Safety concerns

In June 2011, The Spine Journal (TSJ) published an article entitled “A critical review of rhBMP-2 trials in spinal surgery: emerging safety concerns and lessons learned.” The impetus for this retrospective review was an obvious disconnect: on one hand were 13 published articles regarding company-sponsored studies none of which reported any recombinant bone morphogenetic protein 2 (rhBMP-2)–associated adverse events or complications and on the other hand TSJ alone had a backlog of nearly 40 articles submitting a range of serious complications apparently associated with BMP-2 use; an additional half-dozen letters of complaint from surgeons involved in these clinical trials claiming clear BMP-2 complications in their own patients; and Food and Drug Administration (FDA) findings associating BMP-2 with the development of new malignancies and other life-threatening complications.

What accounted for this disconnect? Three of this editorial’s authors (EJC, ELH, BKW) tried to address this question by reviewing original data summaries available from the FDA or other public sources on as many of the published trials as possible. Our review discovered that rhBMP-2 appeared to work no better than iliac crest bone graft for fusion but that the potent growth factor did appear to have a number of potential drug- and implant-associated adverse events, including some very serious complications. Comparing our review with the published findings from the company-sponsored trials that had used the “same data,” it was concluded that those early journal publications may not accurately represent the effectiveness and harms of rhBMP-2.

The firestorm that followed is well known. The critical review and accompanying editorial were seized on by media, patient advocacy groups and, inevitably, litigation attorneys. Our review was praised by some authors of the original articles yet displeased others who aggressively defended their work and at times personally attacked the authors of the critical review. The Spine Journal special issue became part of an ongoing Senate Finance Committee investigation, whose findings in October 2012 suggested that significant potential financial conflicts of interest existed between the sponsors and some of the original study authors, up to tens of millions of dollars, and, in some cases, went undisclosed in the publications. The Senate report also suggested that there may have been inappropriate ghost writing, deletion of specific adverse-event data, and instances in which the company appeared to edit or author parts of the articles without attribution.

The combination of the FDA concerns of BMP-2–associated cancer and life-threatening complication concerns, the TSJ special issue, and the Senate Report stimulated a reassessment of BMP-2 use and potential early reporting bias. At professional conferences (including OREF, AAOS, AOA, and NASS), the spine surgery community presented symposia and debates specifically devoted to the subject.
What was not always in sight during this melee was the most important issue “patient safety.” To its credit, Medtronic funded $2.5 million to allow for the independent assessment by Yale University of the totality of rhBMP-2–related data. The “Yale University Open Data Access” (YODA) project, under the leadership of Harlan Krumholz, MD, asked the independent assessments to be carried out at two centers known for their expertise in systematic reviews—Oregon Health and Sciences University and the University of York (UK).

The results of these groups’ independent assessments were published in mid-June in *Annals of Internal Medicine* along with several editorials. The YODA findings confirmed the *TSJ* findings and, indeed, identified several additional research problems including the apparent misrepresentation of effectiveness and safety in the early articles through selective and incomplete reporting and the fact that the research design limited the ability of the studies to precisely assess safety. They concluded that “rhBMP-2 provided little or no benefit compared to bone graft and may be associated with more harms, possibly including cancer.” They could identify no clear indication for using rhBMP-2, including its “on-label” approved use. They also suggested that the Medtronic-associated authors had “misrepresented” efficacy and underreported complications “for both on-label and off-label indications” and “selected analyses and results that favored rhBMP-2 over ICBG.” The YODA findings not only appeared to confirm the findings of *TSJ*’s critical review of 2011 but also go further.

**Lessons learned**

There is much to be learned by all parties now that the firestorm has abated. Some of which is about rhBMP-2 in particular, but much more is about moving forward with other emerging technologies. Here are a few take-home points:

- For patients: Recent surveys suggest that surgeon’s financial relationships are not a concern to patients. Indeed, some patients appear to be “impressed” that such relationships somehow suggest expertise. Patients should be educated that these scenarios are often the final common pathway of direct and indirect pharma/device company money filtered to surgeons and aimed at garnering business with or without a legitimate evidence base for support. Surgeons in such relationships simply cannot be universally expected to serve as impartial partners in the shared decision-making process or as arbiters of informed consent.

- For readers of articles: The scientific literature on bias (because of financial conflicts of interest) in company-sponsored publications is ever expanding. The authors’ biases can be conscious or unconscious, but studies on reciprocity suggest they are almost always present. Unless the totality of patient-level data has been independently assessed, by independent reviewers such as YODA, editorial review boards, and so forth, it should not be trusted. Ed Hanley, MD, after a debate on these issues at AOA this year, suggested that the real solution is to have a separate journal for company-sponsored trials, so that the readers know what they are getting.

- For journal editors: Journal editors should increasingly require full access to data (eg, *BMJ*), in some cases down to the individual case level if necessary. Otherwise, company-sponsored articles should not be published without substantial critical review. Although, ideally, editors should have no conflicts of interest, they should recuse themselves when applicable.

- For authors working with companies: The development of novel truly beneficial treatments is an important part of what high-quality medical research is all about and those involved should profit financially. However, once a developed product reaches the stage of needing to demonstrate clinical efficacy and safety, those with financial conflicts should recuse themselves and allow independent trials to be undertaken. Most academic medical center institutional review boards now have this as a policy.

- For companies: Once clinical efficacy and safety are to be assessed, involved surgeons and authors must be independent of conflicts of interest and must be independent to access, control, and publish their data and findings freely. Trial methodologies should be published a priori and the data open and available (at least to some third party) throughout the process.

- For the FDA: The BMP-2 saga raises again the persistent question whether the panel system for approval as currently employed is the best way to do this. Should there be transparent mechanisms to compare published articles to FDA data? Some responsibility for a decade of risky rhBMP-2 use must rest here.

- For potential users of rhBMP-2: Some reasonable-use scenarios have been suggested but continue to be based on speculation or very low levels of evidence. The best evidence may be for use in anterior lumbar interbody fusion when there is an insufficient native graft available, neither retrograde ejaculation nor cancer concerns, and very low doses are sufficient. There is less evidence for use in posterolateral lumbar fusion involving multilevels when there is a high risk of pseudarthrosis and, again, little cancer risk. In all patients, there is a need to understand that the risks of malignancy are unclear, and each patient should have a full understanding/informed consent of the risks and paucity of data for clear benefit. These indications may be reasonable, but we note that some of the YODA authors and the *Annals* editors suggest that there may be no clear indications for use.

- For the research system: The YODA findings suggest that the entire research system, at least for
commercial products, has broken down in a fundamental way and needs to be redesigned. After more than a decade of high-profile research, “no one seems to have known” what the full body of data on rhBMP-2 actually said: not the FDA, not the sponsored researchers, not the incoming CEO of Medtronic, not the research and development team at Medtronic, and certainly not the authors of the TSJ review. This is, perhaps, the ultimate disconnect. It provides the clearest argument for reform of the current system and open access to data, to protect the health and safety of patients, and the ability of health-care providers to provide humane and effective treatment. The BMP-2 issue is just the most recent example (eg, Vioxx, Tamiflu, Paxil, Avandia) to show that questionable behavior has been going on in medical research for years, resulting in publication/reporting bias, biased systematic reviews, and public health and patient harm. It is well past time that open access to clinical trial data be the norm rather than the exception.

- For all: Really, it is about putting patient safety ahead of personal financial profit, professional pride/ego, and surgical convenience.