EDITORIAL

Industry-sponsored research

John R. W. Kestle, MD

Department of Neurosurgery, University of Utah, Salt Lake City, Utah

THE efficacy and cost of antibiotic-impregnated catheters (AICs) for shunts and external ventricular drains (EVDs) are reviewed in the paper by Edwards et al.⁴ Using a decision analysis approach, the authors conclude that AICs reduce infections, days in hospital, and cost. They acknowledge variation in the data and perform a sensitivity analysis to address this. Taken at face value, it is a reasonable summary of the literature but the following limitations should be kept in mind: 1) Most of the available studies are observational and retrospective. 2) The one randomized controlled trial of AICs in shunts had a high control group infection rate. 3) The authors were not able to adjust for covariates. 4) The definition of infection (“clinically symptomatic” with “confirmatory laboratory data”) is not very precise. 5) Pediatric and adult data are pooled together.

In addition, the authors’ relationships with the manufacturer and the study sponsorship are worth discussing. The manufacturer is appropriately acknowledged in the paper. The question is whether involvement of industry should alter our impression of the work. Industry sponsorship of research often generates discussion. Doubt is sometimes expressed simply because of the involvement of industry. The assumption is that the company has a vested interest in the outcome and that its perspective alters the results and/or their interpretation. In other words, the study is “biased.”

Bias is any systematic deviation from the truth. There are many sources of bias in clinical research, and these are well described in the literature. Biases are present regardless of the source of funding. Bias may occur at the time of study design, patient selection, and assignment to treatment, evaluation of outcome, analysis of data, interpretation of the results, and public dissemination of the information. In papers that pool existing data, bias may impact the articles that are available (publication bias), the process of selecting articles for inclusion, the assessment of outcomes, and the interpretation of the results. Evaluations of surgical procedures and devices are more

susceptible to certain types of bias than medical studies. Peer reviewers may introduce personal bias into the review process. Bias is a risk in everything that we study and write about.

In addition to these well-known and identifiable sources of bias, there is evidence that the funding source may introduce additional bias. Bhandari et al.¹ looked at 332 randomized trials of medical and surgical therapies and compared 122 with industry funding to those with other sources of funding. Industry funding almost doubled the odds (OR 1.9 [95% CI 1.3–3.0]) of a statistically significant result in favor of the industry product. This remained true even after the analysis was adjusted to account for study quality and sample size. Industry-funded surgical trials were 8 times more likely (OR 8.0 [95% CI 1.1–53.2]) to have a result in favor of the industry product. Similarly, a Cochrane review in 2012 found that industry-sponsored studies more often had favorable efficacy results and had less agreement between the results and conclusions than nonindustry sponsored studies.⁸

So how do we move forward? Can we collaborate effectively to produce helpful unbiased studies that improve patient care? Brinjikji and Kallmes² argued that industry-sponsored research may pass the “sniff test” of scientific validity if it is investigator initiated rather than industry initiated. In this model the investigator’s role is to “plan, design, conduct, monitor, manage data, prepare reports and provide oversight for the study.” For industry-sponsored studies, the *Journal of the American Medical Association* now requires that the entire raw data set be given to an independent statistician for analysis, and studies analyzed only by statisticians employed by the company will not be accepted.⁶

Recently, some interesting changes have occurred in the pharmaceutical industry in response to these concerns. In 2012, GlaxoSmithKline announced that they would make detailed raw data from their clinical trials available to researchers.³ Last year, the European Medicines Agency developed a policy that will make its patient

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level data publicly accessible.⁵ Medtronic partnered with the Yale University Open Data Access (YODA) program to allow public access to their patient level data on bone morphogenetic protein-2.⁷

The impact of these changes is yet to be seen, but they may be steps in the right direction.

In the meantime we, as investigators, should be constantly on the lookout for sources of bias and take measures to minimize them. As readers, we should be able to identify the potential biases in a study and decide how they might affect our use of the results. This is true regardless of the funding source.

<http://thejns.org/doi/abs/10.3171/2014.1.JNS132818>

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Response

Natalie C. Edwards, MSc,¹ Matthew J. McGirt, MD,² and Luella Engelhart, PhD, MA³

¹Health Services Consulting Corporation, Boxborough; ²DePuy Synthes, Raynham, Massachusetts; and ³Carolina Neurosurgery & Spine Associates and University of North Carolina, Charlotte, North Carolina

We thank Dr. Kestle for his helpful commentary on our article. We would like to address his concerns regarding the research presented.

Making resource allocation decisions requires that relevant clinical and economic consequences of interventions are considered simultaneously. Health economic evaluation is sometimes viewed cautiously due to it being complex or not reflective of actual clinical practice. It is our view that there are 2 key factors required for a

satisfactory and meaningful health economic evaluation: 1) convincing clinical evidence for differences between or among comparators; and 2) transparency of methods so that the analysis can be appraised and ideally duplicated by other investigators. We feel that our evaluation of AICs meets both of these criteria.

In terms of the clinical evidence, 12 of 14 studies of AIC shunts demonstrated a significant decrease in infection rates. Only 2 of 14 AIC shunt studies did not show a significant decrease in the rate of infection with use of AICs. In the case of Hayhurst et al., more than a quarter of patients with AICs were patients with an especially higher risk for infection due to previous shunt infection, meningitis, EVD-associated ventriculitis, or conversion of an EVD to an indwelling shunt.² In the other study by Ritz et al., 3 of the 5 infections in the AIC cohort were the result of skin ulceration or neurosurgical procedures with CSF leak after shunt implantation.⁵ The AIC EVD studies also consistently showed a substantial decrease in the rate of infection with the use of AICs. To further evaluate the strength of evidence for differences between AICs and non-AICs, we conducted subanalyses that only used data from Level I studies. The subanalyses for both shunts and EVDs resulted in lower effect sizes, but they confirmed the overall results of the decision analysis models that AICs are associated with lower infection rates and cost savings.

For the transparency criterion, the methods we used were clearly and thoroughly described, and the information provided in the publication can be used to fully replicate the analysis.⁴ Dr. Kestle mentions that the definition of infection was not very precise; however, the referenced meta-analysis article upon which the study was based does define the meanings of “clinical symptoms” and “laboratory confirmation.” In addition, since the sources of our data are the published, peer-reviewed literature, readers can freely access the individual studies utilized in our evaluation and ascertain their quality and relevance. The economic component of the evaluation (the “model”) is a simple decision analysis that was created using a Microsoft Excel spreadsheet. We encourage those interested in recreating the model to do so using the economic inputs described in *Methods* and the clinical inputs summarized in Tables 1 and 2 of the paper. Readers may be interested in customizing the model to their particular environments, or in entering other plausible model input values and conducting their own sensitivity analyses.

Systematic health economic evaluations can be useful to help decision makers understand trade-offs in periods of financial constraints for improving resource allocation. Clinical decision analysis is regularly practiced (though perhaps intuitively and less explicitly) by clinicians in their daily practice. Treatment decisions are routinely made based on the likelihood of various risks and outcomes for patients, striving to maximize the net benefits attained. Health economic evaluations seek to make decision analysis explicit, attaching costs to the outcomes of care such that the economic implications of decisions can be simultaneously considered alongside the clinical outcomes, thereby hopefully improving the decision-making process. The clinical and economic relevance of

technologies and treatments that have real differences in clinical outcomes can be more thoroughly expressed and quantified.

As is the case with clinical research, all options for collecting health economic or value data are not without their limitations and flaws. “Piggyback economic evaluations” (economic data collected alongside clinical trials) are focused on causal inference, and study populations, protocols, and circumstances are often not reflective of the real world and may not be appropriate for diverse populations. Retrospective database analyses and prospective cohort studies contain real-world data, but making comparisons across interventions or technologies is difficult given the lack of randomization. Even the gold standard for health economic evaluation, a randomized prospective observational study, falls short in that it is typically unblinded. It has been argued that, because of these shortcomings in primary data collection, economic modeling should always be used to make adjustments and projections when appraising clinical and economic value.³

We recognize that economic evaluations are not intended to replace health care providers’ insight and judgment. They summarize only a subset of information needed to make decisions about resource allocation. Since they provide details regarding the implications of alternative decisions, however, they can be quite valuable. Other decision-making considerations such as choice and process factors may also come into play.

AcademyHealth, the leading national organization serving the fields of health services and policy research, notes the biases and conflicts of interest that may arise from research sponsorship by industry, academic, and government sources in its *Ethical Guidelines for Managing Conflicts of Interest in Health Services Research*.¹ The guidelines have highlighted some of the conflicts associated with publication and the peer-review process and the implications for career advancement. As more and more authors, journal editors, and readers become aware of how these conflicts can occur from all perspectives, the information that becomes publicly available and the ensuing debate benefits us all by expanding our understanding of the complexities involved in sponsoring, conducting, and disseminating biomedical research. Efforts like YODA⁶ that allows public access to their patient-level data from clinical research are helping to elevate the analyses and dialogues derived from these studies. Johnson & Johnson, through its subsidiary, Janssen Research and Development, LLC, has entered into a novel agreement with YODA that will extend its commitment to sharing clinical trials data to enhance public health and advance

science and medicine. Codman Neuro, as well as other companies of Johnson and Johnson, has, as a matter of policy, a standard operating principle to publish data from all company-sponsored clinical studies, regardless of outcome. Inclusion in this paper’s analysis of a company-sponsored study for EVD infection prevention that failed to demonstrate a statistically significant difference in outcomes is an example of this principle in action.

Biases certainly exist in the medical literature, and we appreciate Dr. Kestle’s acknowledgement that this is true regardless of the funding source. This research should be evaluated in the context of the full body of evidence on the efficacy and reductions in costs with the use of AIC shunts and EVDs. We believe this research builds upon the base of evidence other researchers have put forth. There are many significant changes occurring throughout health care, and we anticipate that these will serve us all well collectively as information becomes more abundant and perfect. The common ground we share—whether we work in the private or public sector, at the patient or population level, or whether we are providers, researchers, or payers—is that we all care about improving the health of individuals. It is what drew us into our professions and is what drives us and sustains us in our daily work. Working together, we move health care forward, bringing our unique perspectives, knowledge, skills, and enthusiasm.

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