

Setting the RECORD Straight

Steven E. Nissen, MD

THE FOOD AND DRUG ADMINISTRATION (FDA) recently announced another Advisory Panel scheduled to meet in July 2010 to consider whether or not to remove rosiglitazone from the market. Central to the discussion will be the results of a recently published cardiovascular outcomes trial that randomized patients to receive rosiglitazone or alternative diabetes therapies, the RECORD trial.¹ On February 20, 2010, the US Senate Finance Committee released a 334-page investigation of rosiglitazone and drug maker GlaxoSmithKline (GSK).² The documents released by the Senate include internal company e-mails that provide an extraordinary window into the conduct of an industry-sponsored clinical trial. The implications of these e-mails and other documents released by the Senate have profound consequences for academic oversight of commercially sponsored clinical trials.

On May 1, 2007, Wolski and I submitted for publication a meta-analysis of 42 randomized rosiglitazone clinical trials, showing a hazard ratio (HR) for myocardial infarction (MI) of 1.43 (95% confidence interval, 1.03-1.98, $P=.03$).³ On May 2, the journal sent the manuscript for review and on May 3, an academic reviewer faxed the draft manuscript (in violation of journal rules) to GSK with a cover page marked “confidential” and “urgent.”^{2(p5)} Rather than destroying the inappropriately obtained manuscript, GSK embarked on a comprehensive internal analysis of the study, circulating the manuscript among more than 40 scientists and executives at the highest levels of the company.^{2(p3, footnote 30)} Within a few days, company statisticians concluded that “there is no statistical reason for disregarding the findings as presented.”^{2(p6)} It is also apparent from internal e-mails that the company and FDA had already come to similar conclusions. The director of research at GSK commented, “FDA, Nissen, and GSK all come to comparable conclusions regarding increased risk for ischemic events, ranging from 30% to 43%!”^{2(p6)}

Faced with the potential loss of revenue for a drug that had reached more than \$3 billion in annual sales, company officials, in internal e-mails, proposed a strategy to preserve the company’s market share.^{2(p3)} GSK management de-

cidated to unblind and publish the ongoing RECORD trial, an extremely unusual procedure that would seriously undermine the statistical validity and credibility of the final trial results. In e-mails, the company officials extensively discussed unblinding the trial. One official wrote, “My personal view is that short pub of the planned safety interim is warranted (as is) followed in short order by what might be coined as an orderly close out of the main phase of the trial and that accompanying full publication (sic).”^{2(p180)} But the company faced a dilemma. Although the RECORD study was an industry-controlled clinical trial, the company had appointed an academic steering committee to oversee the study. It is always expected that such oversight includes authority over critical decisions about trial conduct and reporting of results.

However, internal GSK e-mails proposed a strategy for handling the steering committee. On May 24, 2007, one official wrote, “if the SC believe that publishing interim data will fatally damage their ability to bring the study to a completion,” GSK will inform them “that a decision has been made, live with it.”^{2(p184)} Fortunately for GSK, the steering committee was convinced to publish an interim analysis, even though the analysis was so underpowered that no conclusions could be drawn about the safety of rosiglitazone.^{4,5} The steering committee never knew that GSK had actually already unblinded the study 2 weeks earlier.^{2(p181)} These physician-scientists apparently believed it was their decision (not the company’s) to unblind the study and publish the interim results.

The company faced yet another dilemma: what to do about the pending meta-analysis manuscript.³ The company scheduled an appointment to visit me on May 10, 2007, in Cleveland, 11 days before our meta-analysis was published.³ The 4 GSK scientists and executives with whom I met had full knowledge of the content of our manuscript, although they never hinted that they had inappropriately obtained a copy of the confidential manuscript (as a result of the ethical breach by the peer reviewer who sent the manuscript to them).⁶ At the time, I was aware that the company had previously threatened

Author Affiliation: Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio.

Corresponding Author: Steven E. Nissen, MD, Department of Cardiovascular Medicine, Cleveland Clinic Foundation, 9500 Euclid Ave, Cleveland, OH 44195 (nissens@ccf.org).

For editorial comment see p 1196.

and intimidated an independent physician-scientist who criticized rosiglitazone,⁷ so I sought to protect myself by secretly taping the meeting, which is legal in Ohio.⁶ The recording revealed that during the meeting, a GSK executive said, “let’s suppose RECORD was done tomorrow and the hazard ratio was 1.12.”⁶ This comment was made 4 days before the company claims it unblinded the trial and 14 days before the steering committee was asked to approve unblinding.⁶ The actual hazard ratio reported in the published interim analysis was 1.11.⁴ This exchange raises the question of whether unblinding of the study by the company had compromised the integrity of the data for the RECORD trial.

After the decision to unblind the trial, another series of e-mails documented discussions regarding the content of the RECORD trial interim analysis manuscript. Some of the academic authors pushed back at the attempts by the company to present this manuscript in a way so as to limit the harms associated with rosiglitazone. In an e-mail message to GSK employees and fellow steering committee members, one of the authors wrote, “The HR ratio (and 95% CI) for MI in RECORD is not inconsistent with Nissen’s—and he had more events.”^{2(p197)} This author also stated, “Manuscript looks to downplay the 239 percent INCREASE in HF.”^{2(p197)} However, according to documents in the Senate Finance Committee report, the final manuscript was so strongly supportive of the drug that, after obtaining reviews, the journal editors wrote the following: “The editors feel strongly that your data do not support the statement that the RECORD results for MI contradict the Nissen meta-analysis; this statement must be removed or modified.”^{2(p201)}

When the final RECORD manuscript was published 2 years later, there remained additional concerning inconsistencies.¹ The event rate for MI was extremely low (about 0.5% per year), less than one-third the rate observed in a similar trial conducted with pioglitazone, suggesting that most MIs were never ascertained.⁸ The manuscript claimed that rosiglitazone was administered during 88% of potential person-years of follow-up, but in response to questions from journalists, the company acknowledged that 40% of patients were no longer taking the drug by the end of the study.⁹ Indeed, at the time of the interim analysis in 2007, the authors reported that 27% of patients in the rosiglitazone treatment group were no longer taking the assigned medication.^{4,9} Thus, the reported 88% overall adherence is mathematically implausible. This is a critical issue because, in a safety study, if patients are not actually taking the drug or cross over to the alternative treatment group, the HR converges on 1.0. Another factor that may have affected the outcomes was a significant imbalance in statin administration ($P = .01$) favoring the rosiglitazone group.

The experience with RECORD raises important questions about the conduct of industry-sponsored clinical trials. There are 2 general approaches to academic gover-

nance. In one approach, the steering committee is composed of academic investigators and has full access to all of the study data and reports. In another approach, the steering committee is appointed by the company, but the clinical trial database is exclusively controlled by the company and “access” provided to the investigators. In general, this means that the authors can send queries to the company, but the steering committee does not have a copy of the database and no outside statistician has independent access to the raw data. Although the final RECORD articles report that external statistical confirmation was obtained,^{1,4} the extent and depth of these confirmatory analyses remain uncertain.

As illustrated by the problems with the RECORD trial, absence of independent access to all of the data in the trial may allow physician-scientists to be manipulated by the sponsor, resulting in a manuscript that does not provide the most accurate assessment of the risks and benefits of the therapy. Some medical journals require independent outside statistical confirmation of trial results.¹⁰ Although this procedure does not guarantee the integrity of the resulting manuscript, it is an essential step and should be universally mandated. If all journals adopted such a policy, the quality of reporting of industry-sponsored clinical trials would be significantly improved.

Financial Disclosures: Dr Nissen reports that the Cleveland Clinic Coordinating Center for Clinical Research has received research support to perform clinical trials from Pfizer, AstraZeneca, Sankyo, Takeda, Sanofi-aventis, Lilly, Roche, Daiichi-Sankyo, and Novartis. Dr Nissen consults for many pharmaceutical companies, but requires them to donate all honoraria or consulting fees directly to charity so that he receives neither income nor a tax deduction.

REFERENCES

1. Home PD, Pocock SJ, Beck-Nielsen H, et al; RECORD Study Team. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet*. 2009;373(9681):2125-2135.
2. Staff Report on GlaxoSmithKline and the Diabetes Drug Avandia. Prepared by the staff of the Committee on Finance, United States Senate, Max Baucus, Chairman, Chuck Grassley, Ranking Member. <http://finance.senate.gov/press/Gpress/2010/prg022010a.pdf>. Accessed March 3, 2010.
3. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes [published correction appears in *N Engl J Med*. 2007;357(1):100]. *N Engl J Med*. 2007;356(24):2457-2471.
4. Home PD, Pocock SJ, Beck-Nielsen H, et al; RECORD Study Group. Rosiglitazone evaluated for cardiovascular outcomes: an interim analysis. *N Engl J Med*. 2007;357(1):28-38.
5. Nathan DM. Rosiglitazone and cardiotoxicity: weighing the evidence. *N Engl J Med*. 2007;357(1):64-66.
6. Harris G. A Face-off on the safety of a drug for diabetes. *New York Times*. <http://www.nytimes.com/2010/02/23/health/23niss.html>. February 22, 2010. Accessed March 3, 2010.
7. The Intimidation of Dr. John Buse and the Diabetes Drug Avandia. Committee Staff Report to the Chairman and Ranking Member, Committee on Finance, United States Senate. <http://finance.senate.gov/press/Bpress/2007press/prb111507a.pdf>. November 2007. Accessed March 3, 2010.
8. Psaty BM, Prentice RL. Variation in event rates in trials of patients with type 2 diabetes [published correction appears in *JAMA*. 2010;303(8):734]. *JAMA*. 2009;302(15):1698-1700.
9. Stiles S. Avandia on the RECORD: No “overall” CV risk increase, but trial remains controversial. <http://www.theheart.org/article/976685.do>. June 5, 2009.
10. Fontanarosa PB, Flanagin A, DeAngelis CD. Reporting conflicts of interest, financial aspects of research, and role of sponsors in funded studies. *JAMA*. 2005;294(1):110-111.