

Incorporating Pharmacoeconomic Research into Clinical Trials

CHAPTER

11

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As the United States and other healthcare systems continue to evolve, so do the requirements and expectations of decision-makers regarding “proof” of the value of pharmaceuticals. While some of the expectations have been transformed into specific requirements in other countries (eg, Australia, Canada, the United Kingdom), there are unwritten rules or expectations created not by edict, but by the marketplace. Regardless of the source of the incentive, it seems that greater efforts are being made in terms of trying to demonstrate more fully the value of pharmaceutical interventions.

It is important to remember that these evolving expectations are in addition to, not replacements for, the well-established requirements of safety and efficacy. Given that the basics of safety and efficacy have not changed markedly, the only place to start to understand the value of the drug is within the clinical trial process.

Pharmaceutical companies are increasingly being called on to document the value of their products, not only clinically, but also in terms of economic and humanistic value. This value can be measured via appropriate data collection and analysis techniques. Information collected early in clinical trials regarding

the impact of a new product on the healthcare system can help determine its price and provide initial information to prospective purchasers regarding the value this new product will have versus current therapy. Once a product is on the market, its value must be continually assessed relative to its role in providing comprehensive pharmaceutical care.

Pharmacoeconomic Versus Traditional Research

Pharmacoeconomic research methods can be used to place value on therapies by identifying and measuring variables expected to be affected by healthcare interventions. Such research asks: What happened to the patient after an intervention? What impact did it have on the use of other healthcare resources? What were the outcomes? Was the patient relieved of symptoms? Was a condition cured, an illness prevented, or functional status restored? Until recently, such outcomes of medical care received little research attention. There is a paucity of data regarding the outcomes of medical care, surgical procedures, and behavioral interventions. Even diets generally are not thoroughly evaluated before they are incorporated into medical practice. In fact, drugs are considered to be the best paradigm for clinical outcomes in the United States because of the rigorous testing required for their approval.¹

In order for a drug to be approved for marketing in the United States, safety and efficacy must be demonstrated, usually by presenting evidence from two adequate and well-controlled clinical studies. This experimental model is well established; safety and efficacy are critical factors to address, but that model, in outcomes terms, is incomplete. To obtain a complete assessment of the outcomes of healthcare procedures and treatments requires scientific evaluation in three dimensions: clinical, economic, and humanistic. Although economic and humanistic measures are not currently required for approval of a drug by the Food and Drug Administration (FDA), because of their mandate to regulate the promotion of pharmaceutical products, the FDA has demonstrated significant interest in the area. The FDA Modernization Act (FDAMA) was passed in November 1997; Section 114 became effective in February 1998. Section 114 created a new standard for healthcare economic information requir-

ing “competent and reliable scientific evidence” (as opposed to data from adequate and well-controlled clinical trials) encompassing standards “widely accepted by experts in the relevant fields.” The FDA has not yet published any formal guidance regarding Section 114. Health-related quality of life (HRQOL) is separated from healthcare economics, and the agency is working on developing guidance in both areas. This may have significant implications regarding how HRQOL and/or healthcare economic information generated from trials (or elsewhere) can be used in the United States. If the goal of incorporating pharmacoeconomic variables into clinical trials is to use the information via traditional means of promotion, the reader is encouraged to visit the FDA’s Web site (www.fda.gov) to determine the current status of FDAMA and other guidances that may impact how pharmacoeconomic information can be used.

Additionally, committees making decisions on whether to include a drug in a health maintenance organization, hospital, or other formulary are gaining an appreciation for the importance of evaluating its use in the clinical, economic, and humanistic dimensions. Increasingly, these formulary committees and other purchasing groups are expecting pharmacoeconomic issues to be addressed in a standard fashion prior to approval or inclusion on the formulary.

How are the three dimensions of outcomes from pharmacotherapy measured? The clinical dimensions of safety and efficacy are evaluated during the drug development process in clinical trials. The economic and humanistic dimensions of outcomes are measured using research methodologies and data collection techniques within and alongside the traditional drug development process. Although the process of drug development has been described elsewhere,² a brief overview of the process will provide a better understanding of how and where pharmacoeconomic research fits into the process.

Clinical Research: The Drug Development Process

After basic animal research has been conducted and the pre-clinical studies have shown that a compound warrants further testing, a pharmaceutical candidate is then tested in humans.

This process is divided into three study phases. In Phase I studies, the drug is tested in small numbers of healthy volunteers to evaluate safety. If the drug appears safe, Phase II studies begin in patients who have the disease for which the drug is expected to be indicated. Phase II studies are designed to define initial efficacy parameters and optimal dosing of the drug using a small number of patients in various controlled clinical trials. After the demonstration of safety and initial efficacy, Phase III studies begin in large numbers of patients in controlled trials. Phase III studies are conducted to gather additional evidence for specific indications and usually are considered to be the pivotal safety and efficacy studies that support a New Drug Application (NDA).

The results of these three phases of studies, along with preclinical results, are compiled into an NDA or International Registration Dossier (IRD) and submitted to the FDA and other regulatory agencies worldwide with requests for approval to market the drug. While regulatory agencies are reviewing the data contained in the NDA/IRD, most companies initiate Phase IIIB studies to provide additional information regarding use of the drug. These studies usually involve a large number of patients, with safety and efficacy as major endpoints. They also address practical questions regarding the drug's use in more realistic situations.

Although this traditional method of evaluating drugs via safety and efficacy studies is well established, from an outcomes measurement perspective, it is incomplete. Because of the controlled nature of clinical trials, the safety and efficacy data obtained are likely to only approximate the effectiveness of the drug under real-world, or less-controlled, conditions. When conducting and interpreting clinical trials, it must be kept in mind that efficacy information indicates whether a drug can work under controlled conditions; it is the effectiveness of a product that is a measure of how the drug works in the real world, under average conditions created by, for example, nonadherence, use of concomitant therapy, or lack of access to care. Results obtained early in controlled trials may be compared and contrasted with results from Phase IV studies, which may have fewer controls, to determine the consistency of outcomes results. Pharmacoeconomic researchers and evaluators must keep in mind that data collected within any controlled study may not be representative

of the drug effects experienced by all patients who take the drug. Study design and the pharmacoeconomic methods used will help to determine the degree to which data gathered will approximate what might be observed in the healthcare setting.

The shifts that are now occurring in the basic foundation of the medical care system necessitate incorporating pharmacoeconomic research within the context of clinical trial research. This chapter identifies issues and discusses considerations surrounding the incorporation of pharmacoeconomics into clinical trials. Establishing a benchmark, design issues, instrument selection and administration, data management, analysis and interpretation, and reporting of results are discussed.

Establishing a Benchmark

It is difficult to know whether a treatment has been successful if the natural course (condition without treatment) of the disease is unknown. The absence of baseline information markedly reduces the value of any information generated by the incorporation of pharmacoeconomics into an isolated clinical study since there is no benchmark with which to compare the results. Thus, it is crucial that a baseline be established before beginning the clinical research. Early incorporation of epidemiologic research and methods into the drug development and pharmacoeconomic research plans will aid in the interpretation of later study results. Epidemiologic research methods can be used to identify the natural course of the disease and current treatments, as well as provide information that will be useful in determining the burden of the disease to patients, healthcare systems, and society.

Before developing the research plan, a thorough review of the literature should be conducted. The literature search can be generated via MEDLINE using typical clinical search terms. Literature sources such as *Social Science Abstracts*, *International Pharmaceutical Abstracts*, government documents, and other databases also should be considered. However, not all information desired will be found in the literature; knowledge gaps can be identified from the literature review, providing a platform for the researcher to expand.

Identifying what is known about the condition and its current treatments helps focus the research effort. Questions of interest typically include: Who does the condition most affect? In what ways? Who bears the burden of the illness? For example, asthma may affect a child clinically and in terms of lost school days. However, in an economic sense, it may also affect a working parent or the parent's employer. Likewise, Alzheimer's disease has tremendous economic and humanistic consequences on the caregivers. Additionally, some diseases have no effective treatment, and the healthcare system can provide only minimal care for the patient. However, these conditions may incur costs outside of the healthcare system. Depending on the perspective taken, those costs may be as important as the costs incurred within the system. For example, the cost of AIDS is great in terms of the morbidity costs incurred outside of the healthcare system.

It is initially important to assess the humanistic factors affected by the disease to capture the total burden of the illness and establish baseline information. Likewise, patient satisfaction with specific aspects of current treatments or interventions should be considered and measured. These baseline humanistic (satisfaction, HRQOL) assessments may indicate the degree to which there is room for improvement from the patient's perspective. If baseline scores indicate minimal dissatisfaction or impairment, it is unlikely that an intervention will result in significant improvement in satisfaction or HRQOL, assuming valid, reliable, and precise instruments are used. For example, migraine headaches have been demonstrated to impact the quality of life of people who experience them compared with those who do not, even between headaches.³ The HRQOL impact of nausea and vomiting associated with highly emetogenic chemotherapy has been documented.⁴ Similar work has also shown that patients with osteoarthritis have a worse HRQOL (and therefore room for improvement) than those without that disease.⁵ Baseline HRQOL assessment may involve cross-sectional data collection or longitudinal collection. Cross-sectional data collection provides a fingerprint of HRQOL at one point, with patients reporting their health status during the past week or month. Following a group of patients over time to collect longitudinal data can provide information about changes in health status during the measurement period.

It also is valuable to establish baseline levels of resource use. The basis for economic evaluation is an appropriate and complete assessment of the resources being used as opposed to dollars being spent. This is particularly true when collecting data from multiple locations and within environments where costs are subject to change. Resources used also represent, in part, the processes of care involved in patient diagnoses and treatment. Until recently, there have been only minimal attempts to link such processes of care to patient outcomes. If resources are limited, it is important for decision- and policy-makers to ensure that providers are using resources efficiently and effectively. If it is not known what or how much is being used to achieve an endpoint, it is impossible to know whether efficiencies are being attained. As resource use comes under greater scrutiny, it becomes more important to know what resources are involved in treating a condition to make proper use of the existing resources and ensure that new treatments are properly framed.

Although prospective studies may be required to capture the baseline data, there are other sources to consider. Some of these sources include patient diaries, government surveys, and medical charts. These sources can be used to conduct longitudinal studies to capture resource use over time. Various databases exist that can provide some information regarding resources used to treat conditions. These databases exist because many health-care providers, including health maintenance organizations, have been paid based on the resources they use, so there is an incentive to provide such data. However, administrative databases do have shortcomings since they were not designed to provide complete outcomes information; they were designed to pay claims. If the condition is clearly and easily defined by a disease or treatment computer code, claims databases may provide information regarding the processes of care. However, medical claims data should never be assumed to be accurate. Appropriate validation techniques should be used to demonstrate the accuracy of the claims.

The importance of establishing appropriate and rigorous benchmarks for pharmacoeconomic assessment cannot be overstated. The management of outcomes is dependent on the ability to measure them, and measurement must have a frame of reference.

Study Design

RATIONALE

After benchmarks have been established, the next critical step is to incorporate pharmacoeconomic parameters into clinical trials. The goal of this step is to provide data that will demonstrate the value of the product or intervention from various perspectives. Pharmacoeconomic research attempts to answer the “so what” question to the observed clinical change; that is, it documents the economic and humanistic consequences of pharmacotherapy. Ideally, pharmacoeconomic and clinical study plans should be developed in tandem. The degree of pharmacoeconomic involvement will most likely be a function of the phase of research in which the study is being conducted, the clinical study design, the condition of interest, and the information gathered at baseline regarding the condition and its impact. Key questions to address include:

1. What is the primary purpose of the study?
2. Are economic and HRQOL measures of primary or secondary importance?
3. Why does this study need to be conducted? (eg, support registration, clinical experience)

The process defined to address these questions should be clear and transparent so that potential issues surrounding study design or bias are easily addressed.

OBJECTIVES

The pharmacoeconomic research question(s) should be defined in consideration of the clinical research question(s) raised. The questions should be clearly stated so that the study can be designed to answer the questions. Pharmacoeconomic research may be incorporated into a clinical trial as a secondary or primary objective. For example, if the study is a pivotal Phase III trial in which the primary goal is to measure safety and efficacy for an NDA/IRD submission, pharmacoeconomics may be considered as an “add on,” and it is unlikely that the study will be (or should be) extensively modified to make it more appropriate for a pharmacoeconomics study.⁶ On the other hand, a Phase IIIB or Phase IV study, with the primary intent of measuring

HRQOL or resource use in a general population with the condition under consideration, should be designed with the objective of answering a pharmacoeconomic question. Having a study designed primarily to collect pharmacoeconomic parameters does not mean that safety and efficacy are ignored; clinical data must be collected to associate resource use and HRQOL changes with the clinical response.

DESIGN ISSUES

The pharmacoeconomic endpoints should be clearly identified in the protocol. The protocol should be closely adhered to, and standard precautions should be taken to minimize potential biases or systematic error that may lead to erroneous conclusions. If the major purpose for conducting the study is to assess pharmacoeconomic changes with treatment, then completion of baseline pharmacoeconomic evaluations also should be part of the protocol's inclusion criteria.

When designing pharmacoeconomic studies, it is critical to adhere to sound scientific principles. Randomized controlled trials are generally considered to provide the strongest level of evidence of efficacy. Hence, clinical trials, especially those intended to be part of an NDA or supplemental NDA (sNDA) are typically randomized, double-blind, and placebo-controlled. However, other study designs (observational, pretest/posttest, modeling) may be better suited for evaluating a pharmacoeconomic question, where blinding may mask the actual use of resources or the impact of a means of drug administration on HRQOL. Observational studies are sometimes used by health services researchers if the goal is to evaluate resource use in a realistic setting for various populations using one intervention or another. The results must be interpreted cautiously and should not be viewed in isolation.

If resource use assessments are incorporated into the study, the perspective (eg, patient, society, employer) must be identified as well. Several perspectives may be of interest. As the healthcare system undergoes further shifts, some perspectives will no doubt be of greater interest than others. Clearly, society and patient perspectives are of interest because, as a society, certain types of healthcare resources, such as vaccinations, are

highly valued, in part because of their external benefits. Third-party payer perspectives are of interest because of the decision-making power that they have in the current healthcare system.

It is difficult to collect resource use and other economic data that are representative of realistic situations in a clinical study designed primarily to assess safety and efficacy. This is particularly true for chronic conditions, such as hypertension, or studies designed to prevent disease that use intermediate outcomes as endpoints (cholesterol-lowering studies designed to reduce the incidence of coronary artery disease or studies on preventing the sequelae of osteoporosis). On the other hand, some clinical trials of acute conditions may very closely mimic reality (eg, treatment of sepsis). The researcher must be aware of the extent of the limits imposed by the clinical trial design and document them in subsequent publications or presentations.

Likewise, the extent to which humanistic data collected in controlled clinical trials are indicative of expectations in the true population of patients is a function of the type of patients enrolled in the trial and whether the study design reflects a realistic use of the drug. For example, an antihypertensive clinical trial may include only individuals with mild to moderate hypertension and exclude those with other preexisting conditions. Conversely, a study of migraine with strict enrollment criteria may enroll only patients with the most severe symptoms. The patients participating in a clinical trial may serve as a proxy or may provide an indication of what to expect in future use outside of trial conditions. If mildly affected patients show some improvement, one might expect to see larger improvements in patients affected more severely. If the intervention is linked with the improvement, results will indicate what aspects (economic or humanistic) have changed; this can be predictive of the expected results of future studies. The results from pharmacoeconomic evaluations in early clinical trials will allow for more focused research in later studies.

SAMPLE SIZE

In planning the design of a study, it is essential to determine the appropriate sample size. Sample size may be a function of efficacy parameters, specific HRQOL parameters, or economic

parameters. If pharmacoeconomics is the primary objective of the study, the sample size should be estimated based on changes expected in those parameters. Currently, there is little information about sample size based on pharmacoeconomic parameters. Norms for the SF-36 Health Survey scales in the general United States population have been published by age and gender.⁷ However, until more information becomes available, pilot studies with pharmacoeconomic parameters, or previous trials, also may provide useful data. As an alternative, clinical parameters may be used to generate sample sizes; however, such an approach does not guarantee an appropriate estimate. For example, the number of subjects needed to show a clinical difference in asthma treatment might be 40 based on forced expiratory volume in one second; however, a cost-effectiveness study might require 140 subjects if the power calculation is based on the expected difference in number of emergency department visits. Post hoc power calculations will provide support for future studies. Additionally, in cases where pharmacoeconomic measures were not used to estimate sample size, sensitivity analysis should be used to place the results obtained from a study in proper perspective.

INSTRUMENT SELECTION

Selection and design of the data collection instrument is another important aspect of this research plan. Recognizing the symptomatology of the condition and how the population is affected will enable the researcher to select or create an instrument to measure how an intervention might lessen the economic and humanistic burden of the condition in question. Instrument choice is critical. If HRQOL measures are to be included, the condition in question will be the determinant of whether a disease-specific instrument is required. If no appropriate instrument exists, an existing instrument may have to be modified or a new instrument designed. If it is not clear whether a disease-specific HRQOL instrument is needed, it is better to err on the conservative side and use one. A feasible approach is to use a standardized, validated core instrument to collect HRQOL measures, with customized additions to address the specific considerations warranted by the condition under study.

The issues of validity, reliability, and instrument sensitivity should be considered before an instrument is selected for use in baseline measurement and in a clinical trial. It is certainly possible to use a new instrument in a clinical trial without previous knowledge of its validity or reliability; however, the risk the researcher takes is that, after the fact, the instrument may be shown to lack those desired properties. Before using an instrument in a controlled trial, if possible, one should consider conducting a pilot test to verify that it is valid, reliable, and sensitive. If time does not permit it, one needs to consider the risks involved in ending up with data that are not usable.⁸ Resource utilization questionnaires also should be carefully developed and tested prior to use within a clinical trial. Data to be collected directly from patients by use of these instruments require special considerations. Some points to consider before any instrument is selected are literacy and translation of clinical terms into language that the patients will understand. The number of items one intends to include will be a function of the disease of interest.

Proper administration of the data collection instruments also is important. The protocol should specify how data will be collected, who will collect them, the specific time(s) during the study that data will be collected, and who will provide the information. Investigators need to be informed of their responsibilities in providing and/or collecting data. Anticipating these questions and addressing them before data collection starts is important to the success of the data collection and, therefore, the study results.

Selection of investigators is another important consideration that affects the success of the study. The number of sites involved in a study may vary. Increasing the number of sites increases the potential complications from a management perspective. However, multiple sites are often needed so that sufficient numbers of patients can be enrolled within a reasonable time frame.

If the patient is the main source of pharmacoeconomic information, the burden placed on the patient needs to be considered. Most patients will not object to providing information; however, if the patients are going to be asked to provide information, they must be notified via informed consent. Patients should be told how much is expected of them, what they are to do, who will answer their questions, and other facts about the

study and its effect on them. These issues must be clearly stated in the patient consent form.

Data Management

DATA COLLECTION

In most traditional clinical trials, data are collected in the practitioner's office, hospital, or clinic. Since the physician is usually the investigator and may be making decisions about clinical efficacy, this method is appropriate. Pharmacoeconomic data are frequently, but not always, collected from the patient. Knowledge of the disease helps indicate who can provide the most reliable information about its burden. The patient and the physician are often respondents of choice. However, if the trial involves children, elderly people with cognitive dysfunction, or patients with other mental impairment, the patient may not be the most ideal source of information. Rather, caregivers or parents may be more appropriate respondents.

There are also trade-offs between asking for information at the healthcare provider's site (eg, office, pharmacy) versus collecting it at home. Collecting data at the provider's office means that pharmacoeconomic data are collected at the same time that clinical data are collected. If questionnaires are completed at home, the ability to link the response with a clinical response may be a bit more difficult. On the other hand, patients or caregivers may feel rushed at the provider's site, especially if they are asked to provide additional information during the visit. The likelihood of obtaining complete responses is higher if the data collection forms are completed before the patient leaves the site, and the completeness can be checked by the investigator or another staff member. Also, if questions arise, someone is close by to answer them.

Another potential concern of asking questions at the provider's site is that the patient or caregiver may respond in the manner they think will please the provider as opposed to how they really feel. The issue of social response bias should not be ignored, but it should be kept in perspective. It is, in part, a function of what questions are being posed. If patient satisfaction with the provider is the issue, a social response is of concern. But if the questions focus on the patient's ability to work or attend school,

response bias may not be as significant. Response bias is not limited to a physician's office; it also could occur in a home where a spouse may coach a patient as to the "right" responses.

Social response bias may be reduced by changing the data collection medium. A personal interview in a waiting room is not likely to generate any information that the patient considers confidential. Patient self-report via a paper-and-pencil format or computer may provide a better sense of security. There is no generally agreed-upon means to collect such data, as each method has its pros and cons, but whatever method is used, it is important to be consistent across all patients and throughout the study. For example, the SF-36 Health Survey, a commonly used, validated instrument, consistently generates higher scores when data are collected over the telephone as opposed to a paper-and-pencil completion.⁹ If change over time is of interest, consistent use of one approach is most appropriate.

FREQUENCY OF DATA COLLECTION

How often should pharmacoeconomic data be collected? If change is to be measured, a baseline and final assessment are required, at a minimum. Additional data collection points will be a function of the trial design and the condition being evaluated. When making the frequency decision, one should consider the pattern of intervention, and whether measures can be concentrated on where the maximum response to treatment is expected. Distinguishing between early and late effects of an intervention may be useful. The frequency with which data are to be collected should be stated in the protocol. Conservative estimates are recommended as data can always be aggregated, but cannot be disaggregated any finer than the original data collection points. Patient burden should also be considered when making these decisions. For an acute treatment, a baseline and final assessment may be appropriate; for a long-term trial, more frequent measures may be necessary to reduce the time period for which patients are asked to recall drug effects.

DATA ENTRY

Proper procedures must be in place to ensure that data being analyzed are of acceptable quality. As with most studies, expect-

ed problems in the analysis of such data will surround missing data, multiple responses to single-item questions, illegible items, and stray marks. As the data proceed through data entry, quality assurance, and quality control, procedures such as how missing data are to be handled should be identified and then adhered to scrupulously. A code book should be developed addressing each variable to be entered and decisions made beforehand on how to deal with likely problems. When new problems arise with data entry (and they will), decide the response, be consistent, and note it in the code book.

In the case of HRQOL analysis where several items may comprise a scale, it will be important to state at what point missing items will negate the use of an observation. In the case of economic data, missing items may reduce the usable sample size. Lack of critical demographic information may mean that work status cannot be identified. Missing data can be minimized by using appropriate questionnaires that are easy to complete with minimal burden on the patient or caregiver.

Analysis and Interpretation

An analysis plan also should be developed and either stated in the protocol or maintained as a separate document. The data analysis methods included in the statistical section of the protocol will be dictated by the types of data collected. Variables should be identified that are hypothesized to change over time. As is the case for the clinical component of many studies, a single variable may not suffice as “the answer” for a pharmacoeconomic study. Therefore, primary and secondary measures should be identified. The more measures identified to be of primary importance, the larger the sample size needed and the greater the likelihood of having one measure reach statistical significance due to chance. In the case of resource use, variables of interest may be length of hospital stay or intensity of resource use.

Economic variables need to be evaluated as was determined before the study started. In the case of HRQOL measures, an index, a profile, or a battery of measures may be primary variables. If HRQOL is evaluated via a standard instrument, the instrument should be scored according to the developer’s instructions. Multiple analyses of data not specified or planned for in the original

study protocol will have less impact (seen as data dredging) than prespecified analyses, unless it is a pilot study intended to generate hypotheses as opposed to testing hypotheses.

The patients to be included in the analysis need to be identified. In some cases, the *intent-to-treat* sample is the appropriate choice. This typically includes all patients enrolled in the study, whether or not they actually followed the protocol, who received at least one dose of study medication. The intent-to-treat analysis is considered to most closely reflect actual use of a drug. Not everyone is adherent, and not every patient provides data for all collection points. Another option is to analyze only patients who completed the study *per protocol*. This subgroup may be of interest if HRQOL of an intervention is being evaluated (eg, there is interest in evaluating only patients who took the drug properly). Analysis of both intent-to-treat and per-protocol groups and a comment on the similarities and differences also is an option, but it is more time consuming.

There are a variety of methods by which pharmacoeconomic data may be analyzed. Clearly, which analytic method to use will be a function of what level of data is collected (eg, nominal, ordinal, interval), its distributional properties, and the number of time points at which data are collected (cross-sectional or longitudinal). Direct comparisons, trends, percent successes, survival analyses, repeated measures, and multivariate analyses all have been used. Whichever method is chosen, it should be stated and justified in the protocol. In general, it is best to keep the analysis as simple as possible. Results should be reported in unweighted averages, in standard form. If HRQOL is measured using a profile, each dimension should be reported separately. Treatment groups should be separated and analyzed by treatment.

Potential confounders of data also need to be considered. Before one can attribute an effect to a specific intervention, it is important to minimize the likelihood of that effect being due to other variables. Randomization into groups, control groups, adequate sample sizes, and appropriate control of baseline parameters help to minimize confounding.

Uncertainty can be addressed in two ways. Statistical methods can be used to address uncertainty that may be due to sampling techniques.

Sensitivity analysis can be used to address uncertainty due to lack of knowledge. Sensitivity analyses ask “What if?” and test the robustness of the data. When assumptions are made about certain parameters, sensitivity analysis quantifies how comfortable one can be with those assumptions. For example, there is no general agreement on the precise discount rate that should be used to discount future healthcare benefits or costs. Since the precise rate is unknown, it is reasonable to test study results with a low, high, and middle value. If study results vary widely, one can have less confidence in any single set of results. Sensitivity analysis can demonstrate the dependence of a conclusion on a certain assumption or that an assumption does not affect results significantly. It also can be used to establish a minimum or maximum value that a variable must possess for study results to be positive.

If the study is multinational, cross-cultural differences must be considered. Before clinical data such as blood pressure and laboratory values can be pooled for analysis, the data must be evaluated for homogeneity. In the same vein, neither HRQOL nor economic data should be pooled without cultural and homogeneity issues being taken into consideration. There may be substantial differences in HRQOL responses across cultures.¹⁰⁻¹² Thus, instruments need to be translated to ensure linguistic and conceptual equivalence. From an economic perspective, different countries may have different pricing policies, and the decision as to what monetary value to use is not always clear. It may be simpler to express economic evaluations in terms of resources used rather than in monetary increments, although some researchers have attempted to estimate country-specific cost-effectiveness from multinational trials.¹³⁻¹⁵ Despite attempts to control for various parameters, differences may still exist and, in those cases, data should not be aggregated.

Reporting the Results

When reporting pharmacoeconomic data that were collected in clinical trials, it is useful to keep the presentation simple. If the initial questions asked were clearly stated, such an approach is realistic. One should avoid discussions of individual patients; rather, summary measures should be used to discuss

the differences between treatments over time. One should be aware of potential censoring of HRQOL or economic results by death and/or early dropouts. For example, if patients in an osteoarthritis trial who do not experience pain relief are dropped from the study because the treatment is considered a failure, these patients may be using significantly more resources than subjects who are doing well and are still in the study. If the patients in whom treatment fails are lost to follow-up, it will be very difficult to trace the real impact of treatment due to limited knowledge of what happens to people in whom the treatment does not work. Likewise, the value of treatment may be underestimated if the patients in the placebo group are dropping out. The components of variance should be discussed and sensitivity analyses should be conducted so the reader can have an idea of the robustness of the data.

Conclusions

The decision to incorporate pharmacoeconomic parameters into a clinical trial depends on the healthcare environment and what information is being requested to make rational decisions about healthcare choices. Some regulatory agencies require and others are considering requiring economic information as a component of the drug approval and/or reimbursement process. Just as resource availability may limit a pharmaceutical company's ability to develop all of the potential drugs it has in its pipeline, resources also may limit the extent to which pharmacoeconomics will be incorporated into specific drug development programs. Realistically, some pharmaceutical products and healthcare interventions will be in greater need of pharmacoeconomic support than others. For example, drugs that are expected to be used for chronic conditions, to palliate symptoms, or slow the spread of an illness, but not cure it, are more likely to generate queries regarding their pharmacoeconomic benefit than a drug that cures an acute condition. Marketplace competition and demands also play roles in the decision. If a company plans to enter a market in which a number of similar drugs already exists, it may be sufficient to compete only on the basis of price as long as equal efficacy and safety can be demonstrated. HRQOL studies may be of interest only if there is a reason to suggest a differ-

ence in the adverse effects or functional status as a result of the intervention.

Pharmacoeconomics is a valuable tool used for making rational choices about pharmaceutical care interventions. Data can be collected in controlled trials before a drug has been approved, and such data can be very useful as long as certain caveats are acknowledged. Whatever pharmacoeconomic assessment is chosen, it is imperative that all aspects of the study be transparent and able to stand the tests of reproducibility and appropriate criticism.

References

1. Wennberg JE. Improving the medical decision making process. *Health Affairs* 1988;7:99-106.
2. Spilker B. Designing the overall project. In: *Guide to planning and managing multiple clinical studies*. New York: Raven Press, 1987:36-62.
3. Osterhaus JT, Townsend RJ, Gandek B, Ware JE Jr. Measuring the functional status and well-being of patients with migraine headache. *Headache* 1994;34:337-43.
4. Lindley CM, Hirsch JD, O'Neill CV, Transau MC, Gilbert CS, Osterhaus JT. Quality of life consequences of chemotherapy-induced emesis. *Qual Life Res* 1992;1:331-40.
5. Briggs A, Scott E, Steele K. Impact of osteoarthritis and analgesic treatment on quality of life of an elderly population. *Ann Pharmacother* 1999;33:1154-9. DOI 10.1345/aph.18411
6. Cady RK, Dexter J, Sargent JD, Markley H, Osterhaus JT, Webster CJ. Efficacy of subcutaneous cumatriptan in repeated episodes of migraine. *Neurology* 1993;43:1363-8.
7. Ware JE Jr, Snow KK, Kosinski M, Gandek B. *SF-36 health survey manual and interpretation guide*. Boston: The Health Institute New England Medical Center, 1993.
8. Young TL, Kirchdoerfer LJ, Osterhaus JT. A development and validation process for a disease specific quality of life instrument. *Drug Info Assoc J* 1996;30:185-93.
9. McHorney CA, Kosinski M, Ware JE. Comparisons of the costs and quality of norms for the SF-36 health survey collected by mail versus telephone interview. *Med Care* 1994;32:551-67.
10. Hurny C, Bernhard J, Gelberg RD, Coates A, Castiglione M, Isley M, et al. Quality of life measures for patients receiving adjuvant therapy for breast cancer: an international trial. *Eur J Cancer* 1992;28:118-24.
11. de Haes JC, Olschewski M. Quality of life assessment in a cross-cultural context: use of the Rotterdam Symptom Checklist in a multinational randomised trial comparing CMF and Zoladex (Goserelin) treatment in early breast cancer. *Ann Oncol* 1998;9:745-50.
12. Bullinger M, Alonso J, Apolone G, Leplege A, Sullivan M, Wood-Dauphi-

- nee S, et al. Translating health status questionnaires and evaluating their quality: the IQOLA Project approach. *International Quality of Life Assessment. J Clin Epidemiol* 1998;51:913-23.
13. Schulman K, Burke J, Drummond M, Davies L, Carlsson P, Gruger J, et al. Resource costing for multinational neurologic clinical trials: methods and results. *Health Econ* 1998;7:629-38.
 14. Willke RJ, Glick HA, Polsky D, Schulman K. Estimating country-specific cost-effectiveness from multinational clinical trials. *Health Econ* 1998;7:481-93.
 15. Jonsson B, Weinstein MC. Economic evaluation alongside multinational clinical trials. Study considerations for GUSTO IIb. *Int J Technol Assess Health Care* 1997;13:49-58.