Letter to the Editor

ClinicalTrials.gov: Is the Glass Half Full?

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To the Editor:

The Food and Drug Administration Modernization Act (FDAMA) of 1997 required the US Department of Health and Human Services to establish an easy-to-use Web site for clinical studies of experimental treatments for serious and life-threatening diseases sponsored by government, industry, and not-for-profit organizations.^{1,2} The legislation resulted in the creation of the Web-based ClinicalTrials.gov (<http://clinicaltrials.gov>) site, which was made accessible in February 2000. It was the beginning of a new era for meeting the needs for transparency by reporting accurate information on new therapeutic options for patients, their family members, and the clinicians taking care of them. The site was created to avoid selective bias in both academic and industrial research of clinical trials in which favorable results are published while unfavorable ones are withheld. Such practices can mislead the public into believing that inferior treatments are more beneficial than they might actually be. It risks the possibility that physicians, who rely on these studies as a source to guide clinical treatment, may be steered in the wrong direction toward inferior treatments because clinical trials showing the inefficiency of certain drugs, for example, may never have been published. In addition, the transparent sharing of knowledge might avoid the waste of researchers' time and resources spent on redundant projects.

The scope of the ClinicalTrials.gov was further expanded after the passage of the Food and Drug Administration Amendments Act (FDAAA 801) in 2007, which requires the sponsors of all interventional phase II to IV studies under FDA jurisdiction to register no later than 21 days after participant enrollment and report summary results (including adverse event information) no later than 1 year after the trial's primary completion day.³ The FDAAA expanded the list of studies and required documentation. Both registration and results are reported via the Protocol Registration System (<http://prsinfo.clinicaltrials.gov>).

The ClinicalTrials.gov basic results database was launched in September 2008.³ Additionally, the law included provisions for fines and penalties to be imposed for not complying with registration, including fines of \$10,000 per day and withholding of National Institute of Health (NIH) grant funding.⁴

To further eliminate publication bias, the International Committee of Medical Journal Editors (ICMJE) required registration of all interventional studies around the world in the ClinicalTrials.gov or World Health Organization (WHO) primary registry to qualify for publication in journals that followed the ICMJE's Uniform Requirements for Manuscripts in 2005.⁵ The requirement includes registration of interventional phase I to IV studies prior to enrollment of first participant. This landmark decision sparked a dramatic increase in registration in 2005.⁶ The requirements set by the 11 voluntary members of the ICMJE are followed by hundreds of journals around the world. However, ICMJE has no verification process to ensure that these requirements are truly being met.⁷

Based on recently published reports,^{8–12} it appears that patients, researchers, and clinicians are unable to gain maximum benefit out of the registry database. Incomplete and deceptive clinical trials data hinder the ability of the health care providers to deliver the best evidence-based care to patients. Studies have reported that between 25% to 50% of drug trials remained unpublished more than 5 years after approval by the FDA.^{13,14} For example, clinically important results on the safety and efficacy of erythropoiesis stimulating agents, antidepressants, and rosiglitazone were not published in the medical literature and caused public uproar.^{15–17} It is extremely challenging for the clinicians to choose an appropriate therapeutic modality, because less than 15% of the major guideline recommendations are based on high-quality evidence.^{12,18–21} Often the guidelines are based on trials with smaller sample sizes and inappropriate study designs or outcome measures.

The creation of ClinicalTrials.gov filled a long-awaited need for an effective assessment of clinical trials. Currently, 1,300 new clinical trials are registered on ClinicalTrials.gov every month, and the registry contains information on over 100,000 trials.⁸ ClinicalTrials.gov accounts for more than 80% of all trials registered in the WHO's International Clinical Trial Registry Platform.¹² Between 2004 and 2011, the information on clinical trials increased almost 10-fold.^{8,22} This is undoubtedly a profound achievement since the passage of FDAMA in 1997. However, registries are only useful when the records are valid, accurate, and complete. First, we need to address the under-registration of trials on the site. Thirty-nine percent of clinical trials are registered late, even after the mandate's deadline.¹⁷ Additionally, the recent trend in which more clinical trials are being conducted overseas has added to the complexity, because US federal mandates have no jurisdiction over other countries.¹⁷ Second, more stringent and strongly enforced registration requirements will likely be necessary to decrease the incidence of incomplete reports, catch retrospective changes to study results, and increase the reporting of important findings that may otherwise go unnoticed. Most importantly, the trial sponsors are morally obligated to furnish complete and meaningful reports for the sake of patients who take a significant health risk to participate in clinical trials. Full disclosure of trial results, regardless of positive and negative outcomes, is the only reward for the great sacrifice made by the participants of clinical studies. The trust between study participants is severely compromised when the results are hidden and never published, and it affects future participation as well. Third, adequate resources and funding should be provided to build a seamless structure to support the goals of the law. Fourth, we need to find ways to fully enforce the standards set by the ICMJE for both ICMJE member and nonmember journals. A recent study reported timely registration of 60% (272/451) of published articles in 5 ICMJE founding journals between 2010 and 2011. The study also showed an improving trend for trials that were initiated in later years, as 89% of the trials initiated in 2008 and onward were registered within the time frame required by the FDAAA.²³ The improvement over the years shows remarkable progress. However, there is no process to evaluate the compliance by hundreds of other journals claiming to adhere to the ICMJE standards. Compliance should be the benchmark

for publication of any trial data in a journal. Additionally, we need to explore avenues to enforce the same guidelines for the vast number of journals that are not members of the ICMJE. Fifth, the providers should be required to complete comprehensive training on reporting of data elements in a precise manner that allows the readers to easily interpret the results. The responsible individual for reporting must be familiar with the study design and data elements to ensure accurate reporting of study results. Sixth, the search engine used by the ClinicalTrials.gov needs to add synonymy to Medical Subject Headings (MeSH) for easy navigation by a patient who may not be familiar with MeSH terms. Last, penalties for failing to submit trial results need to be reevaluated for effectiveness.

The establishment of ClinicalTrials.gov was undoubtedly a step in the right direction in ensuring transparency of reporting of clinical trial results in a timely manner. However, despite the new regulations and requirements, there is much work to be done in ensuring that the site meets its goals. We have accomplished a lot since 2000, but now is the time to strengthen reporting requirements for studies registered with the ClinicalTrials.gov to close the gaps between guideline-based treatment recommendations and the evidence derived from clinical trials that serve as the foundation of those recommendations. This will be a step in the right direction to deliver cost-effective, high-quality care to our patients. Timely dissemination of accurate clinical trial results will create the transparency needed to protect our patients from harm.

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