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EDITORIALS

YODA and truth seeking in medicine

Making sense of the curious case of rhBMP-2

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Last month, *Annals of Internal Medicine* published a package of articles unveiling the first fruits of the Yale University Open Data Access (YODA) project. At the core of this novel concept is the idea of a coordinating organization—YODA—simultaneously commissioning two independent systematic reviews of patient level data for a medical product, and subsequently offering the data to researchers more broadly.[1-5]

The YODA project demonstrates one way to redress the problem of incomplete and distorted knowledge by asking industry to put its most detailed clinical trial data in the hands of an independent custodian. The two systematic reviews of data from trials on recombinant human bone morphogenetic protein-2 (rhBMP-2) obtained from Medtronic (Minneapolis, MN) are the first example of applying the YODA concept to seek the truth about the safety and effectiveness of a medical product.

The systematic reviews included trials that compared rhBMP-2 with iliac crest bone grafting, considered the gold standard for spinal fusion surgery. In 2011, a controversy erupted over the safety of rhBMP-2 amid fierce criticism and accusations from the clinical community that Medtronic had understated the product's known harms.[6] This led to an unprecedented collaboration between industry and academia when Medtronic gave YODA data on trials of rhBMP-2 for researchers to conduct independent re-analyses.[5]

The two independent systematic reviews concluded that rhBMP-2 was not superior to bone grafting in effectiveness outcomes such as pain or function. This seems surprising given the way in which rhBMP-2 had been previously described in the literature as superior to iliac crest bone grafting.[7] In contrast, Medtronic stated in a press release that "these [YODA systematic review] findings are consistent with those in the original clinical studies."[8]

Yet both systematic review teams found numerous problems with the published literature and "substantial evidence of reporting bias."[2] In a linked methodological research paper by one of the systematic review teams (doi:10.1136/bmj.f3981), the researchers found that among published trials, only 56-88% of known effectiveness outcomes collected were reported.[9] Furthermore, six of Medtronic's 17 clinical trials remain entirely unpublished (three were randomized controlled trials).

Despite the under-reporting, interpretations about treatment effect based on patient level data and unpublished internal reports were no different from those based on published data alone. Although it is somewhat reassuring that in this particular case the published literature did not misrepresent what is known about the relative effectiveness of rhBMP-2 versus iliac crest bone grafting, it does not excuse under-reporting, and in other cases the situation could have been different.

But the safety of rhBMP-2 remains an open question. Only 23% of all adverse events recorded in the trials were mentioned in journal publications.[9] Even with all the data, neither review reached strong conclusions about the safety of rhBMP-2, although both reviews identified a possible increased risk of harms such as cancer. The reviewers reported that safety data were not systematically collected in the trials and adverse events were classified using Medtronic's own non-standardized "in house" coding system (developed in partnership with the Food and Drug Administration).[9]

These safety conclusions are not entirely surprising. Randomized controlled trials are known to have limitations in evaluating the safety of healthcare interventions.[10] But can safety signals be better detected with access to complete trial data? The two systematic reviews of rhBMP-2 were conducted without the use of case report forms. In clinical trials, case report forms are the original forms on which participant data are collected. Original case report forms can allow systematic reviewers to use standardized terminology to categorize adverse events. These forms also could enable re-adjudication of adverse events when necessary, as the FDA has shown.[11] Finally, case report forms could contain sufficient information to fully understand adverse events at the individual level. Future systematic reviewers might consider these possibilities.

Eleven years after the FDA originally approved rhBMP-2, and with data from more than 2000 patients, the two independent reviews seem unlikely to fundamentally change the community's

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understanding of the safety and effectiveness of rhBMP-2. Some may think that this shows that the current system of drug regulation, in which regulators are the only group that needs access to patient level data, works well. But this ignores the fact that rhBMP-2 was mostly used for indications not approved by the FDA. So physicians interested in knowing what the FDA thought of the product were out of luck—the FDA does not release its reviews of trials for unapproved indications.

Independent reviews of evidence for approved and unapproved indications seem both necessary and inevitable. Does this mean that when patient level data are available, systematic reviewers should treat them as the gold standard and forgo analysis of data from publications or internal reports? Unfortunately not; the BMJ analysis comparing the effects of rhBMP-2 and bone grafting yielded different meta-analytic effect estimates depending on the data source interrogated—internal reports, patient level data, or published data.[9] Thus, the take home message for systematic reviewers is that we still do not know what data source is trustworthy, and until we do, it seems prudent to ask for all the data and to rigorously analyze them.

Despite these two systematic reviews, and the availability of patient level data through YODA, the published literature on rhBMP-2 remains problematic. To reduce the possibility that future research will rely on these publications, Medtronic could restore the scientific record by publishing its unpublished trials and correcting misreported or under-reported trials.[12]

The rhBMP-2 case shows that responsible independent analyses of industry data are possible. With recent pledges from other companies to make their patient level data available, systematic reviewers, who are used to working primarily with journal publications, have their work cut out for them.

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