Study Design. Economic evaluation provides a framework to explicitly measure and compare the value of alternative medical interventions in terms of their clinical, health-related quality-of-life, and economic outcomes. Computerized economic models can help inform the design of future prospective studies by identifying the cost-drivers, the most uncertain parameter estimates, and the parameters with the greatest impact on the results and inferences.

Objective. An economic analysis of bone morphogenetic protein versus autogenous iliac crest bone graft for single-level anterior lumbar fusion poses several methodologic challenges. This article describes how such an economic evaluation may be framed and designed, while enumerating challenges, offering some solutions, and suggesting an agenda for future research.

Summary of Background Data. An evidence-based modeling approach can incorporate epidemiologic, clinical, and economic data from several sources including randomized clinical trials, peer-reviewed literature, and expert opinion. Sensitivity analyses can be conducted by varying key parameter estimates within a reasonable range to assess the impact on the results and inferences.

Results. Preliminary results suggest that from a payer perspective, the upfront price of bone morphogenetic protein is likely to be entirely offset by reductions in the use of other medical resources. That is, bone morphogenetic protein appears to be cost neutral. The cost offsets were attributable largely to prevention of pain and complications associated with autogenous iliac crest bone graft, as well as reduction of the costs associated with fusion failures.

Conclusions. Future research should focus on quantifying the health-related quality-of-life impact of bone morphogenetic protein relative to autogenous iliac crest bone graft, as well as the impact on lost productivity. [Key words: autogenous iliac crest bone graft (AICBG), bone graft, bone morphogenetic protein (BMP), donor site morbidity, donor site pain, economics, lumbar spine fusion]


Low back pain is a common condition that imposes a substantial economic burden on individuals and society. Approximately 151,000 lumbar spine fusions are performed annually, using harvested autogenous bone from the iliac crest. Bone morphogenetic protein (BMP), when placed on an absorbable collagen sponge inside a stand-alone interbody fusion device, has the potential to obviate the need for autogenous iliac crest bone graft (AICBG), eliminate the associated donor-site morbidity, and improve the fusion success rate. To the authors’ knowledge, the economic impact of replacing AICBG with BMP for single-level anterior spinal fusion has not been evaluated.

The authors recently initiated research to assess the economic impact of BMP versus AICBG for single-level anterior lumbar fusion. Economic evaluation is a tool that has been used as a decision-making aid for optimal societal resource allocation. It provides a framework for explicitly measuring and comparing the value of alternative medical interventions in terms of their clinical, health-related quality-of-life, and economic outcomes.

Use of new technology generally is presumed to be more expensive. However, there may be substantial cost offsets, which are not always obvious. For example, a recent cost analysis compared two anterior cervical fusion procedures. Castro et al used a more expensive implant, which resulted in decreased in operating room time and shorter hospital length of stay. If a new technology provides improved outcomes at a lower cost or improved outcomes at the same cost, then it is likely to be widely adopted. If, however, a new technology provides improved outcomes (including decreased morbidity) at a slightly increased cost, then the technology still may be widely adopted.

During the course of the current research, the authors encountered several methodologic challenges to an economic evaluation of BMP. In this article, they describe how such an economic evaluation may be framed and designed, while enumerating challenges, offering some solutions, and suggesting an agenda for future research.

Approach

Economic analyses require close collaboration between health care providers and health economists to frame and design the economic analysis appropriately. It is recommended that economic analyses proceed under recommended guidelines for minimizing bias in the conducting and reporting of sponsored economic research.

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### Framing and Designing an Economic Analysis

Framing the analysis is an important first step in conducting an economic evaluation. A researcher needs to choose the appropriate type of analysis, as well as the appropriate perspective, comparators, outcome measures, time horizon, and costs for the analysis. In addition, the most appropriate method for conducting the analysis must be considered on the basis of the types of available data and the means for incorporating these data into the economic analysis.

Parameter estimates used in an economic evaluation should be selected from the best-designed and least-biased sources that are relevant to the population and outcomes being studied. The hierarchy of evidence for study designs least prone to bias includes (in decreasing order) randomized controlled trials, observational studies (including case-control studies, cross-sectional studies, and health insurance claims analyses), and synthesis methods (i.e., meta-analysis, expert opinion, and consensus panels). Each of these designs has inherent advantages and disadvantages. For example, a prospective clinical–economic trial is a very time-consuming and expensive endeavor, yet it can produce rigorous data. In contrast, health insurance claims analysis and medical chart review are less resource intensive, but generally do not include days lost from work or health-related quality-of-life measures. Furthermore, studies reported in the literature often do not adequately describe the demographics and comorbidities of the patient population or the fusion technique. They frequently do not use a standardized definition of fusion success.

Because data from any one trial, observational study, or synthesis inevitably will be incomplete or derived from many different sources, it often is necessary to rely on appropriate analytic methods in piecing together all of the evidence to conduct a meaningful economic evaluation. One such approach involves developing a flexible, computer-based model that incorporates epidemiologic, clinical, and economic data from several sources. For situations in which fewer data exist for particular parameter estimates, conservative assumptions should be made that would bias the results against the new intervention. However, the results of an economic model are only as reliable as its parameter estimates. Economic models address this limitation by allowing the researcher to vary uncertain parameter values over a reasonable range, thereby assessing the robustness and generalizability of the results.

This approach is called “sensitivity analysis.” For the current analysis, an economic model was selected as a practical and efficient means for conducting an economic evaluation of BMP because of the multiple data sources available for the analysis (randomized clinical trials, peer-reviewed literature, and expert opinion) and their inherent limitations. An economic model also is a valuable tool for informing future research.

### Type of Analysis

Before conducting an economic evaluation, the type of analysis that best illuminates the subject of the study should be determined. Cost-minimization analysis is a type of cost-effectiveness analysis in which the effectiveness of the intervention and that of the comparator (i.e., alternative intervention) are presumed to be relatively equal. The implication of two interventions being approximately equal in effectiveness (e.g., in life expectancy) is that decisions will revolve mainly around costs. As such, a cost-minimization analysis focuses on changes in process of care and costs, for example, costs offset by increasing the fusion success rate or eliminating pain and complications associated with AICBG.

A second type of analysis, cost-effectiveness analysis (CEA), is a method for evaluating the costs and outcomes of an intervention or program designed to improve a patient’s health. The CEA evaluates a given health intervention through the use of a cost-effectiveness ratio. In this ratio, all the changes in medical resource use relative to an alternative intervention are captured in the numerator and valued in monetary terms, whereas all the changes in health effects or outcomes of the intervention relative to an alternative intervention are captured in the denominator. The cost-effectiveness ratio often is expressed in terms of the incremental cost per incremental gain in life expectancy. Because BMP is not intended to extend life expectancy relative to AICBG, a cost-effectiveness analysis of this sort is less relevant.

Cost–utility analysis is a special type of cost-effectiveness analysis in which outcomes are adjusted for quality of life, for example, quality-adjusted life-years (QALYs). More specifically, a cost–utility analysis incorporates the concept that diminishing levels of health may compromise the quality of life. This is accomplished by applying different utility weights to life expectancy according to the level of health experienced over time. The utility weights reflect the preference for a particular health outcome and range from 0 (death) to 1 (perfect health). Utilities can be derived directly from preference-based health-related quality-of-life instruments, such as the Health Utilities Index (HUI) or EuroQol (EQ-5D), or indirectly from instruments such as the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36). Disease-specific instruments, such as the Oswestry Disability Index or the Roland-Morris Disability Questionnaire, are not utility-based measures. Depending on the type of utility measure being used, indirect costs, such as lost productivity, may be incorporated implicitly in the utility values, so they would not need to be estimated and incorporated directly. A cost–utility analysis comparing BMP to AICBG would be important to conduct, given the expected health-related quality-of-life impact of eliminating donor site pain and complications. However, to the authors’ knowledge, such preference-based quality-of-life data presently are not available.
The perspective of the analysis usually is chosen on the basis of the intended audience and the availability of relevant data. The perspective dictates the costs and outcomes that are incorporated in the economic analysis. For health policy decisions at the national level, the societal perspective is recommended because all relevant costs and benefits are captured, regardless of who incurs the costs or accrues the benefits.\textsuperscript{1,2,7} A societal perspective can include indirect costs (e.g., lost productivity) or intangible costs (e.g., health-related quality of life) in addition to direct medical costs to capture the total economic burden on society. Other perspectives, however, such as the hospital, health care system, or payer perspectives, also may be of interest. For example, an economic evaluation from the hospital perspective would consider only direct medical costs and clinical outcomes that are relevant to the hospital (e.g., cost of medical devices, medical and surgical supplies, room and board, and operating room time). On the other hand, a health care system or payer perspective would include not only the direct medical costs incurred during the spinal fusion hospitalization, but also the costs of follow-up care, rehabilitation, and rehospitalization for fusion failures.

\textbf{Comparators}

An economic evaluation should include the most relevant comparators. As a rule, such evaluations should compare the intervention of interest with the existing practice or practices for addressing the health problem.\textsuperscript{20} The current standard of care in spinal fusion procedures includes two surgical sites, one for the spine and one for a bone graft, where autogenous bone is harvested from the iliac crest. Therefore, in an evaluation of improved spinal fusion techniques, the most appropriate comparators would be the new innovative procedure using BMP and the current standard of care for spinal fusion, AICBG. The elements of the surgical procedures should be described in sufficient detail so that it is possible to evaluate the clinical and economic impact of each procedure. Relevant medical resources used during the index hospitalization include inpatient physician services, operating room time, anesthesia time, recovery room time, blood units, room and board (hospital length of stay), autograft extenders and harvesters, drain, iliac crest backfill, and management of complications associated with harvesting of the iliac crest such as pain, infection, hematoma, wound dehiscence, prolonged wound drainage, vascular injury, herniation, and iliac crest fracture. Relevant medical resources used during the subsequent follow-up period include physician office visits, rehabilitation visits, and pseudarthrosis repair.

\textbf{Outcomes}

All health economic evaluations involve the selection of relevant health outcomes for the interventions being compared.\textsuperscript{7} To determine the outcomes for consideration in the economic evaluation, the study author should address the main differences among the effects of the interventions, the potential side effects of the interventions, and the outcomes of interest for the intended audience or decision maker.\textsuperscript{7} In an economic evaluation of BMP, the effect of BMP on several types of clinical outcomes should be considered including the fusion success rate, the rate of pain at the bone graft site, and the rate of complications at the bone graft site. In a cost-minimization analysis, clinical outcomes for BMP would be considered only insofar as they influenced medical resource use and costs.

Evidence about the safety and efficacy of BMP versus AICBG (e.g., the rate of pain at the graft site and the rate of fusion success) should be based on available clinical trial data. On the other hand, the rates of infrequent complications associated with harvesting of the iliac crest (e.g., vascular injury or iliac crest fracture) could be abstracted from the literature. The values for other parameters that either have not been reported or are difficult to quantify because of practice variation, such as the frequency of using autograft extenders/harvesters or drains, could be based on clinical expert opinion or a survey of physicians.

\textbf{Time Horizon}

The time horizon, or the length of time over which an economic evaluation is conducted, can have a great impact on the results and conclusions. If the time horizon is too short, important benefits or costs that occur later may not be included.\textsuperscript{9} To inform decision makers about the total direct medical costs of BMP relative to those of AICBG, an economic evaluation should focus on the total process of spine care costs and not just on the initial episode of care. The total process of spine care would include the initial spinal fusion hospitalization, follow-up physician office visits, outpatient surgery center visits, rehabilitation visits, usage of internal or external stimulators, and any additional hospitalizations (e.g., for pseudarthrosis repair). An analysis conducted from the hospital perspective would include medical resources used only during the index hospitalization, whereas an analysis from the health care system or payer perspective would include medical resources used during a longer period (e.g., 2 or 3 years).

\textbf{Costs}

The economic component of the analysis is composed of several types of data. Medical resources typically are among the major cost components and include hospitalizations, medical devices, implantable materials, outpatient and emergency room visits, drugs, laboratory tests, and diagnostic imaging tests. Not all of these resources are necessarily applicable for every economic evaluation. Usually, one or two cost drivers tend to be responsible for a large portion of the total costs or cost offsets. Economic analyses generally are performed using estimated costs rather than charges. Charges (i.e., the amount a physician or hospital lists on a bill) can be misleading when used as a proxy for costs. The cost (and reimbursement) for a particular medical resource often is 40% to 80% lower than the charg
Table 1. Possible Costing or Evaluation Approach

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital facility services</td>
<td>Health insurance claims data</td>
</tr>
<tr>
<td>Inpatient and outpatient physician services</td>
<td>Medicare resource-based relative value unit payment schedule for relevant Current Procedural Terminology codes</td>
</tr>
<tr>
<td>Anesthesiologist services</td>
<td>Medicare anesthesiology payment schedule</td>
</tr>
<tr>
<td>Operating room, anesthesia, recovery room, and room and board</td>
<td>Hospital cost accounting data (for example, cost per minute or cost per day)</td>
</tr>
<tr>
<td>Diagnostic tests</td>
<td>Medicare resource-based relative value unit payment schedule for relevant Current Procedural Terminology codes</td>
</tr>
<tr>
<td>Drugs</td>
<td>Average wholesale price (AWP) listed in the Drug Topics Red Book</td>
</tr>
<tr>
<td>BMP, autograft extenders, autograft harvesters, iliac crest backfill, and drains</td>
<td>Manufacturers’ suggested or listed price</td>
</tr>
<tr>
<td>Lost productivity</td>
<td>National wage rate obtained from government surveys and applied to the number of missed days of work</td>
</tr>
<tr>
<td>Health-related quality of life</td>
<td>Directly from preference-based health-related quality-of-life instruments, such as the Health Utilities Index or EuroQol, or indirectly from instruments like the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36)</td>
</tr>
</tbody>
</table>

60% lower than the charge for that item or service. Indirect costs, often measured as lost productivity, are not considered in analyses from the hospital, health care system, or payer perspective. However, in an analysis from the patient or societal perspective, productivity losses could be estimated in monetary units by applying a national wage rate obtained from government surveys to the number of missed days of work.

In an economic evaluation of BMP, standardized costs can be assigned to each of the medical resources that could be influenced by BMP. For example, relative to AICBG, BMP could potentially reduce operating room and anesthesia time by 30 minutes. To estimate the direct medical costs offset by a reduction in operating room time, the expected reduction in operating room time could be multiplied by the operating room cost per minute, which could be estimated on the basis of hospital cost-accounting data (e.g., 30 minutes × $18 per minute = $540 offset from a reduction in operating room time). Using a similar costing method, the estimated cost offset associated with a reduction in anesthesia time by 30 minutes could be $60 (30 minutes × $2 per minute = $60).

Table 1 provides a summary of possible costing approaches. Hospital facility costs are likely to account for a large portion of the cost offsets. In addition, it must be recognized that hospital payments for lumbar spine fusion procedures include multiple payers, for example, private insurers and managed care organizations (44%) and Medicare (29%). As such, hospital facility costs for the index surgery and rehospitalization could be based on charge data from an all-payer health insurance claims database. Hospital facility costs then could be derived by multiplying the charge data by hospital- and year-specific cost-to-charge ratios.

Because professional fees likely will not account for a large portion of the cost offsets, it is sufficient to estimate professional fees for inpatient and outpatient physician services using the Medicare physician fee schedule derived from the resource-based relative value scale (RBRVS). Medicare payment levels serve as a reasonable proxy for costs, and often are used for costing medical resources in economic evaluations. Appropriate procedural codes could be determined by consulting the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes and the Current Procedural Terminology (CPT) codes. The professional fees for anesthesiologists can be estimated from the Medicare anesthesia payment schedule.

Drug costs can be estimated from the Drug Topics Red Book, a compendium of wholesale drug prices in the United States. The average wholesale prices (AWPs) listed in the Drug Topics Red Book often do not reflect the true costs of drugs. Therefore, 20% generally is deducted from the AWP to obtain a more accurate estimate of actual drug costs. The costs of autograft extenders, autograft harvesters, iliac crest backfill, transcutaneous electrical nerve stimulation, and drains could be obtained from the manufacturers of these products.

The opportune time to conduct an economic analysis of a new medical technology is before the technology’s approval for marketing in the United States. However, at that time, the manufacturer price of the technology (i.e., the cost to the hospital) is not yet available, which means that researchers must estimate the price that the manufacturer might charge. The estimated price then should be varied over a reasonable range to determine the price at which the technology becomes cost neutral (i.e., the price of BMP at which the total direct medical costs for BMP patients equals the total direct medical costs for AICBG patients). Because BMP was not yet approved for marketing in the United States at the time the economic model was developed, the manufacturer provided the estimated price of BMP.

Sensitivity Analysis

All economic evaluations contain varying degrees of uncertainty regarding parameter estimates, model structure, and relations between variables. In a sensitivity analysis, key parameter estimates are varied within a reasonable range to assess the impact on the results and inferences. For example, a series of sensitivity analyses could be performed to determine the consequences of alternative assumptions about the price of BMP, the fusion success rates of BMP and AICBG, and the rates of donor site pain and complications averted with the use of BMP. A special type of sensitivity analysis, known as a threshold analysis, also could be conducted to determine the price at which BMP would need to be established to result in cost neutrality (the point at which the total di-
When the values of parameters, such as rates for the use of autograft extenders or harvesters and reductions in operating room time or hospital length of stay, were varied within a plausible range, the results and inferences did not change. However, sensitivity analyses confirmed that, as expected, the results and inferences were highly sensitive to changes in assumptions about the price of BMP, and to the difference between BMP and AICBG fusion success rates. Table 2 shows the relation between the price of BMP and the increase in fusion success rate (BMP relative to AICBG) required to achieve cost neutrality (the point at which the total direct medical costs for BMP patients equals the total direct medical costs for AICBG patients). For instance, when an analysis was conducted from a payer perspective that considered only the price of BMP and the costs associated with an unsuccessful fusion (e.g., follow-up visits and resurgery), a 22.7% increase in fusion success rate was required to achieve cost neutrality at a BMP price of $4000. On the other hand, when an analysis was conducted from a payer perspective that considered these factors as well as the cost offsets associated with obviating the need for AICBG (e.g., iliac crest backfill, autograft extenders, and autograft harvesters) and eliminating the associated donor site pain and morbidity (e.g., infection, hematoma, and vascular injury), a 9.3% increase in fusion success rate was required to achieve cost neutrality at a BMP price of $4000. The analyses reported in Table 2 do not consider the health-related quality-of-life impact of eliminating donor site pain and complications. In addition, the required increase in fusion success rate (BMP relative to AICBG) could be lower than presented in Table 2 after the value to the patient or society of eliminating donor site pain and morbidity is considered.

**Future Research**

Computerized models can help to address some of the challenges and limitations of alternative approaches for assessing the economic impact of BMP versus AICBG for single-level anterior lumbar fusion. For example, a
model can help to inform the design of future prospective studies by identifying the cost-drivers, the most uncertain parameter estimates, and the parameters with the greatest impact on the results and inferences. A model also can be used to explore various hypothesis-generating scenarios such as “What if BMP were used for posterior or multilevel lumbar fusion, or in patients who smoke?”

During their preliminary research, the authors identified the price of BMP and the rates of BMP and AICBG fusion success as the primary cost drivers. Reductions in recovery room time and rates for the use of autograft extenders, autograft harvesters, and drains were the most uncertain parameter estimates (derived from clinical expert opinion or survey data). However, because varying these latter rates within a plausible range did not have an impact on the results or inferences, the panel- and survey-derived estimates should be considered sufficient for the economic analysis. On the other hand, because the results and inferences changed substantially under different assumptions about the price of BMP and the rates of BMP and AICBG fusion success, the authors recommend updating the economic model once additional data become available from the manufacturers and other clinical trials of bone graft substitutes. The generalizability of the model results also can be assessed further once data on the fusion success rates, bone graft time, and donor site morbidity are available from community practice. Finally, future research should focus on quantifying the health-related quality-of-life impact of BMP relative to AICBG, as well as the impact on lost productivity.

Key Points

- Preliminary results suggest that from a payer perspective, the upfront price of BMP is likely to be entirely offset by reductions in the use of other medical resources. That is, BMP appears to be cost neutral.
- The cost offsets were largely attributable to prevention of pain and complications associated with AICBG as well as reduction of the costs associated with fusion failures.
- Future research should focus on quantifying the health-related quality-of-life impact of BMP relative to AICBG, as well as the impact on lost productivity.

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