this is not necessarily the case, giving as an example serum cholesterol concentration in relation to ischaemic heart disease. A risk factor with an $RO_{Q1\text{-}5}$ of 10 or greater is unusual. Few risk factors in epidemiology are as strongly associated with a disease as this. A risk factor with an $RO_{Q1\text{-}5}$ would, however, perform poorly as a screening test. It would have a detection rate of about 20% for a false positive rate of 5% if the SDs were similar for affected and unaffected individuals. Even if the SD in affected individuals was 20% greater, the detection rate would only be 30% for a 5% false positive rate.

The fact that a strong risk factor can be a poor screening test may seem counterintuitive. The paradox is explained when it is recognised that the relative odds (or relative risk), usually used to evaluate risk factors as possible causes of a disease, is usually assessed by comparing the risk of disease at each end of the distribution of the risk factor. In this way the effect of being highly "exposed" to the factor is compared with being slightly "exposed." The groups being compared are mutually exclusive and most people in the middle of the distribution are ignored. When the risk factor is examined as a screening test, the likelihood of having (or developing) a disease given a positive result (say, ≥95th centile) is estimated relative to the average risk in the entire population, which not only includes all those below the cut off but also those above it. The aim in screening is to identify a group with a high risk relative to everyone.

Another reason why strong risk factors may make poor screening tests is that there may be little variation in exposure within populations. For example, we know that smoking cigarettes is a risk factor for lung cancer. However, if everyone in a certain population smoked 20 cigarettes a day, asking about cigarette consumption would not distinguish those who are more likely to develop lung cancer from those who are not.

Failure to recognise the above considerations may explain why serum cholesterol determination was proposed as a screening test for ischaemic heart disease even though it performed poorly as a screening test when cut off levels corresponding to the 95th centile were used.[1] Before a risk factor is considered as a screening test it would be worth determining the $RO_{Q1\text{-}5}$ and then examining the table. This should help to determine which tests are potentially useful in medical screening.

We thank Tiesheng Wu for his help in preparing the figures and Malcolm Law for comments.

Competing interests: None declared.

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(Accepted 19 July 1999)

Registering clinical trials

Alison Tonks

Randomised trials of medical interventions are the foundation of evidence based health care, but most are effectively conducted in secret. Few people—usually an elite network of investigators, funding agencies, and government regulatory bodies—know about a trial from its inception. Most trials become public knowledge only when the investigators publish their completed project in a journal—if they ever do.[1] In the meantime, others may be duplicating the effort or, worse, ignoring early warning signs that an intervention is dangerous. One trial of the class I antiarrhythmic drug lorcainide, for example, went unreported for over a decade even though the data suggested that the drug increased mortality in patients with myocardial infarction. During that time, use of such drugs continued and shortened the lives of up to 70 000 people each year in the United States alone.[2] A register of clinical trials is one way of opening up the process and avoiding these problems.

The idea was first mentioned 13 years ago[3] and has been refined since then by an international group of trialists, academics, and enthusiasts campaigning for a comprehensive, up to date, and searchable archive of ongoing and recently completed randomised trials, including trials done by the pharmaceutical industry. This article reports a recent conference on trial

Summary points

Clinical trials should be registered so that essential details are made public from a trial's inception, rather than from publication many years later

Openness about trials in progress reduces the impact of publication bias, prevents duplication of effort, promotes collaboration, and can save lives

Hundreds of trial registers already exist, but the information on them is not standardised and is incomplete; most contain only a subset of trials, often in high profile areas such as cancer or AIDS; and there are few incentives for researchers to register trials

Initiatives have begun to unify the existing web of registers, but they are at an early stage

Registration of clinical trials should be compulsory, either by law or by linking it to ethical approval of research

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BMJ 1999;319:1565–8

Box 1: Individuals and organisations with a stake in trial registers

- Cochrane Collaboration, and other organisations conducting systematic reviews and meta-analyses
- Investigators doing primary research
- Agencies that fund research, including governments, research charities, and medical research councils
- Drug licensing agencies
- Pharmaceutical companies
- Publishers of medical science
- Bodies responsible for the ethical review of research
- Patients

registration hosted in London by the *BMJ*, the *Lancet*, and the Association of the British Pharmaceutical Industry. The article was prepared from conference presentations and subsequent debate, discussion with selected speakers and delegates, reviews by those speakers who are running their own registers, and a bibliography of studies prepared by Iain Chalmers, director of the UK Cochrane Centre.

What is a trial register?

Registering a clinical trial of a new drug or intervention means putting on public record some basic information about the trial from its inception. The aim is to provide reliable intelligence about research in progress to the public, health providers, researchers, and funding bodies (box 1 lists the people and organisations with a stake in trial registration). There is still no consensus about the kind of details that should be registered, but the hierarchy of options is listed in box 2. Comprehensive registration of full protocols and eventual results makes the enterprise richer and more useful but may discourage pharmaceutical companies wanting to safeguard commercially sensitive information. There is also no international agreement about what sort of trials should be included. Randomised trials of new drugs are top of everyone's list, but other interventions, such as surgery or new diagnostic techniques are surely as important.

Box 2: Details that could be included in a trial register (least controversial items listed first)

- Title of trial
- Research question
- Study population and interventions
- Lead investigator or institution
- Funding organisation
- Unique identifier to prevent repeat registrations
- Status of trial—Ongoing or completed? Is trial still open to accrual? Contact address for potential participants
- Other details of methodology—Design, power calculation, outcomes, analysis
- Ethical aspects—Type of consent, information given to participants, approval by ethics committee
- Results—Published or unpublished? Abstracts presented? References to best account of results
- Full protocol

Why register trials?

Pioneers of trial registration have been writing and talking about it for decades. Their most powerful argument is that unregistered and unreported trials cannot contribute to the evidence base for healthcare decisions. Only a biased subsample of all trials—the published ones—is included in systematic reviews and meta-analyses. Publication bias is a serious problem that costs lives. Box 3 lists other good reasons to register trials. There are few dissenting voices in this debate. Patients, researchers, funding agencies, governments, publishers, and two leading international pharmaceutical companies (the others are watching and waiting) all agree that clinical trials should be registered in the interests of evidence based medicine and freedom of information.[4] The remaining question is not whether it should be done but how the effort should be coordinated.

Box 3: Why register trials?

- To mitigate against publication bias—the underreporting of trials with disappointing, negative, or inconclusive results—which misleads researchers conducting systematic reviews and doctors making decisions based on published evidence
- To prevent unnecessary duplication of research effort, while encouraging appropriate replication and confirmation of results
- To alert researchers to gaps in the knowledge base
- To foster international collaboration among researchers and stimulate recruitment to clinical trials, enhancing their chances of success
- To provide reliable intelligence about ongoing trials that will help funding bodies target their money where it is most needed
- To aid recruitment to trials by direct appeal to the public
- To enable research into research. Who is doing what, and how?
- To improve accessibility and therefore credibility of research performed by the pharmaceutical industry
- To satisfy public demand for unbiased evidence on the effectiveness of treatments, and to promote the public accountability of medical research in general

Who is doing it?

There are already hundreds of clinical trial registers worldwide. There is even a register of registers, begun in 1987 and held at Brown University in the United States, which lists over 500 online registers of clinical trials. Three case studies (a selection of registers presented at the conference) illustrate the kind of initiatives being developed by the pharmaceutical industry, national governments, and science publishers. Clearly, many trials are already registered, but often in registers that are inaccessible even to researchers. Most are managed in isolation, using "stand alone" software, which frustrates the simplest search for information. Recorded details vary dramatically among registers. There is no guarantee that a register is complete, accurate, or comprehensive. Worse, registered trials seem to be a biased subset of all trials: 60% of registers are confined to AIDS or cancer trials, and most cover only drug trials and not other interventions

Case study 1: Trial register developed by national government

Britain's National Research Register (www.update-software.com/nrronline/Default.htm) is an online register of current or recently completed projects funded or supported by the NHS. It contains details of about 1500 randomised trials from all aspects of health care, of which 733 are ongoing. Nearly 50 000 projects are listed. The register is free and gives contact details for the lead researchers as well as the research question, brief methodological details, and key words. The proportion of trials that find their way on to the register is unknown. Searching the database is straightforward, and will also retrieve trials listed in other UK databases, including the Medical Research Council's clinical trials directory and a database of research from the Centre for Health Economics and the NHS Centre for Reviews and Dissemination in York.

Advantages—It is free, easy to search, and covers all areas of health care. Entries are clear, useful, and updated quarterly by submission from researchers
Limitations—It is incomplete and entirely British

Case study 2: Trial register developed by publishing companies

Current Controlled Trials (www.controlled-trials.com), a new web based publishing company, has recently established a register of registers of controlled trials, with electronic links to over 50 registers, and a "metaRegister of Controlled Trials." The metaRegister has six contributors: Canadian HIV trials network, Schering Health Care, Medical Research Council (UK), Coordinating Committee for Cancer Research (UK), National Research Register (UK), and the Medical Editor's Trials Amnesty.[6 7] Participating organisations submit a core set of data items for inclusion, and there are links to all participating registers.

Advantages—It is free, easy to search, and displays the serial number of each trial given at source. The register is confined to controlled trials but not to particular diseases
Limitations—There are only six contributors to the metaRegister so far

(K Dickersin, personal communication). The existing network of registers is therefore valueless to anyone but a small group of cognoscenti, and only of limited value to them.

Many countries have legislation covering the conduct of clinical trials, and in some, such as the United States and Spain, trials cannot begin legally until they have been cleared and registered with a central body, usually the drug regulatory agency. The US government is leading the charge with its Food and Drug Administration Modernisation Act 1997, which requires the establishment of a prospective database of all trials of new treatments for serious or life threatening diseases.[5] The system is under construction at the National Library of Medicine, and at least some parts of it should be publicly available soon. In Britain the only legal imperative is that trials of new drugs must be registered with the Medicines Control Agency as part of the licensing process. Details are submitted in confidence by pharmaceutical companies and kept secret by the agency. The Medical Research Council, a leading source of funding for UK research, also requires investigators to register their trials before it releases funds.

Why isn't everybody doing it together?

The barriers to unifying trial registration across the world are formidable and fall into two main categories. Firstly, there are practical difficulties such as capturing all trials without duplication from a wide variety of sources, finding money to fund free access, agreeing on a minimum dataset, navigating different legal systems, and developing information systems sophisticated enough to search within and between different registers. Maintaining a register is hard work, can be tedious, and is certainly expensive—an unpromising trio of attributes.

Secondly, there are trickier human problems such as cultural differences between commercial and research organisations, lack of incentives for researchers to spend time registering trials, competition among organisations running their own registers for profit or influence, questions of ownership and copyright, and the legitimate concerns of the drug industry about releasing sensitive information before a new drug is licensed. From an industry perspective, sharing information means sharing power, and so far only Glaxo Wellcome and Schering UK have signed up. Others will follow their lead only if they see that these companies gain credibility without financial penalty.

Making it happen

The dialogue about trial registration, which has been gathering momentum for two years, is poised to move from good intention to a new phase of implementation with the help of four influences: the law, the consumer movement, ethical review of research, and advances in information technology.

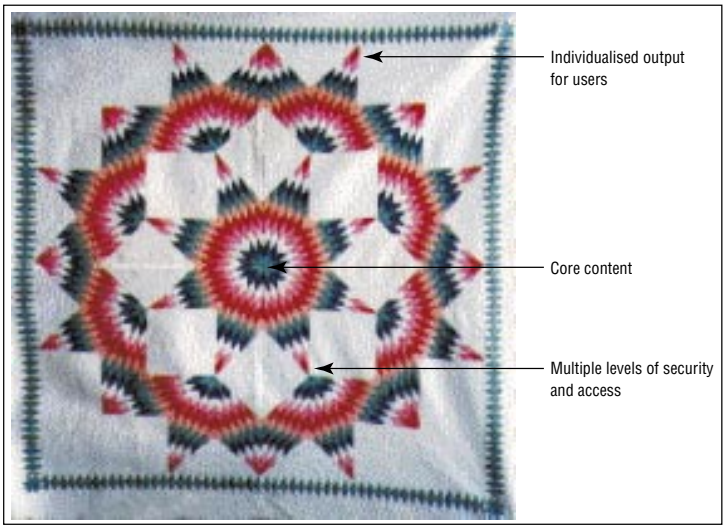
Linking ethical approval to registration

Capturing trials is a major problem for register organisers. Linking registration to funding is one option, but

Case study 3: Trial register developed by pharmaceutical industry

GlaxoWellcome launched a drug trials register in 1998 (http://ctr.glaxowellcome.co.uk/). It is password protected and accessible only to scientists and healthcare professionals. The company posts details of all its phase IIIb and IV studies prospectively and adds details of phase II and III studies once a drug is licensed. References to published results (including abstracts) are included when available. The register is updated yearly.

Advantages—The register is a pioneering effort by a pharmaceutical company to increase openness within the industry by listing ongoing trials which would otherwise have been a closely guarded secret. The register is international
Limitations—Access is restricted and granted only on request. Patients are denied access. Important developments may occur between updates



"Broken star" quilt illustrating a web of registers based on a minimum data set, with individual outputs for users and flexible levels of access

what about all those trials without an external source of funding? All clinical trials must go through a process of ethical approval, and opinion leaders have suggested that the machinery for this (ethics committees in Britain, institutional review boards in the United States) should be used to guarantee registration.[8 9] If research ethics committees policed the system by insisting on registration before granting ethical approval, accrual would leap to almost 100% overnight. Disappointingly, this relatively simple step has not yet been taken in Britain despite clear signals that it would be. The Australian research ethics community also supports the notion of registration before ethical approval. Again, institutional ethics committees have been earmarked for the job.

The law

It is too early to tell whether legislation can be used to force the issue, and in which cultural environments it is best used. The Food and Drug Administration Modernisation Act 1997 has worked in the United States, although its prototype register took two years to develop. The force of law will be of value only if the legislation makes registers open to the public. In Spain legal regulation of drug trials has supported a national trial registry since 1982, but the Spanish government has yet to allow access to researchers and the public. Negotiations between the Spanish Cochrane Centre and the government are continuing about what information should be released and when. Finally, there are plans for a European directive on controlled trials to unify international trial efforts. It states that a European database of trials should be set up.

The consumer movement

Patients are the real consumers of medical research. They buy it through taxation and charitable donation, participate in it, and use the results (mediated by doctors) to improve their health and alleviate disease. They rightly expect that clinical decisions are based on all available knowledge, not just the biased sample that appears in medical journals. A forceful consumer lobby is a powerful ally when it comes to persuading politicians to promote trial registers. Pressure from advocacy groups for patients with breast cancer ultimately led to a change in US law. In Australia the Consumers' Health Forum is one of several consumer organisations that advocate prospective registration of trials. Patients' organisations in Britain, however, have been largely silent on the subject, possibly because public understanding of clinical trials is still inadequate. More could be done to encourage the UK consumer lobby to speak out.

New technology

The recent international explosion of stand alone trial registers and the diversity of organisations running them makes it look increasingly unlikely that a single physical register will ever exist. Fortunately, the need for one is diminishing as internet technology develops to harmonise searching across registers. If all registers were linked, individual organisations would be free to decide how much information to post and who should get it—within an internationally agreed minimum requirement. An Amish quilt illustrates the idea (see fig). Current Controlled Trials has already implemented such a model in its metaregister of controlled trials (www.controlled-trials.com). A group at Brown University in the United States is also working on a virtual unified register made up of a web of existing registers.

Conclusion

Registering a clinical trial is a public declaration of intent by those doing the work, and those paying for it. That such a diverse range of organisations, including commercial companies, are committed to openness about clinical trials is a triumph of common sense over chaos. Many trials are already registered, but there is some way to go before *BMJ* readers and their patients can search the international research effort for information about trials in progress in the same way that they can search the international literature for results of trials. The problems that remain are largely practical ones, which lend themselves to two practical solutions: passing legislation to outlaw unregistered trials, or convincing ethics committees to withhold approval until a trial is publicly registered.

Competing interests: None declared.

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Endpiece

Understanding of the world

Two things are infinite: the universe and human stupidity; and I'm not sure about the universe.

Albert Einstein