EDITORIALS

Transparency for Clinical Trials — The TEST Act

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In the past few years, registration of clinical trials in a publicly accessible database has become routine. In the United States, much of the impetus for registration derives from the Food and Drug Administration Amendments Act of 2007 (FDAAA). As a result of this law and other actions,[1,2] most interventional clinical trials conducted in the United States have been registered at ClinicalTrials.gov, where, in most cases, the trial results must also be reported. The curators of the database have designed a simple tabular format in which the characteristics of the participants enrolled are reported in one table, the key primary and secondary outcomes in a second table, and adverse events in a third table. Journals adhering to the International Committee of Medical Journal Editors guidance for manuscripts submitted to biomedical journals[3] have made it clear that reporting results in this fashion will not be considered prepublication of submitted manuscripts.[4] One of the purposes of trial registration is to provide a third-party storehouse of trial designs and results. However, for this resource to be of value, it is important that the entire portfolio of clinical trials be in the database.

But there are loopholes in FDAAA that have made it possible for some entities to conduct clinical trials without registering them or reporting the results. On August 2, 2012, Representative Edward Markey (D-MA) introduced into the U.S. Congress the Trial and Experimental Studies Transparency (TEST) Act (H.R. 6272) to close these loopholes. The TEST Act expands reporting requirements under existing federal law by broadening the scope to include all interventional studies of drugs or devices, regardless of phase (i.e., including phase 1), design (i.e., including single-group trials), or approval status (i.e., making no distinction between trials of approved vs. unapproved products); requiring all foreign trials that are used to support marketing in the United States to be registered; mandating results reporting for all trials within 2 years after study completion (including trials of unapproved drugs or devices); and extending results reporting to include the deposition of consent and protocol documents approved by institutional review boards.

This legislation is important. The bill requires that any trial that could be used to support an application for FDA approval be registered in ClinicalTrials.gov and that the results be reported in a timely fashion. It requires that early-phase trials (those in which a drug is initially tested in humans) be registered. Thus, these trials will become public knowledge.

The bill also requires that results be reported whether the drug is submitted for FDA approval by the manufacturer or not. For example, in a case in which a novel therapeutic strategy is associated with adverse outcomes, information about these outcomes would be in the database, even if the product were subsequently abandoned by the manufacturer. That way, if another entity pursued the same treatment approach with a different intervention, the trial designers would be aware of the potential dangers and could develop means for monitoring and mitigating the potential toxic effects.

Consider the disastrous results obtained when studies were conducted with an anti-CD28 antibody.[5] All the healthy volunteers injected with the agent fell ill, some gravely ill, within minutes after receiving the treatment. Given that this trial did not need to be registered in a public database, would the data have become public knowledge if the volunteers had not been admitted to a public hospital? By requiring both registration and results reporting, the government would ensure that the data accrued became part

of the public record and could guide further work in a given area.

Another provision of the TEST Act would require that trials conducted outside the United States, but used to support an application to the FDA, be registered and that their results be reported in the database in a timely fashion. This provision would ensure that the participants who put themselves at risk to test new treatments see the fruits of their altruism in the public domain. Simply put, a trial could be moved offshore but could not be hidden.

We can make progress in medicine only if people are willing to put themselves at risk to test new diagnostic and therapeutic approaches. To recognize and reward these participants, and in keeping with the Declaration of Helsinki, clinical trials should be conducted in the open, with full public knowledge of the question asked, the intervention tested, and the results obtained. The TEST Act is another step toward this end, and we strongly support it.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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Lifelong Management of Amyloid-Beta Metabolism to Prevent Alzheimer's Disease

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Twenty-five years ago, the cloning and localization to chromosome 21 of the Alzheimer's amyloid-beta (Aβ) precursor protein (APP)[1] made clear that the early-onset form of Alzheimer's disease that occurs in all patients with Down's syndrome[2] is apparently attributable to an extra copy of *APP*. Proamyloidogenic *APP* missense mutations were subsequently identified in families with autosomal dominant Alzheimer's disease,[3] and a substantial proportion of cases of autosomal dominant Alzheimer's disease have been linked to more than 200 proamyloidogenic mutations in the catalytic subunits of γ-secretase (known as presenilin 1[4] and 2[5]) that are responsible for the liberation of Aβ from APP.

By 1999, Aβ-depositing transgenic mice had been vaccinated with Aβ and were found to form anti-Aβ antibodies that could prevent cerebral amyloidosis.[6] The first clinical success in humans was reported in 2003 in a postmortem study showing that vaccinated participants had extraordinarily sparse levels of cortical amyloid plaques.[7] In 2010, passive immunotherapy with a monoclonal anti-Aβ antibody was shown to retard the progression of the carbon 11–labeled Pittsburgh compound B (PIB)–positive fibrillar cerebral amyloid burden by 15 to 25%.[8] However, this modest reduction in plaque burden was associated with no obvious clinical benefit or arrest in the progression of cognitive decline. A larger study with the same monoclonal anti-Aβ antibody but with more power for detecting treatment effects confirmed the absence of clinical benefit.[9]

The absence of cognitive benefit may have been because the modest reduction of PIB-positive fibrillar amyloid was insufficient to effect substantial retardation of neurodegeneration or because anti-Aβ monoclonal antibody treatment was too late. There is growing interest in Aβ-lowering therapies for presymptomatic disease.[10,11] In this issue of the *Journal*, Bateman et al.[12] report findings from a study focusing on imaging and biomarker assessments in presymptomatic autosomal dominant Alzheimer's disease, called the Dominantly Inherited Alzheimer Network (DIAN) study.

In collaboration with the DIAN investigators, Bateman and colleagues identified, clinically characterized, and followed (by means of imaging and measurement of body-fluid biomarkers) many of the families with autosomal dominant