Clinical Trials and Public Trust

In July, hope was expressed on this page about new developments in the accessibility of clinical trial data. Several leading medical journals had pressed for a requirement that all clinical trials be placed in a public registry, a proposal endorsed by the American Medical Association (AMA) and the Association of American Medical Colleges. The AMA had urged the institutional review boards (IRBs) that review trial protocols to require such registration before approval of a drug. The World Health Organization further supports an international registry.

That good news has proved transitory, as subsequent events have damaged the public’s faith in a process that is, after all, vital to its health. The alleged failure of Merck and Co. to release damaging data about cardiac risks associated with its blockbuster pain drug Vioxx (a COX-2 inhibitor) has prompted congressional hearings, with charges that the company knew of the risks earlier but didn’t say so. That scandal followed another: a year-long delay by the U.S. Food and Drug Administration (FDA) to warn about the suicide risks of certain antidepressants given to children.

What’s needed to restore confidence in the system that brings us new medicines? It is natural to focus blame on the drug companies. After all, they’re rich, and people are mad about their prices. Although clinical trials can be well run, the companies that sponsor and organize them want the “right” result, and opportunities for influence abound. An important trial may involve many centers, each with an IRB of tired and overstretched members. One resistant IRB can be pressed for approval because “all the others have approved.” Many trials are outsourced for management by clinical research organizations (CROs), which are motivated to please the employer (after all, doesn’t the wedding coordinator want to please the bride’s mother?).

But the FDA’s end of the process is a natural target, too. The agency has had good external advisory committees in the past. But the recent history of administrative removals, particularly that of COX-2 critic Curt Furberg from a panel considering those drugs, has invited public suspicion. This and other questions about other already-marketed drugs have raised concern about the FDA’s susceptibility to drug company influence. These have now led to several actions: a request by the agency for a comprehensive review by the Institute of Medicine; a system of internal appeals, in which an employee concerned about a drug safety issue can be heard by a panel with participation from outside the agency; and a renewed search for a director of the Office of Drug Safety.

Some critics have urged that the situation is so bad that we need a new government agency charged with the conduct of all clinical trials, using funds supplied by the manufacturers. That might be a solution, but political enthusiasm for it will be low for a while. Meanwhile, there are possible short-term fixes. Regional or national IRBs might do a better job, but institutions are reluctant to use them because of the added liability they could take on. Better, perhaps, to provide resources to beef up existing IRBs. Second, require that all late-stage clinical trials, including those testing for unapproved uses of already-marketed drugs, be entered into a registry that would make all results, including the negative ones, available publicly, which is a step beyond the proposals contained in legislation now under Senate consideration.

The most important task is to provide one essential tool. Through no fault of the FDA, the United States has lacked a system than can detect things that go wrong with an already-marketed drug. Physicians are asked to make voluntary reports and manufacturers are required to tell the FDA when they spot a problem, but there’s little incentive for either. Moreover, there is no centralized way of knowing how much of a given drug is being used, so there is no denominator and no adverse reaction rate can be calculated. That’s not to say that it can’t be done right. Kaiser Permanente, the health plan giant, maintains electronic patient records and its doctors do report problems, allowing them to conduct adverse reaction epidemiology (a Kaiser study spotted the Vioxx problem early). The absence of an effective national adverse event reporting and analysis capacity is an embarrassment. Instead of complaining about the FDA, Congress should fund it to support an effective Office of Drug Safety, with the authority needed to encourage physician reporting and a way to audit prescriptions.

Donald Kennedy
Editor-in-Chief

10.1126/science.1107657
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Science 306 (5702), 1649.
DOI: 10.1126/science.1107657