Advocates Pursue a Public Registry for All Clinical Trials

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When can a well-designed clinical trial provide only minimal help in evaluating a new drug? It is when the trial’s results go unreported.

Medical journals are filled with reports on the safety and effectiveness of new medications, but they represent only a portion of all the studies conducted. For the most part, published reports reflect the exciting news about drugs that show therapeutic promise. Studies that cast doubt on the value of new medicines are less likely to find their way into print, but the bad news can be as important as the good news in making clinical decisions.

The paucity of reported negative findings can be a disadvantage to physicians and their patients when they need to weight treatment options. They may not know of suspected safety hazards or of the questionable effectiveness of some widely used medications in population subgroups. They also may not be able to accurately assess the promise of entering a trial of an experimental drug.

This dilemma reached widespread public notice recently, when the New York State Attorney General sued GlaxoSmithKline for not publishing unfavorable studies on the use of its antidepressant paroxetine (Paxil®) in children. British medical authorities had suggested that paroxetine might actually exacerbate pediatric depression and increase the risk of suicide.

When the Food and Drug Administration (FDA) initially reviews a new drug, it considers the results of all studies, both positive and negative. These results then become available to the public. However, when the agency denies a manufacturer’s subsequent request that the drug be approved for a new indication or for a labeling change, it does not publicly acknowledge any of the new data submitted, even if the data reveal previously unreported safety risks. It is up to the manufacturer to decide which of these results find their way into the public domain or onto the product’s label.

A PUBLIC REGISTRY AS A SOLUTION

One solution to the problem of disclosure, according to several health care organizations, is to require a listing of all clinical trials and their results in a public registry. Physicians, patients, and even regulators would then stand a better chance of seeing all the findings and of making more informed decisions. The American Medical Association has proposed that a registry be maintained by the Department of Health and Human Services (DHHS), the European Science Foundation has recommended a registry for trials across Europe, and the World Health Organization plans to propose a worldwide registry of its own. One large drug company, Merck, has endorsed the idea as well.

An intriguing proposal is under consideration by the International Council of Medical Journal Editors, a group representing 12 of the most prestigious medical publications, including The New England Journal of Medicine, The Lancet, The Journal of the American Medical Association, and The Annals of Internal Medicine. The journals would require that pharmaceutical companies register clinical trials, at their start, in a public database, or the results would not be eligible for publication. Because manufacturers often point to published results in prestigious journals in marketing their drugs, the incentive to participate in the registry would be significant.

The pharmaceutical industry itself has shown increasing receptiveness to fuller disclosure of clinical trial results. Pharmaceutical Research and Manufacturers of America (PhRMA) recently issued voluntary guidelines for trials that include a directive that meaningful study results be communicated in a timely manner regardless of the outcome. In response to the lawsuit concerning paroxetine, GlaxoSmithKline posted all clinical findings related to the drug on a Web site (www.gsk.com/media/paroxetine.htm). As noted, Merck has publicly endorsed the creation of a registry, although it would be limited to late-phase and post-approval studies.

Eli Lilly recently announced the most ambitious initiative among pharmaceutical manufacturers. Starting late next year, it plans to publish, on a Web site, all clinical trial data from all phases of testing for its approved drugs, including the results of trials for off-label uses.

BENEFITS AND DRAWBACKS OF PUBLIC DISCLOSURE

Proponents point to a range of benefits to be gained from public disclosure of all clinical trial results. The most obvious advantage is the increased transparency of findings that suggest health risks or questionable efficacy of a medication. Patients and physicians would have a more powerful tool to compare different drugs for similar medical conditions. Registry data could also help investigators to design future trials more efficiently, perhaps enabling them to use fewer subjects and simpler protocols by targeting their research.

However, opponents caution that a public registry may pose risks as well, for several reasons. First, public disclosure of a manufacturer’s early-phase clinical trials might help competing companies to get a quicker start in designing similar products. Smaller companies, including biotechnology firms, would be particularly vulnerable to public disclosure because their products tend to spend...
more time in the early stages of testing. Second, in some instances, the confidentiality of trade secrets could be at risk. Third, early-phase clinical trials, which typically involve fewer study subjects and shorter time frames than later-phase trials, are especially prone to producing misleading results. Therefore, a listing of test data related to a drug’s early testing has the potential to mislead unsophisticated users of the information.

AN EXISTING, LITTLE-KNOWN REGISTRY

The creation of a universal public registry might actually be closer than even many advocates realize. Although it is not well publicized, a limited registry already exists. The Food and Drug Administration Modernization Act of 1997 required that clinical trials to assess the effectiveness of drugs (primarily those in phases 2, 3, and 4) for serious and life-threatening diseases be listed in a database maintained by the National Library of Medicine. It is available to the public at the Web site www.clinicaltrials.gov.

To date, nearly 11,000 trials have been listed; however, most of them are sponsored by the National Institutes of Health rather than by drug manufacturers. More privately sponsored studies have been listed since 2002, when the FDA issued guidance to drug companies on compliance with the registry, but the pace of listings has been slow because of disagreement over the law’s intended scope. The FDA is reportedly reviewing its authority to enforce registration, which is limited under the law, and Congress is considering the addition of new enforcement provisions.

The original purpose of the law was to provide patients with information on trials that they might wish to join rather than to publicize study findings. Therefore, the existing database is not a complete answer for advocates of a public registry that would list clinical results. For example, it would not have ensured public access to all findings regarding paroxetine. However, the existing database could provide a platform on which a broader registry could be built.

IS A REGISTRY IN OUR FUTURE?

With many prominent organizations, including some in the pharmaceutical industry, behind the idea, the creation of a clinical trials public registry in some form seems a good bet. Other trends in health care are also pushing toward the same end, particularly the move toward “consumer-driven health care,” in which patients guide more of their own care directly. Consumer information is the key to any such plan.

The growing popularity of the Internet as a source of self-directed patient medical education has further accelerated pressures for greater disclosure of data throughout the health care system. As both advocates and opponents of disclosure acknowledge, the effects of wider clinical trial reporting on drug development, pharmaceutical marketing, and clinical decision-making could be profound.