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Moving Forward from rhBMP-2: Open Science and Data Sharing

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A few years ago, a storm of controversy not only called into question the safety of recombinant bone morphogenetic protein-2 (rhBMP-2) [1], but also introduced an approach that addressed a fundamental weakness in the foundations of evidence-based medicine. Nearly half of all clinical trials are never published [2–4]; those that are often exclude important data and may face long delays to publication [5–6], and individual patient level data has rarely been available for re-analysis [7–8]. Moreover, financial conflicts of interest have been associated with actions that have had the potential to bias the conduct and dissemination of clinical research. All of these foundational weaknesses were at issue when a series of publications in the *Spine* Journal [1] suggested that the investigators behind the key publications supporting rhBMP-2 had significant financial conflicts of interest and that the published reports of these industry-sponsored studies may have incompletely reported important adverse events.

In response to these concerns, Medtronic (Minneapolis, Minnesota) provided the Yale University Open Data Access (YODA) Project with the opportunity to apply its model [9–10] of data transparency and data stewardship to clarify the effectiveness and safety of rhBMP-2. This model entailed the oversight of two independent systematic reviews based on individual patient level data from all clinical trials conducted by Medtronic and the subsequent availability to scientists of the individual patient-level data from the trials. As part of this initiative, Medtronic fully granted jurisdiction over the data to the YODA Project and funded the effort. This project was conceived as a new type of industry-academic partnership to address the problem of unpublished and selectively published clinical evidence, with the hope of advancing open science, developing norms for good stewardship of clinical trial data, and serving patients and society, all while respecting legitimate industry concerns about the use of previously proprietary clinical trial data.

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The device(s)/drug(s) is/are FDA-approved or approved by corresponding national agency for this indication. My manuscript includes unlabeled/investigational uses of the products/devices listed below and the status of these is disclosed in the manuscript: We briefly summarize the findings from two systematic reviews of rhBMP-2, including both approved uses and unapproved uses.

Relevant financial activities outside the submitted work: grant, stock/stock options, grants/grants pending, endowed scholarship, and board membership.

Clinical Decisions Made on the Totality of Evidence

Currently, even the most conscientious physicians keeping up with the latest literature make decisions based on an incomplete view of the evidence available. Industry sponsorship has been associated with more favorable study findings not only in spine surgery [11] but also in the wider biomedical literature [12]. The published literature also often presents an incomplete reporting of outcomes relevant to patients [13]. The sharing of scientific data can help solve some of these problems and allow physicians and patients to make more informed decisions. Clinical trial data sharing comes with legitimate concerns [14], notably the misuse of data including misleading secondary analysis, which must be overcome to reach widespread adoption.

The first step in this project was to address these potential sources of bias and mitigate these concerns with two independent and comprehensive systematic reviews that were carried out by groups from Oregon Health and Science University [15] and the University of York [16] which were selected through an open and competitive process for their expertise in meta-analysis and the use of individual patient data.

Though at times the groups employed different methodological strategies and techniques, results were broadly similar. One group found a small advantage to rhBMP-2 over iliac crest bone graft (ICBG) in inducing spinal fusion combining data across all approaches, but this difference was perhaps too small to be detected when data was stratified by surgical approach. Neither group found a clinically significant difference in outcomes or complication rates between rhBMP-2 and ICBG in anterior lumbar interbody fusion or posterolateral fusion with the exception of increased reports of pain in the immediate postoperative period. Successful fusion was not associated with improved patient reported outcomes. Increased complications were associated with rhBMP-2 use in anterior cervical surgery. Cancer risk was slightly increased in patients receiving rhBMP-2 at 2 years though this difference did not persist at 4 years. The absolute risk was small and the cancers were heterogeneous. As such, there is controversy about the clinical relevance of this finding. Comprehensive findings from the two review organizations can be found at <http://medicine.yale.edu/core/projects/yodap/rhbmp/index.aspx>.

Toward Open Science

Open science will benefit patients who are able to make more fully informed decisions with the help of physicians. Sharing can help maximize the value derived from datasets by allowing the pursuit of further research questions. It can decrease the waste of research dollars by reducing redundant data collection. For industry, it can help rebuild and strengthen trust and respect with patients and clinicians while allowing an avenue to better target marketing and future trial design toward populations which stand to benefit the most.

The YODA Project sought to set an example for open science by making all of Medtronic's de-identified individual patient data relevant to rhBMP-2 available to investigators seeking to further scientific understanding. This project aspired to share data for the public benefit with the hope that others would follow. Currently, the European Medicines Agency (EMA), Europe's regulatory body, is finalizing rules to make public the detailed clinical study reports submitted for regulatory approval [17]. The Pharmaceutical Research and Manufacturers of America (PhRMA) and its European counterpart the European Federation of Pharmaceutical Industries and Associations (EFPIA) [18] have pledged to release more clinical trial data, and large pharmaceutical companies including GlaxoSmithKline, Roche [19], and Pfizer [20] have joined these efforts.

The result of this effort has been a more complete analysis of the rhBMP-2 clinical trial data. With access to all industry data including previously unpublished studies and a complete reporting of adverse events, clinicians and patients can arrive at a more comprehensive understanding of the balance of benefits and harms for this product which will guide a more informed decision based on clinical appropriateness, patient needs, and values. We hope that these efforts signal a shift toward a new future in science which rewards data sharing, promotes open science, and relegates to history a time when the whole truth was allowed to be hidden from the public. The data from the trials, through this process, is available to researchers now upon request at <http://medicine.yale.edu/core/projects/yodap/rhbmpr/request/index.aspx>

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