic drug and may have failed in part because adequate local concentrations of the drug were not achievable without systemic toxicity. A novel solution to this problem has been the recent development of drug eluting stents, allowing controlled release of a drug directly to the injured endothelium.

In the RAVEL study (randomised study with the sirolimus coated BX velocity balloon expandable stent in the treatment of patients with de novo native coronary artery lesions)[6] the first prospective randomised trial, patients undergoing angioplasty of simple lesions received a stent that was either coated with sirolimus or made from bare metal. Sirolimus, also known as rapamycin, inhibits proliferation of smooth muscle cells by preventing progression through of the cell cycle. The trial showed not only a treatment benefit but also the complete absence of detectable restenosis in the patients receiving coated stents, compared with a rate of 28.8% in the standard stent group.

More recently, the SIRIUS study (multicentre randomised double blind study of the sirolimus coated BX velocity stent) reported preliminary results in 400 randomised patients receiving sirolimus coated stents for longer lesions, at higher risk of restenosis, and including more patients with complex stenoses, diabetes mellitus, and multivessel disease (Paris Course on Revascularisation, May 2002). Nine months' data showed an in-stent restenosis rate of 2% compared with 32.3% in the standard stent group, but a higher incidence of restenosis at the stent margins (total restenosis rate 9.2%, target vessel revascularisation rate 6.8%).

Paclitaxel coated stents, which slow microtubule degradation after cell division, have also been investigated in a parallel series of trials; the initial TAXUS-I (paclitaxel) study reported no instances of restenosis in 61 randomised patients at nine months, and the later ELUTES (European evaluation of paclitaxel eluting stent) trial reported a target lesion revascularisation rate of 5% at 12 months compared with 16% in the standard stent group.[7 8]

These impressive preliminary results have generated enormous expectations and clinical demand for drug eluting stents. All completed trials to date have, however, been small, and none have specifically

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