Chapter 3

Critiquing Research Articles

Objectives
Upon completing this chapter, the reader will be able to:

• List and give examples and explanations of 14 questions to consider when reviewing a pharmacoeconomic research article.
Appropriateness of Methods of Analysis

There is no one standard, agreed upon method used to conduct a pharmacoeconomic analysis; rather, there are many acceptable methods. The appropriateness of these methods depends on many factors, including the specific question or objective, the perspective of the study, the time period needed to determine outcomes of the alternatives, and the resources (e.g., time, money, databases) available to researchers. No study is perfect; thoroughness is balanced with the practicality of the research. However, several authors cite methodology to assist in systematically reviewing the pharmacoeconomic literature.

A summary of review articles that assessed the quality of health economic publications concluded that there has been a modest improvement in the quality of conducting and reporting economic evaluations in the past decade (1990 to 2001). If a study is carefully reviewed to ensure that the author(s) included all meaningful components of an economic evaluation, the likelihood of finding credible and useful results is higher.

Questions to Use When Critiquing Research Articles

The following 14 questions illustrate the types of questions that should be raised when reviewing pharmacoeconomic studies. Most of the following chapters contain an example of a composite article that incorporates the positive and negative aspects found in a mix of real research articles. After each composite article, you will find answers to the list of 14 questions outlined here. (Although topics are taken from actual articles, methods and data have been changed to illustrate points made in the chapter. All medication names in these composite articles are fictitious.)

1. Complete Title: Is the Title Appropriate?

From reading the title, can it be determined what is being compared and what type of study is being conducted—cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA), or a combination of them)? Does the title sound biased?

For example, a title such as “Pharmacoeconomic Analysis of Glipizide versus Glyburide in the Veterans Administration” does not specify the type of study (CMA, CEA, CBA, or CUA) conducted. Although this is not wrong, readers may prefer to know what type of study was conducted when searching for articles that are relevant to their purpose. In addition, sometimes the title is vague about what is being compared. For example, the title “Cost-Effectiveness Analysis of Two Antibiotic Therapies in a Large Teaching Hospital” does indicate the type of study that was conducted but not the alternatives that were compared. When many therapies are compared, the title might get long if listing them all. In some cases, the title itself may seem biased. For example, a title (here using names of medications that do not exist) such as “Ultraceph Found Cost-Effective When Compared to Megaceph” sounds like advertising instead of scientific-based research.

2. Clear Objective: Is a Clear Objective Stated?

Was a well-defined question posed in an answerable form? This should be clearly stated at the beginning of the article. Examples of clear objectives might be: “The objective of this study was to calculate the benefit-to-cost ratio of pharmacist interventions in our hospital.” or “Our purpose was to perform an incremental cost-utility
analysis of standard chemotherapy compared to palliative treatment alone for patients with inoperable lung cancer.” An example of an unclear statement would be “The objective of our study is to determine if Ultraceph is better than Megaceph.” This statement leaves the reader wondering better in what way?

3. Appropriate Alternatives: Were the Appropriate Alternatives or Comparators Considered?

Ideally, the most effective treatments or alternatives should be compared. In pharmacotherapy evaluations, the manufacturers of innovative new products often compare or measure the new product against a standard current therapy. This selection should include the best clinical options or the options that are used most often in a particular setting at the time of the study. If a new treatment option is being considered, comparing it with an outdated treatment or a treatment with low efficacy rate is a waste of time and money. A new treatment should be compared with the next best alternative or the alternative it may replace. Keep in mind that the alternatives may include drug treatments and nondrug treatments (e.g., medication versus surgery). Head-to-head comparisons of the best alternatives provide more information than comparing a new product or service with an outdated or ineffective alternative. In many cost-benefit analyses (CBAs), the options may be thought of as a “with or without” option. The comparison of a service or a preventative therapy (e.g., a vaccination or immunization) is compared with the alternative of not implementing the service or providing the preventative therapy.

4. Alternatives Described: Was a Comprehensive Description of the Competing Alternatives Given?

Could another researcher replicate the study based on the information given? If pharmaceutical products are compared, the dosages and length of therapy should be included. It is not helpful for the researcher to compare a low dose of one drug with a high dose of a competing drug. In some cases, a range of doses is given based on the range given to a specific population of patients or based on a summary of more than one research study used to gather data on costs and effects. In chemotherapy research, sometimes researchers describe the doses as “equitoxic”—a dose based on the amount a patient can tolerate without severe side effects—because patients need to be individually dosed based on their body mass index, their immunity status, and their reactions to the medication.

If pharmacy services are compared, explicit details of the services make the paper more useful. For these services, a description of start-up and continuing resource needs should be addressed, if applicable. For example, additional training for pharmacists and other health care professionals and space, overhead, equipment, or software needs may be required to provide the service. A summary of the services provided should be outlined. For example, if a pharmacist in a diabetes clinic provides services, readers would want to know how patients are identified, what topics are covered with the patient, and what type of follow-up is provided. A large part of the expense of providing pharmacy services may be personnel costs. Information about the measurement of these costs is provided in Chapter 2.

5. Perspective Stated: Is the Perspective of the Study Addressed?

The perspective tells the readers whose costs are measured. It is important to identify from whose perspective the analysis will be conducted because this determines
the costs to be evaluated. Is the analysis being conducted from the perspective of the patient, hospital, clinic, insurance company, or society? Depending on the perspective assigned to the analysis, different results and recommendations based on those results may be identified. Some articles are not clear about what type of costs or whose costs are used in the calculations, and it is up to the reader to guess the perspective. In more recent articles, editors and reviewers are more aware that readers look for a sentence that explicitly states, “The perspective of the study was. . . .” Some articles may use acceptable phrases such as “total third-party reimbursements for prescription and medical services were measured and summed” or “costs to the Canadian health care system were assessed,” indicating the perspective to the readers without using the specific term.

6. Type of Study: Is the Type of Study Stated?

Knowing up front the type of pharmacoeconomic study that is being conducted helps readers follow the rest of the research article. As mentioned, it is helpful if the type of study is mentioned in the title. Some articles contain more than one type of study. For example, an article comparing chemotherapy options may include both cost-effectiveness calculations (cost per year of life saved) as well as cost-utility calculations (cost per quality-adjusted life year) and may compare the results of both.

7. Relevant Costs: Were All the Important and Relevant Costs Included?

Based on the stated perspective, were the appropriate types of costs assessed? Were costs collected for an appropriate time period? If these costs were estimated from other research or source material, they should be referenced. The author's list should be compared with the reader's practice situation. Was there justification for any important costs or consequences that were not included? Sometimes the authors may admit that although certain costs or consequences are important, they were impractical (or impossible) to measure in their study. It is better that the authors state these limitations than ignore them. Other times, the costs are so small that it would not be worth the effort to measure them.

Protocol driven-costs should be excluded from calculations. Protocol-driven costs are costs that occur because of the research protocol of a randomized, controlled trial that would not occur in everyday practice. For example, randomized, controlled trials for medications to treat stomach ulcers may include endoscopy procedures at various intervals to determine the healing rate of the ulcers. In everyday practice, physicians commonly rely on patients' reports of symptoms (or lack of symptoms) to determine the effectiveness of the medication. Costs that are the same for all alternatives are also commonly excluded based on the argument that when conducting an incremental cost-effectiveness analysis, these costs would mathematically cancel out each other.

8. Relevant Outcomes: Were the Important or Relevant Outcomes Measured?

Are these the clinical outcomes that are important to clinicians? Were outcomes measured for an appropriate time period? For example, when comparing medications that reduce blood pressure, clinicians agree that the main outcomes are change in systolic and diastolic blood pressure. But when comparing medications that treat
diabetes, is fasting blood glucose or hemoglobin A1C important (or are both important)? When comparing medications that treat asthma, there is more debate on what outcomes are most important to measure. Some clinicians may prefer to use forced expiratory volume (FEV) measurements, but it is common in pharmacoeconomic studies to use a measure called symptom-free days (SFDs) that are based on patient diaries or reports. When measuring outcomes, is the appropriate time period used? For acute medical problems, such as infections or influenza, following patients until the problem is resolved (an episode of care) entails collecting information for every patient in a short time frame. Conversely, outcomes emanating from chronic conditions, such as high blood pressure and high cholesterol levels, may not be fully captured until many years have elapsed. It is important for the reader to evaluate if the time period of data collection was appropriate for the clinical measures recorded. This is especially important when short-term clinical trial data are incorporated into pharmacoeconomic studies of chronic conditions.

9. Adjustment or Discounting: Was Adjustment or Discounting Appropriate? If So, Was It Conducted?

As mentioned in Chapter 2, if retrospective data were analyzed to assess resources used over a number of years, these costs should be adjusted, or standardized, to value resources at one point in time. In addition, if the costs or benefits were extrapolated more than 1 year out, the time-value of money must be incorporated into the cost estimates, using discount rates to calculate the present value. These are two different questions. It is possible that neither adjustment nor discounting is needed, that only adjustment is needed, that only discounting is needed, or that both are needed.

10. Reasonable Assumptions: Are Assumptions Stated and Reasonable?

Pharmacoeconomic studies frequently require researchers to use of costs or outcomes. Whenever estimates are used, there is a possibility that these estimates may not be precise (or universally agreed upon by the readers). These estimates may be referred to as assumptions. For example, authors may assume the cost of a laboratory test is $50, that patient adherence with a regimen will be 100%, or that the discount rate is 5%. These types of assumptions should be stated explicitly. Authors may include estimates without using the term “assumption,” although using this term helps the reader differentiate between the values that were directly measured and the values that were estimated. Readers should ask themselves if these estimates seem reasonable in the context of their practice or decision-making processes.

11. Sensitivity Analyses: Were Sensitivity Analyses Conducted for Important Estimates or Assumptions?

Sensitivity analysis allows one to determine how the results of an analysis would change when “best guess” estimates, or assumptions, are varied over a relevant range of values. By using a plausible range of values for key assumptions, sensitivity analysis allows the researcher to examine the impact of these assumptions on the study conclusions. For example, if a researcher makes the assumption that the appropriate discount rate is 3%, this estimate might be varied from 0% to 10% to determine if the same alternative would still be chosen within this range. This
method helps determine if the analysis is robust. Do small changes in estimates produce important differences in the results? If the same option or comparator were chosen for the full range of the sensitivity analyses, the analysis is said to be insensitive, or robust, to this range of values, thereby adding confidence in the study results. If the conclusions or choice of therapy changes based on a plausible range of estimates, the results are deemed sensitive to this estimate, and readers should be aware of this when interpreting results.

In the previous chapter, Examples 2.1 and 2.3 provided sensitivity analyses. In Example 2.1, the net savings of a clinic after 3 years was $42,804 if future costs and savings were discounted at 3% and $50,000 if discounting was not conducted (0% discount rate). Either calculation resulted in positive net savings for the clinic; therefore, the choice of whether or not to implement the clinic was not affected by (insensitive to) the range of discount rates used (0% to 3%). Example 2.3 showed that for three multicenter trials of patients with coronary artery disease, the method of cost estimation (charges versus hospital-level cost-to-charge ratios versus department-level cost-to-charge ratios) did not change the answer to the question: “Is there a significant difference in costs between alternatives studied?” Again, this indicates insensitivity to the cost estimation method used. More examples of sensitivity analyses are given in subsequent chapters of this book.

12. Limitations Addressed: Were Limitations Addressed?

Because of practical restrictions, no study is ideal; therefore, the authors should mention the most important limitations of their study. Using retrospective databases may increase the possibility of selection bias. Selection bias occurs when patients with certain characteristics are more likely to receive one treatment over another. Using a specific population may limit generalizability of results (see next critique question). Small sample sizes or missing data may limit statistical comparisons. There may be no data available on some cost or outcome values, which may require broad assumptions. It is better for the authors to address these limitations than to leave them unstated.

13. Appropriate Generalizations: Were Extrapolations Beyond the Population Studied Proper?

If the study is based on data from a specific population of patients who may be atypical (e.g., in age, socioeconomic status, resource use) compared with the general patient population, the researchers should caution readers against generalizing, or extrapolating the results beyond the population studied. For example, results based on patients of long-term care facilities, the Veterans Administration, or state Medicaid may be different (in both costs and outcomes) than results based on a population of ambulatory patients with private health care insurance.

14. Unbiased Conclusions: Was an Unbiased Summary of the Results Presented?

 Sometimes the conclusions seem to overstate or overextrapolate the data presented in the results section. Did the authors choose appropriate alternatives and use unbiased reasonable estimates when determining the results? In general, do you believe the results of the study? Does the study make sense? Rennie and Luft5 make the case
that although there is concern that some studies sponsored by drug manufactures may be biased to show that their medication is cost effective (Example 3.1), health plans that conduct pharmacoeconomic research may have an inclination to show a new treatment is not cost effective and therefore will not be covered by the health plan. Assessment of the level to which research is biased versus unbiased should be based on the questions outlined above, not the funding source.

EXAMPLE 3.1 Review of Pharmacoeconomic Study Funding and Findings

Lexchin et al. (2003) found and summarized previously published research articles that analyzed if methodologic quality or outcomes differed by source of funding. Overall, 30 articles were summarized, and the authors concluded that although research funded by the pharmaceutical companies was more likely to find positive outcomes for their products, there was no difference in the quality of the research. Two of the theories as to why more positive outcomes were found for industry-sponsored projects included 1) that the industry is more likely to fund research when they believe their product has a distinct advantage and 2) publication bias is more prevalent for industry-sponsored research. (Publication bias is based on the premise that only research with positive results are submitted for publication.) Summary information for three of the articles reviewed is listed in the table.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Research Question</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azimi</td>
<td>How often do cost-effectiveness analyses encourage a strategy requiring additional expenditures?</td>
<td>Industry-funded studies were more likely to support a strategy requiring additional expenditures than those without such funding.</td>
</tr>
<tr>
<td>Friedberg</td>
<td>What is the relationship between drug company sponsorship and economic assessment of oncology drugs?</td>
<td>Drug company–sponsored studies were more likely to report favorable qualitative conclusions, but overstatement of quantitative results did not differ significantly.</td>
</tr>
<tr>
<td>Sacristan</td>
<td>What is the relation between drug company sponsorship and results of cost-effectiveness studies?</td>
<td>For general medical journals, three of six cost-effectiveness studies with industry funding had positive results compared with 31 of 63 with no funding or other source of funding. For pharmacoeconomic journals, all 18 cost-effectiveness studies with industry funding had positive results compared with four of six with no funding or other source of funding.</td>
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Summary

In summary, when assessing the soundness and usefulness of a pharmacoeconomic research article, readers need to keep in mind questions such as:

- Were comparators appropriate?
- Was the correct type of analysis conducted?
- Were the costs and outcomes measured appropriately?
- Did the authors account for differences in costs across time?
- Were assumptions reasonable?
- Were sensitivity analyses conducted when needed?
- Were limitations addressed?
- Did the tone of the article seem unbiased?

This chapter has presented general questions to consider. If readers come across unfamiliar terms when evaluating articles, a good source to consult is the *Health Care Cost, Quality, and Outcomes: ISPOR Book of Terms*.

Questions/Exercises

Based on the following abstract (condensed summary of a research article), please answer the following questions:

**ABSTRACT**

**TITLE:** Pharmacoeconomic Analysis of Ultraceph and Megaceph

**BACKGROUND:** Two new antibiotics, Ultraceph and Megaceph, were recently approved by the Food and Drug Administration. Both work equally well on the same spectrum of bacteria (i.e., their scope and efficacy have been shown to be equal), and the products are priced similarly. Ultraceph is dosed intravenously at 25 mg three times per day. Ultraceph is affected by liver functioning, so monitoring is needed. Megaceph is dosed intravenously at 75 mg once per day and is associated with a 0.1% chance of hearing loss, which is reversible if caught within the first 2 days of treatment.

**METHODS:** The purpose of this study was to compare the costs to Mercy General Hospital between patients who received Ultraceph versus Megaceph. Patients admitted to the hospital during the first 6 months of 2008 who met study criteria were randomly given either Ultraceph or Megaceph. Medical and billing records for each patient were used to estimate costs. Costs were estimated using two methods: using billed charges and estimating costs using an overall hospital cost-to-charge ratio of 47%.

**RESULTS:** A total of 212 patients were included in the study (105 on Ultraceph and 107 on Megaceph). Effectiveness for these two groups of patients was similar. Total costs, on average per patient, for Ultraceph were $332 more than Megaceph when using cost estimates based on charges and $156 more when using cost-to-charge estimates.

**CONCLUSION:** Although the efficacy and product cost of the two antibiotics have been shown to be similar, differences in the costs of intravenous administration...
(once-a-day compared with three times-a-day) and additional monitoring for different adverse events increased the overall total cost of Ultraceph to the hospital.

1. Was the title appropriate? Why or why not?

2. Were you able to determine the perspective? If so, what was it?

3. Was either adjustment or discounting appropriate? If so, was it conducted?

4. Was a sensitivity analysis conducted? If so, on what estimate(s)?

5. Were limitations addressed? If so, what were they?

REFERENCES


**Suggested Readings**


