NEWSMAKER INTERVIEW: DEBORAH ZARIN

Unseen World of Clinical Trials Emerges From U.S. Database

No one knew what to expect when Congress created a registry of clinical trials in 1997—then expanded it in 2007, asking researchers to submit a summary of results to a public Web site. Even the number of studies likely to be registered was a complete unknown, and no one had any idea if the results would be informative, says Deborah Zarin, who directs the database at the National Institutes of Health (NIH), called ClinicalTrials.gov. But to date more than 108,000 trials have been registered, and results have been posted for more than 3600 (see graph). Most intriguing, Zarin says, the data are revealing a whole "world of clinical trials" never seen before.

The database includes clinical research funded by the U.S. government and clinical studies conducted by private entities to meet U.S. standards. (Early studies such as phase I trials are exempt from registering.) Since 2008, trials must report outcome data within 1 year of completion. Delays aren't granted for publication.

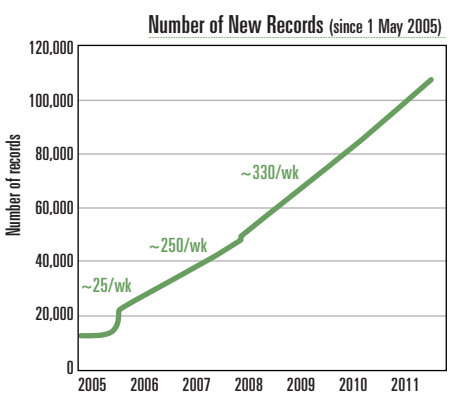
At a conference in June sponsored by NIH's National Library of Medicine and AAAS (*Science*'s publisher), Zarin shared observations based on results submitted so far. At first, only 25% of the trials with results in the database had been published; over time, the published fraction rose to about 52% in that cohort. Some studies are distressingly complex, with tens of "primary endpoints." But so far, despite worries that the reporting format would be rigid, no trial has been too exotic to summarize, Zarin says.

The system wasn't designed to do quality control, but database managers do check data. This has led to surprises, too, Zarin said, including more confusion than expected in summary reports—revealed for example by the use of the phrase "time to survival," or by the study with results, Zarin said, on "more eyeballs than two times the number of subjects." Zarin, a Harvard Medical School graduate, psychiatrist, and expert in evidence-based medicine, recently spoke with *Science*; the interview was edited for brevity and clarity.

–ELIOT MARSHALL

Q: Did you initially meet resistance trying to get the summary data?

A: Total resistance. Certain high-volume drug companies were clearly under pressure [to release trial data] and put a lot of effort into it and are doing an excellent job. Other companies don't seem to be jumping in with two feet. … Academic researchers have been slow to comply. … It really requires a mindset change. The first reaction of academic researchers was, "This will interfere with publication. No one can tell me when to present the results. I'm working on a journal article." It is very clear in the law that this has to be done on a timeline that's legally determined and does not depend on when the publication occurs. … The journal editors … have said that posting of summary results will not interfere with publication. But people need to get the message.



Clinical cornucopia. Deborah Zarin oversees an expanding registry of clinical trials and their results.

Q: How many trials are you missing?

A: There simply is no way to know. … You hear of sporadic cases. Whether there are whole islands of unregistered trials, whether the sponsors have stashes of unregistered trials, we just don't know. If there are any islands, they are getting smaller and smaller.

Q: Were you surprised by what you have been learning from the data?

A: I call it my introduction to the sausage factory. It appears that there are a number of practices in the world of clinical trials that I hadn't been aware of; it surprised a lot of people. For example, researchers might say, this is a trial of 400 subjects, 200 in each arm, and when they came to report results, they would be talking about 600 people. We would ask them to explain. They would say, "We are including 200 people from this other study because we had always intended to do that." … There were a lot of—what would I call it?—nonrigorous practices.

Q: Were the lapses more than clerical errors?

A: We are finding that in some cases, investigators cannot explain their trial, cannot explain their data. Many of them rely on the biostatistician, but some biostatisticians can't explain the trial design.

So there is a disturbing sense of some trials being done with no clear intellectual leader. That may be too strong a statement, but that's the feeling we are left with.

Q: Are reporting requirements changing how research is done?

A: I have not seen the impact on new trials, but I've heard anecdotes. Groups say they are prespecifying their outcome measures much more carefully. I know that journal editors are using the ClinicalTrials.gov site to scrutinize the prespecified outcome measures to make sure that they are in sync with what is being reported in a manuscript—and I know that editors have found problems that way.

Q: Who is the database for?

A: For right now, we view the basic results database as helping experts—whether it be journal editors or people we count on to write good systematic reviews. … It improves clinical practice, and in that way it benefits the public.

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