

## EDITORIALS



## Open Clinical Trials

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On September 27, 2007, President Bush signed into law the Food and Drug Administration Revitalization Act, which aims to improve the FDA's ability to ensure the safety of the nation's drugs and medical devices. The legislation not only reauthorizes the user-fee mechanism that has been part of the agency's funding since 1992, but also increases the agency's overall financial resources. Although the user-fee approach to funding has been controversial because the fees are paid by the pharmaceutical industry, which the FDA is charged with regulating, legislators believed that user fees provide a stable monetary base that is crucial to the effectiveness of the agency.

The act contains other important components that strengthen the FDA's regulatory authority, the need for which was recently underscored by a report from the Office of Inspector General of the Department of Health and Human Services, which oversees the FDA.<sup>1</sup> Under the new legislation, the FDA will be able to require postmarketing studies of drug safety when such studies are deemed necessary. The agency can also require that changes be made to drug labels to reflect new information on safety or efficacy. It has also been given somewhat broader authority to request changes to televised drug advertising directed to the consumer. The act specifies that fewer conflict-of-interest waivers will be granted to FDA advisory committee members. Furthermore, in approving new drugs, the agency must publish its basis for approval as well as any dissenting opinions. Finally, by allowing a prolonged period of marketing exclusivity to manufacturers that undertake pediatric clinical trials, the act encourages the conduct of trials to ensure the safety and efficacy of drugs in children. How these provisions will be implemented depends in part

on the writing of rules and regulations, a process that will occur over the coming months.

Of special interest to us, an additional provision of the act requires sponsors of all clinically directive therapeutic trials to register their studies, at inception, in a public database sponsored by the National Library of Medicine. Although some aspects of this provision are not ideal, such as the delayed public availability of registration information on device trials and the noninclusion of phase 1 trials, mandatory registration represents a critical advance in making clinical trials of new treatments public knowledge. In this regard, the act is in accord with the position of the 12 general medical journals that form the International Committee of Medical Journal Editors,<sup>2,3</sup> which have since 2005 required that trials be registered before they can be considered for publication, and the World Health Organization's International Clinical Trials Registry Platform.<sup>4</sup>

A decade ago a clinical trial could be conducted in secret. The trial's sponsor, claiming proprietary rights, could keep all information about it, including its very existence, private. Thus, if a drug had important adverse effects, this information might never be made public. Legislators believed that such a possibility was not in the best interests of the American people. Once a clinical trial is mounted, the sponsor has an ethical obligation to publicly acknowledge the contribution of the participants and the risk they have taken by ensuring that information about the conduct of the trial and its principal results are in the public domain.<sup>4</sup> With the FDA Revitalization Act, the United States joins other countries in recognizing that the human volunteers needed to complete a trial are more precious than the money required to mount it. Between study subjects and financial

sponsors, it is easy to see who is taking the greater risk.

It is time for participants in clinical trials to take the initiative. People interested in participating in trials should consider only studies whose sponsors have fully registered them in an appropriate public database and agreed to publish their results. All of the required fields in a trial registry must be completed. Entries that obscure a trial's intent subvert a fundamental purpose of trial registration. We trust that database managers will not allow this to occur.

The FDA Revitalization Act sets a precedent in mandating the reporting of trial results in a public database. The table format it mandates — comprising information on trial participants and primary and principal secondary outcomes — is a reasonable approach to results reporting. In the upcoming rulemaking, the secretary of Health and Human Services should consider this format for the reporting of serious adverse events. The format confines itself to simple facts, intentionally omitting any place for interpretation of the trial's results. It encourages sponsors to prespecify and to register their key secondary outcomes, because those would then become part of the results database.

With this legislation, clinical trials in the United States will be played out in the public arena. Research volunteers will know that their participation is part of an unbiased public record. We think that fully open clinical trials will lead to more effective and safer treatments for patients. With several recent blockbuster drugs, including rofecoxib, telithromycin, and rosiglitazone, serious breakdowns in the communication of trial results kept safety concerns from doctors and patients. Open for all to see, future clinical trials can lead to new treatments that will make a difference in safely combating disease.

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1. Office of Inspector General. The Food and Drug Administration's oversight of clinical trials. Washington, DC: Department of Health and Human Services, September 2007. (Accessed October 4, 2007, at <http://oig.hhs.gov/oei/reports/oei-01-06-00160.pdf>.)
2. De Angelis C, Drazen JM, Frizelle FA, et al. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *N Engl J Med* 2004;351:1250-1.
3. Laine C, Horton R, DeAngelis CD, et al. Clinical trial registration — looking back and moving ahead. *N Engl J Med* 2007; 356:2734-6.
4. World Health Organization. International Clinical Trials Registry Platform (ICTRP). (Accessed October 4, 2007, at <http://www.who.int/ictip>.)

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## Another Success for Hepatitis A Vaccine

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Before the licensure of the first inactivated hepatitis A vaccine in 1995, hepatitis A caused a substantial disease burden in the United States. Annual cases reported to the Centers for Disease Control and Prevention (CDC) numbered 25,000 to 30,000, but a more accurate estimate approached 300,000, since infection in young children often was subclinical and mild and self-limited disease in adults was underreported.<sup>1</sup> Infection rates were highest among children younger than 5 years of age, but only 30% of these children were symptomatic. Older children and adults had lower infection rates, but in approximately 70% of cases they were symptomatic. Most symptomatic patients had a self-limited illness manifested by fever, malaise, nausea, vomiting, and jaundice, but up to 15% of adults had prolonged or relapsing illness for up to 6 months. Death from fulmi-

nant hepatitis was rare, typically occurring in people with underlying chronic liver disease.

Since the introduction of the second hepatitis A vaccine in the United States in 1996, recommendations for the use of the two hepatitis A vaccines in children have gradually expanded. Initially, both vaccines were recommended for use in children 2 years of age or older living in states and counties with rates of hepatitis A that were historically above the national average. This regional strategy for children at higher risk for exposure to hepatitis A was so successful that infection rates in states where immunization was recommended decreased to levels below those in states where immunization was not recommended, suggesting robust herd immunity (i.e., protection of nonvaccinated children and adults).<sup>2</sup> The next logical step was to recommend hepati-