

EDITORIALS



Don't Mess with the DSMB

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If the lyrics of the popular Jim Croce song from the early 1970s were adapted for a clinical trialist anthem, the refrain would likely be

You don't tug on Superman's cape
 You don't spit into the wind
 You don't pull the mask off that old Lone Ranger
 And you don't mess around with the DSMB.

Since the DSMB (data and safety monitoring board) is charged with ensuring that clinical equipoise is maintained as trial data are accrued, it is considered very bad, even self-destructive, behavior for people who are involved with the study to interact with DSMB members on trial-related issues. Traditionally, there has been a wall between investigators, sponsors, and the DSMB. This wall prevents preliminary findings from leaking out in ways that would prejudice the trial. For example, if it was known that the DSMB was examining a marginal increase in cardiovascular risk in a trial, then trial investigators might bias future recruitment by excluding patients at risk for such events. In the proper performance of clinical trials, you “don't mess around with the DSMB.”

Recently, a new type of problem has emerged that puts the integrity of the whole clinical-trial enterprise at risk. Two examples of this problem have appeared in the *Journal* in the past few years. In these cases, the integrity of the DSMB has been thwarted or violated.

In May 2007, we published a meta-analysis of randomized clinical trials showing an increased risk of cardiovascular adverse events among patients with diabetes who were receiving rosiglitazone, as compared with patients who were not receiving the drug.¹ Shortly thereafter, the drug's manufacturer, GlaxoSmithKline, went around the steering committee and the DSMB of an ongoing trial known as the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial (ClinicalTrials.gov

number, NCT00379769), an open-label comparison of antidiabetic regimens with and without rosiglitazone, and conducted an interim analysis of the trial data. We published that analysis in June 2007² but were not fully aware of GlaxoSmithKline's manipulations until February of this year.³

What should have happened? The DSMB should have been informed of our May 2007 article and checked the trial data to be sure that patients receiving rosiglitazone in the RECORD trial were not having adverse events at an unacceptable rate. If clinical equipoise was still in play, the trial should have been allowed to continue undisturbed (i.e., without publication of the RECORD interim analysis), without public comment from the DSMB, without communication with investigators, and without disturbing the integrity of the trial. On the other hand, if in the opinion of the DSMB equipoise no longer existed, then the trial should have been terminated — that is the way it is supposed to work. The DSMB protects the participants in a trial.

The second example concerned the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial (NCT00092677), which was designed to determine whether the cholesterol-lowering agent ezetimibe had a salutary effect in patients with aortic stenosis. Analysis of the data from the SEAS trial suggested an imbalance in incident cancers and cancer deaths among patients receiving ezetimibe and simvastatin as compared with those who were not receiving the drugs.⁴ The sponsors, Merck and Schering-Plough, appear to have interacted with the investigators and the DSMBs in two ongoing trials of ezetimibe, the Study of Heart and Renal Protection (SHARP) trial (NCT00125593) and the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT, NCT00202878), which resulted in the unblinding of data on cancer outcomes in these trials. In 2008, we published the outcome of this analysis⁵ but were not fully aware of the

role of the trial sponsors and the extent of the interactions that had occurred among the sponsors, the DSMBs, and the trial investigators until we received information from one of the authors, outlining the process and the considerations that went into the unblinding of the data.⁶ In our opinion, the process should have maintained the primacy of the DSMBs of the SHARP and IMPROVE-IT trials: the sponsors should have informed the DSMBs about the cancer imbalance in the SEAS trial and allowed the DSMBs to perform the required analyses to determine whether clinical equipoise continued to exist. If it did, the trials could have continued without disturbing their integrity and with only a statement to that effect.

Given these experiences, the *Journal* will in the future carefully examine the independence of DSMBs when manuscripts are submitted that involve decisions that should appropriately have been taken by an independent DSMB. Examples include manuscripts reporting early stopping of a trial because of efficacy or toxicity and manuscripts reporting interim analyses of data.

In both of the examples we describe, a commercial entity decided to unblind aspects of trial data rather than let the DSMBs exercise their important and appropriate responsibilities both to the trial participants and to the wider community. Recently, the advocacy group Public Citizen called for the Food and Drug Administration to stop the Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE) trial (NCT00879970), an ongoing comparison of rosiglitazone and pioglitazone in the treatment of type 2 diabetes. Public Citizen has argued that clinical equipoise no longer exists, because in its opinion the data are overwhelming that the cardiovascular safety profile of rosiglitazone is inferior to that of pioglitazone. Certainly, this is a matter for members of the trial's DSMB to consider. They alone should be privy to the data from the trial as it unfolds and will know whether an imbalance in outcomes exists; they should be deciding whether the trial continues, not third parties unassociated with the trial.

These and other episodes have undermined public confidence in the ability of trials to operate independently of the sponsor. The current way that DSMBs are constituted and report has resulted in a loss of faith. First, many commercial entities, as illustrated by the above-mentioned examples, have not given the DSMB the indepen-

dence such a panel requires. Second, outside parties view the DSMB as serving the trial sponsor rather than the selfless volunteers who put themselves at risk to advance our medical knowledge.

We propose fundamental changes in the way DSMBs are constituted, are funded, and report, regardless of whether there is a commercial or a public sponsor. When a DSMB is part of a trial plan, it should be chosen and convened under the aegis of an independent public body, such as the Reagan–Udall Foundation, the Foundation for the National Institutes of Health, or a similar body. The sponsor would provide funding to the third party, which would be responsible for choosing the DSMB members, supervising the panel's activities, and ensuring its integrity. To prevent sponsors from interfering with an ongoing study, the trial steering committee would report only to the DSMB.

Naysayers will argue that such a proposal is naive and impossible to implement. We respond by pointing out that the single most important component of any clinical trial is the trust and goodwill of its participants. This arrangement would put the well-being of the participants where it belongs, under the close watch of a DSMB, whose commitment would be solely to the participants. Such an arrangement would substantially enhance the perceived safety of participation in a clinical trial. For too long, sponsors of trials have considered the DSMB a necessary nuisance whose strings they can pull at will. It is time to remember that you don't mess around with the DSMB.

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