Cataloging clinical trials

If a drug study is performed in a hospital and nobody reports it, does it make a sound?

BY DAVID FILMORE

A task force from the American College of Neuropsychopharmacology published a preliminary report (*www.acnp.org/exec_summary.pdf*) in January assessing selective serotonin reuptake inhibitors (SSRIs) for treating depressed children and adolescents. Consistent with the prevailing view of U.S. psychiatrists, the College recommended continued use of these medicines. The study concluded that SSRIs are effective for youths and that clinical data linking the drugs to suicidal behavior was not statistically significant.

These findings were potentially very significant. Although Eli Lilly's Prozac is the only drug approved specifically for pediatric depression, off-label prescribing of other SSRIs is common practice. Reports of a causal suicide linkage have led to several warnings or advisories from U.S. and British regulatory authorities since 2003.

However, the task force's study had a significant caveat: Its conclusions were made without "access to a substantial amount of unpublished data, including detailed findings held by drug sponsors."

FDA's position has been basically in line with the task force's findings for the past decade. But in September, the agency altered its opinion, based on regulatory filing data that was reclassified by independent experts assembled by Columbia University to more accurately reflect suicide-related adverse events; there is a statistically significant suicidiality increase due to SSRIs, agency analysts acknowledged.

The connection between antidepressants and child suicide has been a contentious matter for over a decade. But the issue's most recent rise in prominence has opened up a broader debate. The inability of scientific organizations such as the American College of Neuropsychopharmacology and the medical community at large to base recommendations on all relevant information is leading to increased questioning of the appropriateness of secret clinical trial data known only to companies and regulatory agencies.

As a result, calls for a clinical trial registry requiring public listing of all trials and, more ambitiously, ensuring public reporting of results, have accelerated.

Trials in plain view?

The issue came to a head in early June, when New York State Attorney General Eliot Spitzer filed a lawsuit against GlaxoSmithKline (GSK) for engaging in "repeated and persistent fraud" by not disclosing all clinical trial information regarding use of its antidepressant Paxil (paroxetine) for children.

Essentially, the suit alleges that by withholding negative safety and efficacy data, GSK encouraged off-label prescribing of Paxil to children to increase sales.

GSK, which stresses that Paxil has not been approved and is not marketed for patients under 18 years old, asserts that all the relevant data had been communicated to health care professionals. But within a week of Spitzer's suit, the company posted on its website complete study reports and summaries for all trials conducted in adolescent and pediatric patients.

By the end of the month, GSK announced a plan, which it says had been under consideration for several months, to create an electronic database of trial protocol summaries and corresponding results related to all of its marketed medicines. In August, the company reached a settlement with Spitzer.

Meanwhile, the American Medical Association (AMA) proposed the creation of a mandatory national clinical trials registry to uniquely identify every clinical trial conducted in the United States and ensure publication or electronic database recording of all results of registered trials.

Only about half of the 1 million controlled trials carried out since 1948 have been reported publicly, according to Kay Dickersin, director of the Center for Clinical Trials and Evidence-Based Health Care at Brown University, and *Journal of the American Medical Association* Deputy Editor Drummond Rennie in a 2003 paper (*J. Am. Med. Assoc.* **2003,** *290,* 516–523).

This is partly a consequence of medical journal review processes that favor more exciting results and partly a result of commercial interests trumping scientific ones, according to a recent AMA Council on Scientific Affairs report (*www.ama-assn.org/ama/pub/article/2036-8608.html*). Industry sponsorship of a trial is associated with a higher degree of publication bias toward positive results, the report said.

If a comprehensive registry had existed before the antidepressant controversy reached its current level, says Dickersin, who is also the director of the U.S. arm of the Cochrane Collaboration, an international organization that produces and disseminates "systematic reviews" of available health care intervention data, it "would have changed things because people would have felt they were fully informed."

Sketchy clinical trial data can make research less efficient as well. For instance, Dickersin says, "Ethics committees want to know what is going on so they don't allow studies to go on if one is already being done or if the answer is in."

All or some

In August, Eli Lilly announced a plan for a

public registry that will disclose the results for all its clinical trials (Phases 1–4), including postmarket off-label studies, once a drug is commercially available. Lilly says it will also report the initiation of all Phase III and Phase IV trials and that an independent third party will audit the registry, which is expected to be in place by the end of the year.

In September, the Pharmaceutical Research and Manufacturers of America (PhRMA) established an industry-wide registry containing the results of all "controlled clinical trials" completed by PhRMA members since October 2002. The registry will include mainly Phase III and IV trials, the industry trade group says.

PhRMA members, however, do not commit to reporting "exploratory trials"—as it would generally categorize Phase I and II studies—because they are hypothesis-generating, as opposed to hypothesis-testing (*www.phrma.org/publications/publications//2004-06-30.1035.pdf*).

PhRMA officials cite trade secrets as a primary concern. Even publicizing that an early-phase or exploratory study is being conducted might signal a company's proprietary development strategy to competitors, Court Rosen, PhRMA spokesperson, says. Furthermore, he adds, releasing any study data to a database without appropriate context might lead to premature conclusions about the safety or efficacy of a drug.

Dickersin counters that hasty conclusions can be made from single studies whether or not they are released selectively to journals or comprehensively to a database. The availability of all study data would give physicians—like those with the Cochrane Collaboration—synthesizing comprehensive reviews a "full deck" to work with, she says.

A lack of trust between the pharmaceutical industry and the clinical community also is at play in calls for a comprehensive registry, Dickersin's comments suggest.

"If pharma had shown that they really did have society's best interest at heart, then maybe we could say 'Okay, we see that there are [trials] where it might be all right not to register,' but I don't think we have seen that," she says.

Easier said than done

The momentum toward establishing a mandatory government-run database is substantial. In June, NIH head Elias Zerhouni told the Boston Globe that there was a "very high" likelihood it would happen soon.

But the logistics involved suggest this is easier said than done.

Gary Zammit, CEO of Clinilabs, a trial management organization, cites the "trucks of documents" that companies submit to the FDA for a single Investigational New Drug Application and the challenges in organizing such information.

Dickersin agrees that it is difficult to put together a data set that accurately explains the analysis. There is also a concern that there be some element of peer review, she adds.

The time and cost of the process are substantial. "I think there has to be a lot more discussion about how results are presented than there has been so far," Dickersin says. To start off, she concedes, the focus should be on establishing a comprehensive registry with basic information.

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By requiring trials to be registered at their inception with unique identifying numbers, she says, clinicians can at least be aware of what is being studied, so even if results aren't published, they can attempt to get missing data from investigators.

The International Committee of Medical Journal Editors, an organization representing 11 of the world's top medical journals, asserted its leverage on this point in September when it announced, in an editorial appearing simultaneously in each of its member journals, a new policy requiring a clinical trial to be registered at or before the onset of patient enrollment to be considered for publication. In addition to the registration number, the editorial specified several points of information that would need to be disclosed, including a description of the drug or intervention, the study hypothesis, and the outcome measures.

ClinicalTrials.gov, a site operated by the National Library of Medicine, is the primary vehicle being discussed to fulfill the needs of a mandatory registry.

The website was established to fulfill a requirement of the 1997 Food and Drug Administration Modernization Act to keep the public informed about efficacy trials available for participation in "serious or life-threatening diseases," says Theresa Toigo, director of the FDA's Office of Special Health Issues. But, she says, it has the potential to fulfill additional objectives.

However, compliance with the current regulations for ClinicalTrials.gov listing is lacking, she says, particularly for industry-sponsored trials. In cancer drug trials, for instance, she found that 48% of the mandated industry-sponsored trials were on the website, compared with 91% of required NIH-sponsored studies.

"There are no penalties specified in the law," Toigo says, but the agency is investigating how it might add an enforcement mechanism.

Meanwhile, there have been several outside proposals for expanding the law to require the posting or linking to results, she says. But Toigo or others at the U.S. Department of Health and Human Services are not commenting on them at this time.

On the international front, the World Health Organization (WHO) is taking steps to expand trial registration. In April, the organization announced that all randomized trials approved by the WHO ethics review board would be listed on the International Standard Randomized Controlled Trial Number Register, a database of trials maintained by Current Controlled Trials, in the same publishing group as BioMedCentral.

This registry, like ClinicalTrials.gov, contains only basic information and is "not updated with progress of trials," says Metin Gulmezoglu from WHO's Department of Reproductive Health and Research. But it is seen as a first step to creating a more complex database that includes results, which, he agrees with Dickersin, "needs more discussion."

Standard-bearer

PhRMA notes that while all trials do not reach the public view, they are submitted to regulatory agencies such as the FDA, which can inspect data sets in context to provide cogent guidance.

In the case of SSRIs, for instance, the agency did re-review all company-submitted

data and eventually altered its advice on antidepressant use in children.

But the process teemed with mistrust. Following a heated FDA advisory committee meeting in February, U.S. House members initiated an investigation into the agency's alleged suppression of SSRI safety data. Several parents who blame SSRIs for their children's suicides called for the abstention of several FDA employees, including medical policy chief Robert Temple, from the proceedings, because of perceived bias toward the drug industry.

From a general standpoint, some question whether the FDA is the most appropriate place for centralized "best practice" recommendations. "There are many more clinical trials than [those included in] New Drug Applications," Dickersin says. She would prefer some sort of national ethics committee to act as a clearinghouse.

Regardless, though, she believes there is a more compelling argument for a comprehensive registry.

"All the people who participated in clinical trials signed a consent form that almost certainly said, 'I will be contributing to knowledge if I participate,'" Dickersin says. "Yet if [trial results are] not made public, then they are not contributing to knowledge." ■