

Howard Larkin



International pressure builds for unified clinical trials registry

Single information source could reduce publishing bias and improve research efficiency

Accusations that a major drug manufacturer may have suppressed some negative drug trial results are lending new urgency to calls by ophthalmologists for establishing a unified clinical trial registry.

Such a registry would likely build on existing national and private registries to establish a one-stop online list of all ongoing and concluded clinical trials. A description of the methodology, status and results of all trials would be included, whether their results were published or not.

Such a trial registry would be useful not only for keeping tabs on off-label uses of drugs approved by various national and international agencies, it could make it easi-

er for ophthalmologists to check out new implantable lenses and other devices that are not regulated in every country, said ophthalmologist Emanuel S. Rosen, FRCS, European editor of the *Journal of Cataract and Refractive Surgery*. "Particularly in the tabloids you get people extolling the virtues of new lenses without the proper trials having taken place."

A unified registry of all trials would also help balance what many believe – and some studies have confirmed – is a bias toward publishing favorable trial results in the peer-reviewed literature. "Every once in awhile something leaks out that the clinical results that don't get published are at variance with those that do get published," said Dr.

Richard E. Bensinger, MD, who is a spokesperson for the American Academy of Ophthalmology and director of the institutional review board overseeing research at the 700-bed Swedish Hospital in Seattle, Washington.

Dr. Bensinger pointed to a case of a well-known anti-infective agent used in ophthalmic procedures that has been shown ineffective in children. Most new drugs are not tested on children before they reach the market, he notes. "As clinicians, we need to have this information, and it doesn't always get published," Dr. Bensinger added.

WHO TARGETS UNIFIED TRIAL RELEASE FOR NOVEMBER

A World Health Organisation advisory committee is developing a proposal for a unified clinical trial registry.

The proposal is slated to be unveiled at the World Health Forum in Mexico this November.

The most likely approach is to recommend upgrades to national registries that are already in place in many countries, and to set up an online portal that would enable researchers to access them all, said Metin Gulmezoglu, a WHO researcher who is leading the registry effort. In addition, an international uniform numbering system would be adopted so that each trial would have a unique identifier to eliminate confusion about whether a trial at a given location is one part of a multi-center effort, or a stand-alone study.

Dr. Gulmezoglu and other WHO staff are currently working with representatives in member countries to iron out the details. "There are technical issues that are not trivial but can be addressed, there is an advocacy side; that we need to inform, consult the stakeholders especially our member states, and then there are the resource-related issues. Our aim is to have a concrete plan by November."

While no country now has a registry in place that can serve as a complete model for the proposed WHO system, several are well on their way, said Kay Dickersin, a professor at Brown University in the United States, and a consultant to the WHO registry committee. The Netherlands, the United Kingdom, Germany, and South Africa are countries with well-developed national registries, said Dr. Dickersin, who is also director of the U.S. Cochrane Collaboration. The Cochrane Collaboration is an international organisation committed to making reviews of published medical literature and trials available to all.

If established, the unified registry will provide a global resource for conducting clinical trials and disseminating important medical information to less-developed countries, both important WHO goals.

"Research is international," Dr. Gulmezoglu said. "We should avoid duplication, base our decisions on best available evidence, both positive and negative, and we have an ethical duty to inform the public about what research is being conducted and their results."

RECOMMENDATIONS FOR A UNIFIED TRIALS REGISTRY

According to the Cochrane Collaboration:

1. All randomised controlled trials should be registered from the time they are approved by an ethics committee or approved for funding;
2. Registered information should be potentially accessible to all interested parties;
3. Registration should be with a register that complies with an appropriate minimum standard of practice;
4. Prospective registration of trials should be part of ethical guidelines for clinical trials;
5. Government agencies should ensure that adequate mechanisms and infrastructure are provided so that all randomised controlled trials can be registered prospectively;
6. Government agencies should explore legislative and other strategies to mandate prospective registration as a condition of, for example, funding, ethics, or regulatory approval.

Source: Cochrane Collaboration, 2004

BUDDING SCANDAL SPARKS RENEWED ACTION

Calls for publicly available registries of clinical trials are nothing new. Organisations such as the Cochrane Collaboration and the World Health Organisation have advocated their development for more than a decade. Now they're being joined by the powerful American Medical Association, which in June called on the U.S. government to create a publicly available registry of all trials in the U.S. The measure has support from several key members of the U.S. Congress, though no action is likely before next year.

The AMA's move followed allegations by a state prosecutor in New York that the UK-based drug manufacturer, GlaxoSmithKline, suppressed studies suggesting that the antidepressant paroxetine was ineffective in children and adolescents, and may be associated with increased suicidal behavior. GlaxoSmithKline denies the allegations and has since adopted a policy of posting results of all trials involving its products on the Internet.

Other drug companies that have announced they will make information on all trials publicly available include US-based Merck & Co. and Eli Lilly and Company. Merck has also backed a unified registry approach. Despite the openness of such companies, significant resistance to publishing remains in the pharmaceutical industry. One concern is that publishing the details of early trials could provide valuable data to competing developers, according to Court Rosen, a spokesperson for the Pharmaceutical Research and Manufacturers Association.

While many doctors acknowledge that manufacturers have legitimate commercial interests in keep trade secrets, they believe

the public good argues compellingly for disclosure.

"The concept is difficult to oppose," said Metin Gulmezoglu, MD, a WHO researcher. "There are ethical arguments as well as those for evidence-based decision-making in favor of a unified clinical trials registry. However, different groups understand or expect different things and we need to communicate our aims appropriately."

WHO is working with its member states to develop a unified trials registry, which it hopes to unveil in November.

"Posting the results of such trials would address growing concerns over publication and outcome bias in clinical trials," said Joseph A. Heyman, a member of the board of trustees of the American Medical Association. "The public and physicians have a right and a need to know the results of clinical trials if they are to make informed treatment decisions."

That's difficult with existing registries. Many countries maintain multiple registries. For example, the U.K. maintains separate registries for private and publicly funded research; a number of countries that have national registries also restrict access, so they can't be used by many physicians. The U.S. National Library of Medicine currently maintains a Web site, www.clinicaltrials.gov, which lists about 10,000 trials. However, the main purpose of the website is to recruit patients, and the list is not comprehensive.

More than 300 public and private clinical trial registries currently exist in the U.S., making it difficult to track all research in a given area. In addition, many trials are completed and never reported anywhere.

Support for clinical trials registries is also coming from the medical publishing community. The International Committee of Medical Journal Editors is considering a policy that would require studies to be registered as a condition of publication.