

Disclosure of Clinical Trials Information

Until recently, information about new trials and the results of new research was often not readily available on the internet. Individual trial sites had their own methods for recruiting patients, by word of mouth or letters, and results of the trials were usually presented at medical meetings and in scientific journals. Information about new and ongoing clinical trials was thus known to the scientists and physicians participating in the trial, to regulators, large patient advocacy groups, and some others, but seldom to the general public and not readily accessible to individual patients.

In addition, results of clinical trials are often published one or more years after completion of the trial. There have been cases, as well, where investigators didn't publish the results of their trial, or they tried to publish the findings but were not successful in getting their paper accepted by a medical journal. The difference, in the likelihood of publication for "positive" clinically-significant results versus results negative studies (studies that fail to show a clinically significant difference), is known as "publication bias". Industry and academic researchers, as well as medical journals, have been criticized for contributing to publication bias.

The Early NIH Registration Database

In 1997, the U.S. Congress passed the Food and Drug Administration Modernization Act. The legislation required that the NIH establish and maintain a "data bank" of information on clinical trials for drugs to treat serious or life-threatening diseases and conditions,¹ on which sponsors would have to register the trial. The goal for the data bank was to create a "one-stop-shop" for information about trials of investigational treatments for serious or life-threatening conditions, such as HIV/AIDS and cancer trials, that patients, their care givers, patient advocates, and scientists could use.

The NIH and FDA launched the Clinical Trials Data Bank on February 29, 2000.²



¹ P.L. 105-115 §113(a)(2) Available at: <http://www.fda.gov/cder/guidance/105-115.htm#SEC.%20113>

² See <http://www.clinicaltrials.gov>

Beyond Registration to Posting of Results

Calls for increasing information about trials included several major initiatives in 2005:

- Research published in some Medical Journals, including the *New England Journal of Medicine*, claimed that many companies were trying to maintain confidentiality about some of their trials that they had registered. The Article reported that a large percentage of trials had entries in the Intervention Name field that were “nonspecific” and/or “noninformative.” The article stated “17 percent of the entries were vague” with respect to the Primary Outcome Measure data field.”³
- Several international pharmaceutical associations, including the *European Federation of Pharmaceutical Industries and Associations*, the *International Federation of Pharmaceutical Manufacturers and Associations*, the *Japanese Pharmaceutical Manufacturers Association*, and the *Pharmaceutical Research and Manufacturers of America* (PhRMA) asked their members to commit to provide results from all confirmatory clinical trials of approved drugs on a publicly-available site sponsored by the associations. Members started posting results on **ClinicalStudyResults.org** in early January 2005. The Industry Position Statement also called for registration of all confirmatory clinical studies.
- The **World Health Organization** (WHO) formed a committee to create a program to generate a virtual registry whereby a single portal could link to the various clinical registries that exist around the world. Such an effort would require all manufacturers to use a unique identifier for trials, the International Standard Randomized Controlled Trial Number (ISRCTN). WHO successfully launched the database in May of 2007.⁴
- The State of **Maine** passed a law requiring that manufacturers of prescription drugs who were marketing their products in the state of Maine must list information about their clinical trials and report “information concerning the results of the clinical trial, including potential or actual adverse effects of the drug.”⁵

³ Zarin, D. et al., “Trial Registration at ClinicalTrials.gov between May and October 2005,” *New Engl J Med*, (2005) 353:2779-2787.
<http://content.nejm.org/cgi/content/full/353/26/2779?ijkey=3af9bfa264875c9cec79472a4d0d03aabae9a728>

⁴ Database available at: <http://www.who.int/trialsearch/>

⁵ See Maine Rev. Stat. Title 22 §2700-A (2005)

<http://www.mainelegislature.org/legis/statutes/22/title22sec2700-A.html>

Pfizer's Efforts to Register Its Trials and Post Results

With the expansion of the scope of what trials were registered and what and when results were posted, many research organization had concerns about reporting detailed information about early phase studies and whether that would help their competitors, make it difficult to file patents on new discoveries (due to prior disclosure of information), or create increasingly complicated obligations to prepare and update these registrations and postings. Perhaps the biggest concern, and one that is unlikely to go away anytime soon, is how much information would be considered enough to satisfy the calls for more transparency.

In response to the *New England Journal of Medicine* article, Pfizer's Chief Medical Officer, Joe Feczko, explained the company's initiative and effort to provide full information:

"... at Pfizer have registered all confirmatory studies at ClinicalTrials.gov. We have included 20 data fields, as developed as part of the April 2005 World Health Organization (WHO) consultation on clinical trial registration standards, but in rare cases, we have delayed disclosure of the Intervention Name and other fields to protect commercial sensitivities. Any delay is a matter of timing only, and full disclosure is to be assumed once any proprietary issues are resolved. Also, remember that, in all trials, complete information is provided to regulatory agencies, institutional review boards, investigators, and each patient who is enrolled."⁶

Pfizer's Chief Medical Officer wanted to be a leader and be "best in class" for trial disclosure. Pfizer thus became one of the first companies to register and report results from *all* of its interventional trials (phase 1 through 4), including results for trials involving marketed products (posted following approval or for post-marketing trials, one year from study completion), and summary results of trials where development of the compound or mechanism is discontinued.

By January of 2009, **Pfizer had registered over 1,000 trials on clinicaltrials.gov. Pfizer had posted results summaries for over 800 trials**, on clinicalstudyresults.org. Pfizer had also begun submitting detailed results information, for studies involving marketed medicines, to NIH (for posting on clinicaltrials.gov). Preparation of the results summaries requires anywhere from five to more than 40 hours, and for the more detailed results summaries submitted for marketing medicines, about 60 hours. The time required to prepare these results summaries is however, likely to go down over time.

⁶ Feczko, J. et al., "Clinical Trials Report Card – Letter to the Editor," *New Engl J Med* (2006) 354:1426-1429. <http://content.nejm.org/cgi/content/full/354/13/1426>

The April 20th NIH Public Meeting

At present, information on [clinicalTrials.gov](http://clinicaltrials.gov) is presented in a tabular format, which helps standardize the reporting across study types and sponsors. Those results are often 40-50 pages of data, and no conclusions or summary of the results are included in the results information. A concern that Pfizer and some others have had with that presentation of results information in that format is that it is very difficult for patients, their care givers, and even physicians and other healthcare professionals to understand.

Pfizer has also posted summaries of its trials on ClinicalStudyResults.org. Those results are however, technical in nature, and not in patient-friendly language.

In its submission to the NIH at the April 2009 public meeting, Pfizer recommended that the NIH allow trial sponsors to voluntarily provide a non-technical summary of the results of the trial. At the meeting, some organizations (including a prominent medical journal) cautioned NIH that summarizing trial results could be tricky and might be misleading to patients.

Pfizer proposed that NIH provide a standard format for that information, such as a frequently-asked questions (FAQ) format, that would ask:

- What medicine or treatment was studied?
- How many patients were involved?
- What kind of trial was this?
- What were the results of the trial?
- Have the trial results been confirmed by other studies or are they preliminary?
- What side-effects were observed?
- Where can I find more information about the trial results?
- Where can I find more information about the medicine or treatment studied?
- What information or questions should I discuss with my physician?

Other questions addressed at this meeting including what trials should have to be registered and subject to results posting requirements (e.g. early phase I trials, as well as later stage trials), whether the trial sponsor should have to provide a technical summary of the results, and whether NIH should require submission of the full protocol (including the proposed analysis of the data) for posting.

Discussion Questions

1. Should pharmaceutical companies be required by law to disclose all study results publicly? If so, when should this data be posted? What if the drug is never approved?
2. Has registering studies improved access to trials for patients? Are there other ways to improve access to clinical trials that Industry and other trial sponsors should be pursuing?
3. Is there scientific value in providing results of trials that are terminated, where the drug is never approved? Is that likely to influence the design of other trials or advance public health in some way?
4. Should patients participating in a clinical trial be entitled to receive study results, from the investigator perhaps? How might this work?
5. What are the advantages and disadvantages of posting clinical trial results in tabular and textual formats? Should such information be simplified to ensure it is understandable to a high school or college-level reader, as opposed to a healthcare professional?
6. Is the sponsor, the principal investigator, or perhaps the government or an independent third-party, the right entity to try to summarize the results of a clinical trial? Would you trust the assessment more if the summary was done by the investigator and the trial sponsor, by the government, or by a medical writer not involved in the trial?
7. Should controlled studies comparing other treatment interventions, for example surgery, or device implantation, or even studies on alternative medicines like herbal supplements, acupuncture or meditation, be required to report the results publicly on clinicaltrials.gov, if they are done in the U.S.?