

Trial Registration

A Great Idea Switches From Ignored to Irresistible

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IN A RECENT ARTICLE IN *JAMA* ON THE REGISTRATION OF clinical trials,¹ Dickersin and I pointed out that, 30 years after the idea of registering trials had been proposed, 18 years after registration of trials at inception had been shown to eliminate publication bias, and despite the presence of numerous trial registers large and small, Manheimer and Anderson² were correct in stating that “No comprehensive system for tracking, organizing, and disseminating information about ongoing clinical trials currently exists.” We described a profound confusion about even the most basic data from, or existence of, clinical trials. Only half of the million or so trials conducted over the past 56 years are likely to have been reported,¹ and of those reported, a substantial proportion did not appear in MEDLINE.

One consequence of this lack of reporting is a persistent bias in favor of positive results and therefore in favor of the newer and more expensive treatments. Another consequence is that harmful effects found in unpublished trials disappear without a trace, since the US Food and Drug Administration (FDA) has no mandate to report them to the public. The bad news about new drugs is disseminated later than the good news or not at all, resulting in widespread publication and outcome bias and in direct and widespread harm to patients.^{3,4}

Because existing laws requiring registration were ignored in the case of commercially sponsored trials, we urged that the law be changed to make mandatory the registration of all trials in all conditions, using an adequately funded and supported national registry such as <http://www.clinicaltrials.gov> or the ISRCTN register.¹ We recommended that the law operate through institutional review boards (IRBs) and that journals also require registration before publishing trials.

The issue is fundamentally an ethical one. Should the results of trials be regarded as “highly proprietary,” a view espoused by the manufacturers who pay for the trials?⁵⁻⁷ Or are trial results essential information for patients and their physicians—information gleaned from studying patients who might have been less willing to participate had they known

the results would be treated as trade secrets and often never made public?

RECENT DEVELOPMENTS

On June 2, 2004, Eliot Spitzer, the attorney general of the State of New York, sued GlaxoSmithKline (GSK), makers of the selective serotonin reuptake inhibitor (SSRI) paroxetine (Paxil).⁸ Shortly thereafter, the Medicines and Healthcare Products Regulatory Agency in the United Kingdom launched an investigation of GSK.⁹ The events leading to this legal action provide a good illustration of the importance of early registration and transparency in clinical trials.

During the year prior to the suit, debate had raged in the United Kingdom and the United States over whether children with major depressive disorder (MDD) had an increased risk of suicide if given particular SSRIs and whether these drugs were more effective than placebos. It seemed that data on SSRIs were suppressed when the existence of an internal memo written in 1998 (Central Medical Affairs team (CMAt)—Division of SmithKline Beecham, October 1998) concerning the preparation of a full report of a SmithKline Beecham trial of paroxetine was disclosed in March 2004.¹⁰ (SmithKline Beecham later merged with Glaxo Wellcome to form GSK.) The memo stated that 2 trials failed to demonstrate any separation from placebo, and it continued, “It would be commercially unacceptable to include a statement that efficacy had not been demonstrated, as this would undermine the profile of paroxetine.”¹⁰

Shortly afterward, Whittington et al¹¹ published a careful review of published and unpublished data on the risks and benefits of SSRIs. These authors concluded that, whereas “Published data suggest a favourable risk-benefit profile for some SSRIs,” the “addition of unpublished data indicates that risks could outweigh benefits of these drugs (except fluoxetine) to treat depression in children and young people.”¹¹ The authors added that when drawing up guidelines for the treatment of depression in young individuals, they had contacted all the relevant manufacturers requesting unpublished data but that such data were not forthcoming.¹¹ Given that it was difficult to conclude that paroxetine was any better overall than placebo, physicians in the United Kingdom were ad-

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vised by the UK's Committee on Safety of Medicines that "paroxetine was contraindicated in patients under the age of 18 with major depressive disorder."¹²

In his suit, Spitzer's chief complaint was that trials of paroxetine to treat childhood MDD, as well as the safety outcomes of other trials, had been hidden from physicians by the manufacturer and thus "GSK deprived physicians of the information needed to evaluate the risks and benefits of prescribing paroxetine for children and adolescents with MDD."⁸ The chief executive officer of GSK responded forcefully in defense of paroxetine¹³—sales of which amounted to \$533 million in the first quarter of 2004¹⁴—but the undoubted existence of the unpublished data and the memo undermined his position.¹⁵

AMA Initiative

Concerned with the issue of data on antidepressants, the American Psychiatric Association and the American Academy of Child and Adolescent Psychiatry had drafted a resolution in 2003, asking the American Medical Association's (AMA's) Council of Scientific Affairs to produce a report on the influence of funding on pharmaceutical research.¹⁶ In June 2004, the AMA House of Delegates, concerned about publication bias, adopted this report and called for the Department of Health and Human Services to establish a comprehensive register of all clinical trials conducted in the United States,¹⁷ with registration to be enforced by IRBs. This initiative attracted considerable attention from the press.¹⁸ At the annual meeting in June 2004, the AMA adopted another resolution, again introduced by the American Psychiatric Association and the American Academy of Child and Adolescent Psychiatry, asking the AMA Council on Scientific Affairs "to study the issue of enhancing access to FDA data regarding safety and efficacy of medications." Since the law prevents the FDA from divulging much information about drugs that are not approved for a given indication, this could be an important step.¹⁹

Pharmaceutical Industry Response

On June 18, 2004, GSK announced a GSK clinical trial register that will provide summaries of trial protocols and corresponding results for GSK-sponsored trials of marketed medicines as well as references to publications.²⁰ A spokesperson said the move was to restore trust in research undertaken by the pharmaceutical industry,²¹ but by not agreeing to disclose the start of trials, the company left open the crucial issue of failure to report negative outcomes.²² Merck & Co has announced that the company will support a government-run register to include late-stage clinical trials or trials after approval,²³ and Johnson & Johnson has said much the same.²⁴

Eli Lilly and Co, makers of fluoxetine, the only SSRI approved by the FDA for use in children with depression, announced a similar move on August 3, 2004.²⁵ The company's online register is to include the design, methods, specified outcomes, and results of all phase 1 through phase 4 clinical

trials of its marketed products, and "the initiation of all Phase III and IV clinical trials."²⁵ For phase 1 to 3 trials, the disclosure will occur on approval of the drug for an indication; for phase 4 trials, disclosure will occur no later than 1 year after completion or after publication in a peer reviewed journal. Lilly also pledges to "continue posting information on the initiation by Lilly of clinical trials for serious and life-threatening diseases via www.clinicaltrials.gov." Significantly, Lilly commits to assigning an "independent third party to audit and verify adherence by Lilly" to their standards.²⁵ If the company follows through, this will be by far the most ambitious register proposed by any pharmaceutical company.

After much delay and resistance, a few manufacturers are finally agreeing that trial registers "could prove useful to both physicians and patients,"²⁴ even though trial registers are still not endorsed in the Pharmaceutical Research and Manufacturers of America (PhRMA) code, updated this summer.^{6,7} It is encouraging that, concerning making the results of clinical trials public, the president and chief executive officer of PhRMA has now written that "PhRMA strongly supports making summaries of these important studies, whether positive or negative, available in a clinical-trials-results database."²⁶ Five years ago,²⁷ Glaxo Wellcome, along with Schering-Plough Health Care, announced plans to register their trials following continued pressure from Sir Iain Chalmers and others in the Cochrane Collaboration.²⁸ However, the companies did not follow through with anything that was useful, permanent, unbiased, and free from the control of those temporarily in charge at the company. Following Glaxo-Wellcome's merger in 2000 with SmithKline Beecham, the register, such as it was, seems to have been abandoned.²⁹

Can Manufacturers Produce a Worthwhile Register?

On May 6, 2003, the Association of the British Pharmaceutical Industry (ABPI) announced that in association with CMR International³⁰ they had set up a voluntary register of "retrospective Phase III and on-going Phase IV clinical trials in the United Kingdom." Fifteen months later, 6 (15%) of the 40 pharmaceutical company clients listed by CMR had posted information about 93 trials involving 44 drugs in the period 1991-2004. The completeness of the information varies widely and often comes nowhere near what was promised in the initial ABPI press release. Information about publication is usually left blank, but in 5 cases (5%) the name of the journal is mentioned, in 1 a press release is referred to, and in 1 a presentation of an abstract is mentioned. Seven of the studies (8%) are specifically marked as "Not for publication." It is a start, but it is not an effective attempt to get at the problem of publication bias or to provide even minimal information on the existence of all clinical trials.

Political Response

The chairman of the Senate Finance Committee has now asked 8 drug companies to turn over their data on antide-

pressants and was, at the time of writing, looking into whether the FDA blocked an internal review.^{31,32} Meanwhile, the House Energy and Commerce Committee is due to hold hearings on the issue on September 9, 2004—hearings that were postponed when James Greenwood, the chair, resigned to join the Biotechnology Industry Organization.³³ The FDA has scheduled a joint meeting of the Psychopharmacologic Drugs Advisory Committee and the newly formed Pediatric Advisory Committee for September 13–14, 2004, to decide on the possible benefits and harms of SSRIs used to treat a condition with a high placebo response rate.^{34–36} The committees will be assisted by the recently published results of a large trial.^{37,38}

This storm over SSRIs is a good demonstration that no clinician can possibly practice evidence-based medicine if prevented from seeing the evidence.³⁴ When that evidence is hidden, especially if the evidence suggests harm to patients, the issue can embarrass and cast doubt on the integrity of the study sponsor, despite all its legal protections. Indeed, in discussing the unpublished trials of paroxetine, Garland³⁴ stated that “there is no requirement that results be published or even made available to investigators. Those researchers, including myself, who *did* see the results of negative paroxetine industry trials were prohibited by nondisclosure contracts from discussing them.”

Meanwhile, the stakes have recently been raised by the FDA, which is pushing to block personal injury suits against manufacturers on the basis that those injured cannot recover damages if the products have been approved by the administration.³⁹ Clearly, this stance will make sense only if the public has access to all the data available to the FDA. Meanwhile, the public is unlikely to accept a solution left to an FDA that is perceived as being subject to the influence of industry.⁴⁰

What Trials Should Be Registered and When?

The worst outcome would be for some companies to fore-stall legislation by announcing individual registers that are obscure, hard to access, idiosyncratic in the sorts of data they post, contain only what marketing departments allow them to contain, and are temporary and dependent on the company's institutional memory and will. Widespread flouting of the law of 1997¹ showed that a central register cannot work unless it is designed to include all trials and not merely those involving some “serious or life threatening” conditions, is adequately funded, is made mandatory, is adequately policed, has substantial penalties for noncompliance, and unless all aspects of the enterprise are taken out of the hands of the pharmaceutical industry.

When sponsors agree to put information about trials into a register, they usually restrict this to phase 3 and 4 trials. But since there is a tendency for even phase 1 trials to be used for gathering data not only on safety but on efficacy as well, trials at all phases should be registered. Entering a trial into a register will do nothing to diminish publication bias if the

register contains only trials that have been completed, found to be favorable to the product, and published. A system must be designed to register all trials (regardless of phase) at inception, so that reviewers can later ask for an accounting. Since there is evidence of selective reporting and deviation from protocols, trial protocols should also be made available.⁴¹ Given the conflict of interest inherent in any decision by sponsors to enter trials into a register, any system must be free of the control of individual sponsors.

The International Committee of Medical Journal Editors Initiative

In this issue of JAMA, there appears a statement by the International Committee of Medical Journal Editors⁴² on registration of trials. The recommendations of the committee seem excellent. But this initiative will work only when all journals cooperate; when IRBs refuse to ratify proposals to conduct trials unless they have first been registered; and, above all, when individual researchers see that the ethical arguments in favor of registration far outweigh any proprietary interest claimed by their sponsors.

CONCLUSION

Physicians and the public are now well aware of the importance of the registration of clinical trials. Indeed, if the pharmaceutical industry and other sponsors had recognized that it is the continued cooperation of the public in their research that enables and legitimizes the research, and if, on that basis, all the pharmaceutical companies had simply agreed to register their trials at inception when urged to do so, they could have completely avoided this medical, political, and public relations fiasco.

The companies are receiving a sharp lesson, and their self-interest seems to be convincing some of them that registration is wise. Progress is being made, but previous experience suggests that, because of inherent conflicts of interest, it is unlikely that industry will ever be able to establish a large, common, complete, useful, trustworthy, up-to-date, and easily accessible register maintained over the long term. Experience also demonstrates the enormous costs of not knowing about trials that bury data showing lack of benefit and that hide the harms of new treatments. The financial cost of an effective, independent, and transparent clinical trial register would amount to a tiny fraction of the costs of the trials themselves, or the costs of not knowing their results, while the personal costs of allowing the present chaotic system to continue are incalculable.

Addendum

On August 26, 2004, New York Attorney General Eliot Spitzer announced a settlement whereby GSK committed to putting summaries of the results of all GSK-sponsored clinical trials of drugs into a clinical trials register, posted on the Internet and conspicuously identified on the home page of the GSK Web site.⁴³

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