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*Pharmaceutical Technology
Assessment for Managed
Care: Current Practice and
Suggestions for Improvement*

*Samuel A. Bozzette, Rebecca D'Amato,
Sally Morton, Katherine Harris, Robin Meili,
Roger Taylor*

RAND Health

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Preface

Increasingly powerful pharmaceuticals are of increasing clinical and economic importance to managed care organizations. Expenditures on pharmaceuticals have also been increasing, a trend driven by a number of factors, including the accelerating development of more-innovative and more-expensive agents; rising pharmaceutical prices; and higher utilization due to the aging of the population, direct-to-consumer advertising, and other factors. More often today, health plans and provider organizations are responsible for managing and paying for these increasing pharmaceutical costs, which creates an incentive for them to go beyond a focus on clinical effectiveness and safety to evaluate the cost-effectiveness of new drugs. In addition, the development of drug formularies and the current focus on best practices require that each new drug be assessed relative to available alternatives. The formal controls and guidelines resulting from managed care processes can increase quality and cost efficiency, but can also be a barrier to desirable innovations. Together, these developments have caused managed care organizations (MCOs) to realize that making good decisions on new pharmaceuticals is to their immediate financial and clinical benefit. Accordingly, many have expressed interest in improving their ability to evaluate new pharmaceuticals.

Four interrelated developments in today's health care system provided the motivation for developing the framework for pharmaceutical technology assessment reported here:

- The rising importance of pharmaceuticals in health care, and the prospect for increasing numbers of more costly new entities, including some that will affect the current pattern of care by creating demand for treatment or substituting for other services such as hospital care or surgery.
- The increasingly wide range of managed care organizations, including health plans and provider organizations, held responsible by purchasers for managing and paying for pharmaceuticals.
- The potential for the quality-improvement, guideline, and disease-management movements—which codify current clinical practice—to affect the diffusion of technology.
- The widely perceived (by government, third-party payers, MCOs, pharmaceutical companies, etc.) need for better tools, processes, and support systems to help managed care organizations evaluate new pharmaceutical technology for possible health plan coverage or patient use.

This report describes the processes by which managed care organizations evaluate pharmaceutical technologies and suggests pathways for organizing improvement. It reviews current evaluation procedures, provides a framework for future evaluations, introduces evaluation approaches, and annotates resources for further research on each topic covered. The report is

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intended to assist managed care organizations, including health plans, medical groups, pharmacy benefit management firms, and others interested in initiating formal pharmaceutical evaluation activities or in improving existing procedures.

The report is based on research conducted by RAND Health. RAND Health furthers RAND's mission of helping improve policy and decisionmaking through research and analysis, by working to improve health care systems and advance understanding of how the organization and financing of care affect costs, quality, and access.

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Executive Summary

Increasingly powerful pharmaceuticals are of increasing clinical and economic importance to managed care organizations. Expenditures on pharmaceuticals have also been increasing, a trend driven by a number of factors, including the accelerating development of more-innovative and more-expensive agents; rising pharmaceutical prices; and higher utilization due to the aging of the population, direct-to-consumer advertising, and other factors. More often today, health plans and provider organizations are responsible for managing and paying for these cost increases, which creates an incentive for them to go beyond a focus on clinical effectiveness and safety to evaluate the cost-effectiveness of new drugs. In addition, the development of drug formularies and the current focus on best practices require that each new drug be assessed relative to available alternatives. The formal controls and guidelines resulting from managed care processes can increase quality and cost efficiency, but can also be a barrier to desirable innovations. Together, these developments have caused managed care organizations to realize that making good decisions on new pharmaceuticals is to their immediate financial and clinical benefit. Accordingly, many have expressed interest in improving their ability to evaluate new pharmaceuticals.

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intended to assist managed care organizations, including health plans, medical groups, pharmacy benefit management firms (PBMs), and others interested in initiating formal pharmaceutical evaluation activities or in improving existing procedures.

The data collection component of our study consisted of a two-part process of interviewing representatives of relevant organizations and reviewing the relevant literature. We performed semi-structured qualitative interviews of decisionmakers at 12 national and regional managed care organizations, at medical groups at some risk for their pharmacy costs, and at pharmacy benefit management firms. Our literature review uncovered over 1,000 articles, which we narrowed to 38 for a thorough review. We then synthesized the results of the interviews and literature review to produce a review of current practices, using five questions to frame the synthesis:

- *Who decides to accept or reject new pharmaceutical technology, and how?*
- *What decision options (e.g., “Exclude drug,” “Assign to high-cost tier,” and “Require prior authorization”) are considered?*
- *What factors affect the timing and resources devoted to pharmaceutical technology assessment?*
- *What types of evaluations are performed and what types of evidence do they use?*
- *How are decisions implemented and the results monitored?*

This review informed the second part of the study, in which we develop a prescriptive framework for pharmaceutical technology assessment and a guide to the major relevant analytic approaches. The appendices to this report provide an annotated bibliography and a copy of the interview questionnaire.

Our review of current practices found wide variation in the process whereby organizations assess pharmaceutical technology and manage pharmacy benefits. The locus of pharmaceutical evaluation varies by organizational type, as does range of decision options available within each organization. The timing of the assessment appears to be a function of the organization’s reason for performing the assessment. The process used by the decisionmakers we interviewed is often neither reproducible nor rigorous, but the level of rigor does appear to increase with the level of controversy or demand for the drug. Finally, the emphasis of the evaluations is usually on safety, efficacy, and direct drug costs rather than on overall potential financial impact or health outcomes, although all respondents were concerned with impact and outcomes.

Those managed care organizations with whom we spoke wanted a structured process, or framework, for assessing pharmaceutical technology, believing that use of such a framework would, over time, increase the ease of sharing information, the rationality of the decisionmaking process,

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and the transferability of best practices. However, some of our interviewees cautioned that for a structured guideline to be helpful in the "real world of managed care," it would need to be flexible, efficient, and adaptable by diverse organizational structures and for a variety of purposes.

With that comment in mind, and in response to the other findings in this report, we suggest a structured process for assessment of pharmaceutical technology in managed care that includes the following steps:

- *Characterize the drug and the disease* by identifying *potential* clinical risks and benefits of the drug, describing the drug in relation to the marketplace, and assessing the importance of the disease in terms of its current and potential future prevalence and impact.
- *Characterize the decisionmaking organization* in terms of the extent to which and means by which it can promote or limit the use of the pharmaceutical in question.
- *Define the decision options* by identifying (but not yet choosing among) the available organizational processes that can be used to control the prescribing and use of the drug.
- *Define the method needed to make the decision*, including rigor and resources required, the agent who will perform the assessment, the timing of the assessment, and the most appropriate methodologies.
- *Perform the assessment* according to standard approaches to systematically obtaining expert opinion, performing evidence assessment, or constructing a mathematical model, whichever is selected.
- *Make, implement, and evaluate the decision.*

In summary, most managed care organizations have internal procedures for assessing new pharmaceutical technologies. Medical directors in a variety of organizations commonly believe these procedures to be less rigorous and less systematic than are desirable for making decisions having substantial implications for the short- or long-term health of the organization and its patients. The decisionmaking framework outlined above and the techniques incorporated in it describe an objective, reproducible process for approaching these analyses. Not a cookbook, it is instead a "road map" for an approach that can help an organization expose hidden biases in current processes, build on its experiences with evaluation, and reduce the risk of illogical or poorly thought-through decisions.

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1. Introduction

Purpose of This Report

The introduction of new drugs, or pharmaceutical technologies, over the past decade has required managed care organizations to perform a balancing act. On the one hand, this rapid progress in drug therapy has improved well-being and decreased the need for intrusive and expensive services in previously unimaginable ways. On the other hand, the cost of new drugs has strained pharmacy budgets and, even though the effect on overall costs varies, has often forced providers and purchasers to balance the competing demands of cost, effectiveness, and access.

Under managed care arrangements, health plans and provider organizations bear substantial clinical and financial responsibility for pharmaceutical use. However, these organizations do not control pharmaceutical use, which is actually driven by the behavior of enrollees and the prescribing patterns of their physicians. As a result, organizations have developed a variety of strategies for influencing pharmaceutical use: fixed or variable co-payments, prior authorization, encouragement of drug substitution, mandatory step therapies,¹ dosing or duration limits, and exclusion of particular classes of drugs from coverage (Schweitzer, 1997).

Although these strategies are usually aimed at controlling expenditures, organizations also employ them to encourage the use of drugs that provide clinical, economic, or organizational advantages. As advances in molecular medicine and human genetics continue to create increasingly powerful but difficult-to-use "designer drugs," strategies for encouraging use may be required more often to optimize clinical outcomes and manage costs. However, new drugs, such as Norplant (left under the skin for prolonged periods), artificial joint fluid (which is injected directly into the knee), or vectors for delivering therapeutic genes, may require novel delivery systems and may have costs that are less like those of conventional pharmaceuticals and more like those of traditional hospital care. Thus, it is often important to fully understand the cost and quality implications of new pharmaceuticals before accepting or rejecting them.

Managed care organizations in particular need to understand how various pharmaceutical policies and procedures will govern the effect of a new drug. Will requiring pre-authorization preferentially reduce inappropriate use of a particular drug? Will step-therapy programs ensure that an effective but potentially toxic drug is used only after first-line drugs are exhausted? Will assigning a co-payment reduce adherence to a drug regimen among patients who may benefit most from it?

¹ In *step therapy*, certain therapeutic substitutes are tried before a more potent, toxic, and/or expensive drug is prescribed.

Why Pharmaceutical Technology Assessment Is Important

Answering these questions and making good decisions on the use of new pharmaceuticals is financially and clinically responsible, and is therefore in the short- and long-term interest of managed care organizations. These decisions are significant because increasingly powerful pharmaceuticals are of increasing clinical and financial importance to health care and health care organizations. Expenditures on pharmaceuticals are rising, to the increasing concern of managed care organizations, health care providers, purchasers, and consumers. In 1998, the retail pharmaceutical market in the United States generated \$93.7 billion on a total volume of 2.4 billion prescriptions, representing a 4% increase in the number of prescriptions in one year (Novartis, 1999). Meanwhile, prescription drug expenditures in the fourth quarter of 1998 increased by 16.8% over the same period in 1997 (Winslow, 1999). At many health plans, prescription drugs now account for 11 to 14% of total medical expenses, up from 7% in the early 1990s (Winslow, 1999). For diseases requiring "high-tech" treatment, the increases have been more dramatic. For example, drug costs per patient per month rose 38% in the two years after the introduction of new highly active combination treatments for HIV (Joyce, 1999).² Researchers for the Health Care Financing Administration (HCFA) are predicting that these trends will continue, with prescription drug costs increasing nearly 10% every year through 2007 (Hagland, 1998). Health maintenance organizations (HMOs) are predicting a 20% increase in annual drug costs, even though overall health care costs are expected to rise only 5% in 2000 (Galewitz, 1999).

Increased expenditures are driven by both increases in the quantity of drugs prescribed and increases in the unit prices of drugs. The National Association of Chain Drug Stores predicts that the number of prescriptions filled in pharmacies will rise and that the dollars spent on prescriptions will rise even more (Harris, 1999). The average cost per prescription rose 7%, to \$38, in 1998, and certain new biotechnology drugs can run as high as \$14,000 per year for individuals with common chronic conditions (Novartis, 1999; Winslow, 1999).³ There are two readily identifiable causes of increasing unit prices in the U.S. market, but the relative importance of these two factors has been the subject of considerable debate (Schweitzer, 1997). First is the possibility that increasing R&D expenses and shareholder demands are pressuring drug manufacturers to price products in the largely unregulated U.S. market to compensate for lower margins elsewhere. Second is that prices have risen in response to increasing patient demand for old and, especially, newer drugs, which are generally more costly than the drugs that they replace or which target new diseases.

²The total cost of HIV care per patient per month declined over this period as a result of declines in hospital care, a fact that underscores the need for comprehensive assessments.

³ This is by no means the limit on cost. For example, the annual cost of the orphan drug alglucerase (Ceredase) for the rare inherited condition Gaucher's disease is many times as expensive.

Innovative drugs—including pharmaceuticals to treat conditions that were previously untreatable, treatable only through hospitalization or surgery, or perhaps even not considered appropriate for medical therapy—tend to be more costly. Significant new treatments are now available for conditions such as AIDS, hepatitis C, breast cancer, and transplant rejection. Some of them produce offsetting savings from avoided morbidity—for example, cholesterol-lowering agents that reduce heart attack rates or by substituting for more-expensive treatment modalities—for example, pharmacotherapy replaces chronic hospitalization for psychosis and surgery for gastrointestinal ulcers in most patients. Some other types of new drugs are unlikely to produce offsetting savings over the short term. These include new therapies for conditions that were previously untreatable or for which drug therapy was poorly tolerated—for example, Cox II inhibitors for pain. Finally, the costs of “lifestyle” drugs for conditions that are not universally regarded as diseases—for example, male pattern baldness or moderate obesity—are likely to translate directly into increased overall costs. Therefore, the effect of new drug use on overall expenditures is variable.

Other factors are increasing the demand for pharmaceuticals. For example, the “baby boom” generation is aging, causing the prevalence of chronic diseases such as diabetes to rise (Hagland, 1998). The number of persons in treatment for some diseases has been increased by disease-management programs. As part of the drive to improve outcomes while controlling overall costs (Epstein and Sherwood, 1996), such programs may systematically identify persons at risk in a population under care—for example, people likely to get diabetes—and intervene with a coordinated, comprehensive program of care along the continuum of the disease—for example, monitoring diet and laboratory work for mild diabetes and adding pharmaceuticals if the disease worsens. In this way, many disease-management programs encourage the use of pharmaceutical therapies at an earlier stage of disease than is usual (Epstein and Sherwood, 1996; Ellrodt et al., 1997).

The preferences of increasingly informed consumers are also dramatically affecting demand. One major reason for this is the rise of direct-to-consumer advertising, which has increased patient awareness and demand for specific drugs. Spending on such advertising increased from essentially nil 10 years ago to \$104 million in 1993, \$600 million in 1996, and \$600 million in just the first half of 1998 (Nordenberg, 1998; Hagland, 1998). The growth of the Internet has also made health information more accessible to consumers. A 1999 telephone survey estimated that, of the 88 million Americans with access to the Internet, 68% have used the World Wide Web to access health care information (Louis Harris and Associates, 1999).

These increases in expenditures directly argue for better decisions on pharmaceutical technologies because payers are increasingly holding health plans and provider organizations

accountable for the costs of care. More and more provider organizations are entering capitation and other risk-sharing arrangements, so they can no longer have others billed for the costs of their clinical decisions. Consequently, prescribers are under mounting pressure to move beyond traditional safety and efficacy concerns to consider cost-effectiveness and other pharmacoeconomic factors, such as ease of administration. Moreover, as purchasers of health care become more sophisticated, managed care organizations are increasingly required to measure and monitor the outcomes of care and to use this information to improve care processes. To the extent that the relationship between medical interventions and disability becomes better understood in the future, organizations may also be held accountable for the productivity and labor force participation of their patients. To meet these new demands, provider organizations have asked for practical models for assessing the potential effects of new drugs, both financially and clinically. These models should account for not only the outcome of a course of treatment with a particular drug but also its effect on the entire care process and beyond. Section 3 describes several approaches to generating such models.

Health plans and providers are being held more responsible for measurable outcomes of care. Quality management, whose tools include clinical guidelines and protocols ("care paths," for example) as means of codifying "best practices," require good information on new drugs. They are intended to act like disease-management programs in promoting best practices in drug therapy. However, guidelines can be static, thereby creating *de facto* barriers to improvements in the process of care. Severe cost pressures and thinning margins can exacerbate this barrier effect by reducing the appeal of new technologies that create initial cost increases. The danger is that if new technologies that improve health and quality of life are not accepted and implemented, limited receptivity to innovation in the short run can create greater costs in the end. Systematic approaches to evaluation that make it easier to assess the complete impact of the drug and predict the longer-term effects of using a new agent can help to overcome these barriers to change. Even though longer-term effects are currently seen as more important to society generally than to individual plans, we would argue that all plans would benefit if longer-term thinking becomes more common. Moreover, longer-term thinking may provide individual plans with a strategic advantage in the marketplace.

Pharmaceuticals As a Technology to Be Assessed

To guide the conduct of the study, we looked to the perspective of technology assessment. One accepted definition of *technology* is "the science of the application of knowledge to practical purposes" (*Webster's Medical Desk Dictionary*, 1986). Pharmaceutical manufacturers use scientific knowledge to develop and produce drugs whose purpose is to improve health and well-being. Thus, new pharmaceuticals are new technologies, and our interest in improving a managed care

organization's ability to review and adopt new pharmaceuticals is driven by the assumption that informed decisionmaking on new technologies will lead to superior outcomes.

Informing decisionmaking is the goal of technology assessment, which draws upon a wide variety of analytic tools and methods to take a comprehensive approach to evaluation. Although it was initially intended to be a mostly centralized activity, a variety of organizations now use technology assessment to assist decisionmaking on technologies from their own perspective rather than a regional or national one (Goodman, 1998). Technology assessment in health care tends to be performed in response to the introduction of, or major shift in the demand for, a new technology. It has been defined as the "evaluation of the safety, effectiveness, and appropriateness of the many devices, medical and surgical procedures, and pharmaceuticals promoted to improve a patient's condition or quality of life" (Matuszewski, 1997). This report presents a narrower focus on pharmaceutical technology assessment to support decisionmaking for populations enrolled in managed care.⁴

For adoption of new pharmaceuticals, pharmaceutical technology assessment should address a range of issues, including safety, clinical effectiveness, and cost-effectiveness in terms of medical expenditures. Depending on the particular condition and the perspective of the evaluator, issues may also include complicating factors such as indirect costs, labor-market outcomes (e.g., absenteeism, work-related disability and injury, and employee turnover), ethics, belief systems, public policy decisions, and impact on provider and patient roles. Finally, the market or public relations implications of decisions can be significant. For example, patient protests made a decision to exclude Prozac from a large health plan's formulary⁵ into headline news.

This report is written from the perspective of payers, providers, and society, rather than from that of the individual patient. We refer to health plans throughout this document because their breadth of responsibility in population-based medical decisionmaking encompasses clinical and financial outcomes. However, this discussion should also be applicable to integrated and hospital-based provider organizations, multi-specialty groups, and independent practice associations.

Organization of This Report

This report focuses on how health plans and provider organizations operating in managed care environments ("managed care organizations") do and could evaluate the opportunities and

⁴ To learn more generally and extensively about health care technology assessment, refer to Goodman's excellent monograph (1998).

⁵ A *formulary* is a list of covered or available drugs, often accompanied by a set of rules or guidelines for their use.

challenges presented by new pharmaceuticals. We discuss how organizational decisionmakers can use the tools of technology assessment to help estimate the likely effect of an emerging pharmaceutical technology, and their response to that technology.

We intend this report to assist managed care organizations interested in initiating formal pharmaceutical evaluation activities or in improving existing procedures. In this study, we identify gaps in the current practices of pharmaceutical technology assessment and propose improvements. We first employed a two-part data-collection process of interviews and a literature review, described in the first part of Section 2. We then synthesized the data into a review of current practices, presented in the second part of Section 2. This review informed Section 3, which contains both a prescriptive framework for future pharmaceutical technology assessment and a guide to the major relevant analytic approaches. Section 4 discusses practical aspects of applying the framework. Appendix A provides an annotated bibliography; Appendix B contains the interview questionnaire.

2. A Review of Current Practices

For our review of current practices, we collected data through interviews and a literature review. We structured the interviews and literature review around five questions that are central to understanding the nature of current assessments for new pharmaceuticals, and how they translate into benefit language and individual coverage decisions:

- *Who decides to accept or reject new pharmaceutical technology, and how?*
- *What decision options (e.g., "Exclude drug," "Assign to high-cost tier," and "Require prior authorization") are considered?*
- *What factors affect the timing and resources devoted to pharmaceutical technology assessment?*
- *What types of evaluations are performed and what types of evidence do they use?*
- *How are decisions implemented and the results monitored?*

Prior to our data collection, we hypothesized relationships between organizational motivations for assessing a new technology and who, what, how, and when pharmaceutical technology assessments were conducted. For example, consider a preferred provider organization (PPO) with indemnity prescription drug coverage for all FDA-approved drugs. Such a provider would likely conclude that it only needs to determine whether a new drug is specifically excluded from coverage because of plan contract language (e.g., is considered a cosmetic or in another excluded-drug class). We would expect that such an assessment would be done with minimum effort and analysis, and that it would likely wait until after the drug becomes available. In contrast, an HMO with full financial risk for drug-benefit costs (i.e., risk contract), a tightly managed formulary, and an extensive authorization program would likely see itself as having much broader and more clinically detailed assessment needs. We would expect that this organization's assessment process would begin much earlier, perhaps even as a result of monitoring the progress of pre-market drugs; that it would probably take longer; and that more resources and more techniques would be brought to bear on the assessment.

In this section, we first describe the data collection that we designed to address these hypothesized relationships, then synthesize the findings.

Data Collection

We collected data about current practices for this study in two ways: (1) by qualitatively interviewing a purposive (i.e., nonrandom) sample of relevant organizations, and (2) by searching the pertinent literature on existing and recommended practices in health care technology assessment.

Interviews

We designed the semi-structured qualitative interviews to review pharmaceutical technology assessment goals and practices at a variety of managed care organizations. Budget constraints prevented us from using probability sampling to select the organizations. Rather, we chose a purposive sample of organizations that reflected the target population in geographic dispersion, position in the market, and activity/risk related to pharmaceuticals. After making our selections, we spoke with the medical director or lead pharmacy contact at three of three selected national managed care plans, three of three regional managed care plans, four of four medical groups (differentiated by structure under which they operate: staff, multi-specialty, IPA or PPO, etc.), and two of three selected pharmacy benefit management (PBM) firms.⁶ Our interviewees at these organizations were senior managers with responsibility for financial liability *and* clinical quality in their organizations. These managers were also typically responsible for pharmaceutical-related administrative, legal, and regulatory compliance. Detailed notes from each of these interviews were taken for internal use; for reasons of confidentiality, they are not included in this report.

The 12 interviews were conducted over the telephone by one of three interviewers with extensive managed care experience, usually with a supporting investigator listening in as a scribe. Interviews lasted from 30 to 60 minutes. The interview questionnaire, which we faxed to interviewees in advance, is included in Appendix B.

Literature Review

For the literature review, we adapted the methods of the Southern California Evidence-Based Practice Center (The Cochrane Library, 1999) to identify and summarize articles containing information on current technology assessment practices, including specific assessment techniques and suggestions for future practice. First, we conducted four separate literature database searches to ensure that our search was comprehensive. With the assistance of a professional librarian, we chose keywords and other search parameters in an iterative manner, using articles we had prospectively identified as important. These four searches located 57, 115, 159, and 765 articles; thus, the unduplicated lists contained roughly 1,000 articles. As well, experts, including colleagues in the pharmaceutical industry, suggested articles that were important to include in our review. In addition to the library searches, we obtained those articles.

⁶ Pharmaceutical Benefits Managers (PBMs) offer drug benefit packages to managed care organizations, employer groups, and other payers. These organizations originally provided claims-processing services for prescription drugs, but they also negotiate prescription prices with pharmacies, implement generic substitute programs, and are developing volume-purchase agreements with pharmaceutical manufacturers (Navarro, 1994).

Next, we screened each article title for relevance, using a pair of readers (a health services researcher and a physician) selected from among three project members. We subsequently obtained the abstract for articles deemed relevant by either of the two screeners, which reduced the initial pool of articles to 126 candidates for further review. We screened the abstracts of these 126 articles and identified 38 general-overview articles describing current practices or recommended future directions. We obtained the full text of these 38 articles.

One project member then scanned each of the 38 articles and chose some key articles for immediate reading by the project team. We used the material contained in these articles to identify the technology assessment methodologies and other subtopics that we wished to include in this report. We then returned to the original search lists and, using a screening process similar to that described above, selected articles relevant to each subtopic. Additional project members read and summarized the subtopic and remaining 38 overview articles. Because these references constitute an important source of material for the text, we have summarized them in the annotated bibliography, Appendix A.

More comprehensive approaches, such as systematic searching for books and non-English literature (see the Evidence Assessment portion of Table 4.1 for elements of a thorough review), were not possible because of time and budget constraints. However, the search methods that we employed were systematic and reproducible, and we believe that we have captured most of the relevant literature.

Current Approaches

Health care organizations use a wide variety of strategies to assess pharmaceutical technology and manage pharmacy benefits. The health plans, PBMs, integrated health systems, and medical groups/IPAs we interviewed all devote resources to reviewing new drugs. However, the purpose, timing, formality, rigor, and criteria for review varied widely, as did the resources allocated to the process and, relatedly, the range of possible responses available to the reviewers. The literature documents a similar variation in the technology assessment process and resulting coverage decisions. The following subsections synthesize the findings of interviews and literature review, by framing question.

Who Decides to Accept or Reject New Pharmaceutical Technology, and How?

Many organizations and individuals make decisions that affect prescription drug benefits and adoption of new drug technology. Health plans decide which benefit plans they will offer to payers, including whether and under what conditions they will offer a prescription-drug benefit or cover a particular drug. Employers and other health plan sponsors decide whether and what kind of prescription-drug benefit they will purchase. PBMs usually recommend a range of prescription-drug

benefit packages for their clients, but they will also administer their clients' own unique benefit plans. Physician groups and hospital systems decide which drugs they will use preferentially in their practices. Finally, patients and their families decide when to request specific drugs, whether they are willing to accept having to make higher payments to get a specific drug, and when to complain about access to a specific drug. Although all of these actors influence pharmaceutical decisionmaking, the remainder of this section focuses specifically on health plan and medical group decisionmakers.

Our interviews indicated that the locus of pharmaceutical evaluation varies by organizational type. National or multi-regional health plans reported that core benefit-design decisions and the assessment of new and emerging technologies are typically made at the corporate-office level. However, their local subsidiaries generally make patient-specific decisions about the medical necessity of specific drugs and physician-specific decisions regarding compliance with clinical use guidelines. Local subsidiaries also have some flexibility in authorizing which benefit plans they offer. Moreover, all of the regional and national plans we interviewed indicated that their local subsidiaries were represented in some way on their pharmaceutical and therapeutics (P & T) committees and/or health plan coverage committees at the organization's corporate level.

Pharmaceutical-coverage decisions can be made at several different levels within a health plan. All of the organizations we interviewed had at least three possible levels for the review and approval of new pharmaceutical technology or new coverage or control decisions: some form of a P & T committee (variously named), a medical director and/or a pharmacy director, and a senior management group that reviewed high cost, controversial or groundbreaking assessment, coverage, or control decisions. Some health plans also had a separate structure for developing and carrying out specific implementation decisions, such as whether to impose prior-authorization requirements or develop and implement clinical guidelines.

Differences in financial incentives and potential financial impact at the organizations that we interviewed affected which organizational level decides to accept or reject new pharmaceuticals. In general, new drugs or indications in existing therapeutic classes are reviewed and approved at the P & T committee and medical-director level, unless they entail major new costs or expansion of benefits, or raise sensitive issues regarding demand and use (e.g., abortifacients, agents with both cosmetic and therapeutic uses). Decisions that are generally referred to a more senior level involve potential blockbuster drugs,⁷ drugs that create a new and potentially expensive therapeutic class, and drugs on which decisions may have particular legal or marketplace sensitivity (e.g., Viagra, Cox

⁷ A *blockbuster drug* is one that is unusually expensive, has a major effect on cost and/or quality, and/or sets a precedent for future coverage or practice.

2 inhibitors, anti-HIV drugs). Decisions to change benefit-plan language typically go through an additional process of review and approval.

Our literature review revealed a similar picture. Steiner et al. (1996) found that small health plans and indemnity plans were generally more likely to rely exclusively on medical directors for technology assessment.⁸ Lyles, Luce, and Rentz (1997) found that 96% of health plans utilize a formulary committee to assess new or innovative pharmaceuticals, 92% said their medical directors are directly involved with the review process, and 46% indicated that the medical director determines whether or not to pursue further analysis. However, these authors also found that group- and staff-model health plans, as well as PBMs, do not usually involve the medical directors in formulary decisions. This is a point of contrast with our interviews, which found that the medical directors usually play a significant role in decisions affecting prescription practice management, control mechanisms, and the timing of drug assessments, even if the organization designates others to manage the day-to-day process of assessing pharmaceutical approvals of use.

Our interviews indicated that who conducts the new-drug assessments is a function of the resources devoted to such assessments. Small plans and medical groups often relied on more-informal decisions by the medical director or pharmacy director to determine which drugs to assess fully. These findings are consistent with Steiner et al. (1996), who found that smaller health plans were twice as likely as larger plans to indicate that the medical director alone either reviews the new technology or has discretion to involve others in the review process. We interviewed one local plan with a closed formulary but an active process to authorize prescriptions for nonformulary drugs. That plan reported that they generally wait until a drug has been in use in their local marketplace for a year before considering it for formulary inclusion. This delayed approach allows their small assessment staff to focus on current priorities and, perhaps more significantly, to depend on assessments from other organizations to assist their review.

All of the organizations had the responsible individuals summarize the results of their assessments in an internal report, although each organization had its own name and format for this report. These reports usually include a description of the drug (generic name and brand name, therapeutic class, mechanism of action, etc.), a discussion of its safety and efficacy, and estimates of its acquisition and, sometimes, administration cost. When alternatives are available, especially if they are already covered or preferred by the organization, the reports generally include a discussion of the comparative safety, efficacy, and costs of these alternatives. Some organizations summarize their assessments in a table displaying the costs, efficacy, and safety for the drug alone and in

⁸ Steiner also found that indemnity plans, which we did not survey, were three times more likely than HMOs to indicate that the medical director alone should be responsible for the final medical-coverage decision.

comparison with existing available therapies. No organization reported being satisfied with its ability to quantify cost-effectiveness.

In most organizations we spoke to, a pharmacist (e.g., the pharmacy director) was responsible for the reports, although a medical director was involved in all cases and consulting specialists in many. The reports tended to advocate a particular decision or recommend further study or review. In all but the smaller medical groups, additional committees and management teams had some responsibility for some of the decisions affecting drug coverage and control policy, so that recommendations go to management for approval and, if appropriate, to others for further review or implementation planning.

Most organizations also employed a separate committee or medical management structure to evaluate recommendations to change drug-control mechanisms, operating programs, provider contracts, or provider education. Those with formal disease-management programs uniformly described a separate management and decision structure for these programs that could choose to coordinate with the P & T committee or make separate and different decisions. Finally, each interviewed health plan had a separate technology assessment committee responsible for reviewing procedures, devices, and other non-pharmaceutical technology. In some cases, though, approving a procedure or device may involve making a decision to cover some drug therapy associated with that procedure. In these instances, the technology assessment committee may either coordinate with the P & T committee or assume responsibility over that specific decision (e.g., localized chemotherapy infusion). The latter avenue is common, because each of the committees and staff groups mentioned may report to separate parts of the organization, complicating the formation of coherent approaches.

Although every interviewee could explain the general logic of who made what decisions regarding new pharmaceutical technology for his or her organization, the assessment criteria that were used varied on a case-by-case basis. All the health plans we interviewed agreed with the literature that a "final decision (on a technology) has to consider the cost to policyholders, the cost for implementing coverage, and business implications such as competition" (Luce and Brown, 1995). The larger the organization, the more likely decisionmaking criteria were formalized into policies and procedures; however, even in large organizations, the definition of which decisions should be referred for additional review or planning appeared to be subjective and subject to management discretion. Recommendations requiring changes to benefit-plan language were an exception; all organizations had a separate committee or senior management group review such actions.

What Decision Options Are Considered?

Choosing the best possible policy requires a clear understanding of what decision options are available without (but, on occasion, after) renegotiating contracts with clients, PBMs, providers, or

manufacturers. Our interviews revealed that each type of organization had a different range of options to consider based on its role and its prescription-drug benefit structure, management control mechanisms, and contractual relationships. The staff-model HMOs and medical groups with in-house pharmacies that we interviewed reported they could easily implement closed formularies and pharmacist-driven utilization controls, whereas such controls would be more difficult in a loosely structured IPA-model HMO or PPO plan. Medical groups indicated that their inability to define the pharmaceutical-benefit plans or the management-control mechanisms of health plans with which they contract greatly limits their decision options. However, some do construct lists of preferred injectables and other drugs to be used in their offices, or an internal lists of preferred "take-at-home" prescription drugs from the formularies provided by the health plans, sometimes coupled with an appeal for an expansion of or an individual exception to the formulary. Some medical groups also choose how to educate, monitor, and enforce drug policies and preferences within their organization. Some of the medical groups that we interviewed concentrate on drug classes with high utilization rates and costs, rather than on all therapeutic classes. Of note, these groups were at some financial risk for drug benefit costs, so it is not surprising that their lists focused on pharmaceuticals for which the group had the potential to divert prescribing habits to more cost-effective alternatives.

Health plans, in contrast, appear to have a broad range of decision options for actions regarding pharmaceuticals. The more common options identified in our interviews fall into one of three categories: actions relating to evaluation, to altering drug-benefit design features, and to implementing management control strategies. We list some commonly mentioned options in all three categories in Tables 2.1 through 2.3. These options are related, since the evaluation options available to a health plan depend, in part, on the decisions it makes regarding plan design features and management control tactics.

Not all the plans mentioned all the options. Entire groups of decision options were unavailable or irrelevant to some plans or PBMs. In some cases, this unavailability related to the design of their prescription drug benefits and the infrastructure available to support the management of pharmaceuticals. Organizations did not need to consider any of the decision options related to closed formularies, such as step programs or prior authorization of nonformulary drugs, if they had open formularies.⁹ Organizations did not develop detailed clinical practice guidelines, local counter-detailing programs, or provider-directed disease-management programs unless they had the provider contractual relationships and the local infrastructure necessary to do utilization review/management, perform on-site physician education, or directly influence clinical behavior.

⁹ This group includes many organizations. Lyles, Luce, and Rentz (1997) found that 41% of the large health plans in his survey had open formularies, and Schulman et al. (1996) found that PBMs use an open formulary plan structure for the majority of their employer and HMO clients.

Organizations also rejected some decision options that they considered to be outside of an acceptable range of management control tactics; that is, options that they consider inconsistent with their benefit design and management-control philosophy.

The literature indicates that organizations may eliminate large groups of decision options because of the costs involved in implementation. For example, Garber (1994) asserted that making indication-specific coverage decisions requires a costly administrative effort. Consistent with that assertion, the organizations we surveyed were quite cautious about creating special categories for prior authorization or limited coverage. In fact, most organizations that we contacted did not have prior-authorization or exception-processing mechanisms, and others used them rarely (for less than 5 to 10% of prescriptions). Some executives also expressed concern that special co-payment rates and unique rules for specific drugs make their benefit plan appear complicated, and thus difficult to market.

Some organizations appear to be simply unaware of some viable options. However, all the organizations we interviewed expressed interest in learning more about the full range of available options. All also indicated that which pharmaceutical technology assessment they would need would depend on the specific decision options available to their organization, and the relative costs and returns to the options.

What Factors Affect the Timing and Resources Devoted to Pharmaceutical Technology Assessment?

None of the organizations we interviewed reported using a formal analysis of the possible impact of every new drug or indication, such as that described by Eddy (1989), to decide which drugs to subject to a more thorough assessment process. Rather, we found that an organization's overall mission and market strategy may determine what pharmaceuticals are assessed, which is consistent with Luce and Brown's findings (1965) about the motivations for medical technology assessment in general. Also similar to Luce and Brown (1995), organizations that we interviewed conducted assessments in order to variously improve care, contain costs, make prudent purchasing decisions, support clinical coverage decisions, determine experimental status, and comply with federal regulations. In this context, we found that an organization's reasons for performing an assessment of a new pharmaceutical technology seems to substantially determine the timing, resources, and rigor devoted to it.

The timing of pharmaceutical technology assessments varied widely among the organizations that we interviewed. Larger health plans, particularly those with full financial risk for pharmaceutical use, but generally not PBMs or provider organizations, specifically tasked individuals with scanning the drug-development pipeline (trade papers, journals, etc.) to ensure that the organization is aware of any potential blockbuster drugs, new therapeutic classes, or other pharmaceutical innovations that might have a major impact on health plan costs or outcomes. This scanning activity consisted of a review of industry and governmental publications, and often involved formal and informal communications and meetings with drug manufacturers. Similarly, Luce and Brown's (1995) observed that larger plans often begin their assessments before Food and Drug Administration (FDA) approval, although many conduct full assessments on only a limited subset of new pharmaceuticals.

Decisionmakers for these organizations have incentives to perform early assessment that appear to go beyond immediate cost. Health plans and health care systems, which must set annual or multi-year premiums many months before a benefit plan year begins, need to anticipate whether any new drugs in the development pipeline will substantially raise or lower their costs. Likewise, plans with formularies that rely on extensive clinical guidelines for prior authorization or step programs need to begin their assessment of important new drugs early, so that their findings can be incorporated into the plan's benefit language and management-control processes.

Our interviews with PBMs supported Luce and Brown's observation that PBMs, which assume little or no financial risk for benefit costs, typically conduct their full assessments after a drug receives FDA approval; and Schulman's (1996) assertion that the PBMs generally wait until about 12 months of clinical experience before formally considering a drug for inclusion on a preferred

formulary list. Subjects from all types of organizations complained that, around the time of approval, information may be limited to that provided by manufacturers who are approaching health plans and PBMs to facilitate coverage irrespective of the organization's own timeline for pharmaceutical technology assessments.

The resources devoted to assessing new pharmaceutical technology vary significantly among organizations. According to our interviewees, the personnel resources devoted to pharmaceutical technology assessment ranged from a staff of 30 and multiple levels of managers and paid committees, to a single director of pharmacy with a staff of one to two persons and a volunteer P & T committee. In contrast, only 75% of the 51 plans interviewed by Lyles, Luce, and Rentz (1997) reported having any employee responsible for pharmaceutical assessment. This discrepancy may be partially explained by the fact that all of our interviewees relied upon internal assessments, whereas only 74% of the plans in the Lyles, Luce, and Rentz study did.

To some extent, these differences in resources reflect the differences in the sizes of the organizations and annual pharmacy expenditures. They also reflect differences in the purposes of the assessments. In staff-model HMOs or large medical groups with in-house or hospital pharmacies, pharmaceutical technology assessment can serve broad functions, such as budget prioritization, improved strategic planning, alleviating pressure from third-party payers, improving quality, and avoiding obsolescence (Luce and Brown, 1995). In fact, early adoption of technology in some organizations may be part of the marketing strategy. However, each of these purposes requires differing levels of staff support and other resources.

The type and rigor of an assessment necessarily affect the resources that an organization devotes to it. For example, a health plan whose drug benefits cover all FDA-approved prescription drugs without regard to indication, unless specifically excluded by the plan, would *need* to devote few resources to pharmaceutical assessment. The only decision options such organizations would *have* to consider are whether the drug in question is excluded by the plan and whether the existence of the new drug or indication requires or suggests modifying the health plan's benefit language. It is important to note that the latter may not be apparent until some evaluation is performed. For example, investigation of an agent that is superficially uninteresting (e.g., expensive, excluded, or not unique or decisive) may suggest that the drug could substitute for those more expensive or less-effective services that the plan is liable for, and that policies that promote the use of the drug are desirable.

The organizations that we interviewed most commonly perform clinical-effectiveness and safety assessments, followed by cost-of-treatment, cost-effectiveness, and, infrequently, quality-of-life assessments (Lyles, Luce, and Rentz, 1997). Our interviews are again consistent with the findings of Lyles, Luce, and Rentz (1997) and Luce and Brown (1995), who reported that cost-

effectiveness and quality-of-life analyses are limited by the lack of directly comparative data between competitor drugs in real-world settings. Therefore, if an organization chooses to prioritize one drug over others in the same class, it will need to devote extra resources to filling information gaps on comparative or incremental cost-effectiveness. On the other hand, if such an organization is considering covering a promising new drug in a new therapeutic class, it might need to review only safety and efficacy data; cost-effectiveness data may be less relevant.

All of the organizations that we interviewed used some externally developed assessment material in their internal processes. In addition, all of the PBMs we surveyed considered new-drug assessment to be a service they can provide to their clients, either as part of a package of pre-determined formularies and control strategies, or as a separate product. Many other organizations also provide assessments of medical technology, including procedures, devices, and pharmaceuticals. (A list of sources of public and proprietary pharmaceutical assessments can be found in *The Directory of Health Technology Assessment Organizations Worldwide*, 1999.) The availability of these materials did not prevent organizations from conducting their own internal assessments on the drugs that they considered important, possibly because of these materials' objective shortcomings but also because of an expressed distrust of some external assessment information

What Types of Evaluations Are Performed and What Types of Evidence Do They Use?

We found that, even within a single organization, varying motives lead to different processes for reviewing different drugs. For example, some interviewees reported that health plans paying physicians or hospitals a flat fee, a *per diem* rate, or capitation do not devote the same resources to reviewing drugs used solely in the office or inpatient setting (i.e., included in the flat rate) that they would to outpatient prescription drugs for which they are financially and administratively responsible. Likewise, physician groups and hospitals did not report spending resources on reviewing drugs that are mandated for coverage by their contracting health plans, except when they expected clear differences in clinical outcomes between drugs in the same class or differences in cost that could significantly impact the organization's finances.

Steiner et al. (1996) documented the degree to which technology assessments vary from plan to plan, that the content of the technology assessment performed by the plans was difficult to predict, and that plan-conducted assessments differ from assessments performed by the scientific community. They note that health plans confer varying levels of authority on their medical directors, differ in the timing of their technology assessment decisions, and view sources and evidence differently. Steiner et al. (1997) also demonstrated that these variations in technology assessment resulted in substantial variation in coverage for emerging medical device technology. Luce and Brown (1995) found that hospitals, HMOs, and other types of insurers all conduct technology assessments, but that the form and sophistication of their analyses range widely. Weingart's

interviews (1993) of 12 Academic Medical Center Consortium institutions produced similar observations: variation in the technology assessment process, lack of explicit evaluation criteria, and the presence of political, informal, or *ad hoc* decisions.

Despite the wide variation in the processes for assessing new-drug technology and new indications for existing drugs, certain assessment components are predictable. Steiner et al. (1996) found that many plans reviewed medical journals, FDA reports, and professional association information, and sought the opinions of local experts. Yet, we found that each plan undertook this activity independently, resulting in considerable redundancy and inefficiency. Matuszewski (1997) described the basic components of technology assessment in this setting, including who does it, how it is done, and its common problems. He discovered, as we did, that plans often find that there is insufficient evidence on which to base a decision, particularly early in the technology's life cycle. Early completion is particularly difficult for what Fuchs and Garber (1990) call the "new style of technology assessment," which goes beyond safety and efficacy to analyze comparative cost-effectiveness and other effects, such as an impact on the labor force. Fuchs and Garber also describe concerns about the trustworthiness of published assessments of new technologies and the incentives and rigor of the investigators. Many of our respondents echoed these concerns. They wondered about the dependability of assessments sponsored by manufacturers (i.e., questions of internal validity) and the possibility that clinical-trial experience may not reflect the drug's use in "the real world" (i.e., questions of the external validity¹⁰), and cited these concerns as reasons they prefer to see a period of market experience before completing a formal evaluation of a drug.

In general, our interviewees indicated that their health plans and provider organizations commonly encounter the same problems with technology assessment that Matuszewski (1997) described: lack of evidence, changing standards of evidence, inconsistent evidence, lack of agreement on how to perform an assessment, special interests, and variation in the breadth and depth of topics, new information, and legal issues.

Our interviews also identified differences in context as a source of variation between and within organizations. The technology assessment literature generally regards these variations in the assessment process as being problematic. However, our interviewees were generally comfortable with variations that they believed to be appropriate for the differences in clinical and organizational context. When asked how rigorous a new drug assessment needs to be, one medical director summed up the other interviewees' viewpoint succinctly: "we do enough assessment to make a decision." He and others expressed concern that a single academic standard for assessing new drugs or indications would be too time-consuming, resource-intensive, and slow to be useful in the

¹⁰ This is really an issue of whether results obtained from selected populations treated in specialized settings can be generalized to the typical patients in usual settings.

"real world." However, all those we interviewed thought a great deal could be done to make the assessment process more consistent and efficient. Many expressed a need for better and timelier information, and for help in increasing the quality of decisionmaking without making the process too slow or costly.

Organizations responsible for pharmacy benefits sometimes choose to evaluate several different aspects of a new drug, such as its clinical effectiveness, safety, cost of treatment, cost-effectiveness, or influence on quality of life. Clinical effectiveness and safety assessments usually begin with a literature review and synthesis of the available information on the drug in question. This process may either be performed by members of the organization or purchased from an external source. When conducting an in-house evaluation, the health plans we interviewed either assigned a staff member (often a clinical pharmacist) to perform the literature reviews or a subcommittee of their P & T committee with expertise relevant to the condition that the new drug is intended to treat. Otherwise, they purchased reviews from PBMs and other organizations.

Literature reviews utilize a range of sources, including peer-reviewed journal articles, unpublished articles, government documents, information from professional organizations, drug company brochures, and reports from assessing organizations (Steiner et al., 1996; Luce and Brown, 1995; Lyles, Luce, and Rentz, 1997; interviews). However, the way in which this information is used and its perceived relevance vary. In a 1996 survey of physicians, Steiner et al. found that decisionmakers at large health plans were twice as likely as those from small health plans to rely on peer-reviewed medical journals in developing evaluations. The survey also found that such decisionmakers relied most frequently on medical journals, followed by local experts, FDA-approval documentation, and information from plan associations. A subsequent survey of decisionmakers at 51 health plans confirmed this general ranking of sources: The plans relied most frequently on peer-reviewed literature, followed by government reports, then industry evaluations (Lyles, Luce, and Rentz 1997). Reports from other HMOs, PBM publications, and non-peer-reviewed literature were less popular. However, the survey respondents ranked PBM assessments first in importance to the decision made, followed in order by assessments from other HMOs, peer-reviewed literature, industry evaluations, non-peer-reviewed literature, and government reports (Lyles, Luce, and Rentz, 1997). This ranking suggests that comprehensiveness and timeliness are major determinants of importance. Other surveys have also found that the timeliness of the information can drive the relative importance of the source, possibly owing to the need to make coverage decisions prior to the publication of peer-reviewed articles (Steiner et al., 1996; Luce and Brown, 1995).

The medical directors we interviewed expressed an interest in meta-analysis,¹¹ but they believed it usually to be impractical for evaluating new drugs because of the general lack of relevant studies. These interviewees also expressed a general frustration over the lack of clinical-trial data relevant to their pharmaceutical assessment needs. Consistent with the literature, the medical directors we interviewed preferred to make coverage decisions based on clinical-trial data while being mindful that such data may provide limited information about the performance of the drug in real-world practice (Steiner et al., 1996; Towery and Perry, 1981).

Although health plans are concerned about costs and they may perform some economic analyses of the impact of new pharmaceuticals, they do not generally perform formal mathematical modeling, such as cost-outcome or decision analyses. Interviewees at only two national health plans indicated that they use formal economic models, such as pharmacoeconomic studies, Monte Carlo simulations, and projections. The other organizations we interviewed did not use formal modeling. Smaller organizations reported performing limited, "relatively crude" or "back of the envelope" calculations only for new drugs expected to have a large financial impact. Cost modeling among larger organizations generally consisted of estimating the impact of a new drug based on the cost of the pharmaceutical and its administration alone. These estimates are typically projected from the "incidence of indications" (the prevalence of the condition that the drug is licensed to treat); the "expected market share" of the drug; and the drug cost per course of therapy. All of these are subject to variation in practice; for example, cost per course is affected by negotiation and volume discounting.

The published literature echoes these findings. For example, in a survey of 231 decisionmakers at HMOs and indemnity plans, Steiner et al. (1996) found that lack of data on cost-effectiveness constituted a major barrier to making optimal coverage decisions. Luce and Brown (1995) also found that HMOs and third-party payers do not perform cost-effectiveness analyses, nor do they generally include such information from other sources in their coverage decisions. They noted that hospitals do perform some in-house financial analysis; however, Luce and Brown did not report on the rigor of those assessments. In contrast, Schulman et al. (1996) found that PBMs occasionally incorporate findings on the costs and outcomes associated with pharmaceutical use. However, the scope of these assessments is limited to pharmaceutical use and does not include the larger budgetary issues of concern to the overall health plan.

Most organizations forecast the potential demand for new drugs, based solely on clinical and epidemiological data. These organizations do little, if any, formal demand modeling to take into

¹¹ *Meta-analysis* aggregates the results of multiple studies, thereby increasing sample size and allowing more statistically powerful conclusions regarding a common treatment or intervention effect across studies.

account non-clinical factors, such as the attitudes and preferences of patients and physicians. If demand modeling is done at all, it uses casual ("back of the envelope") calculations that make simple assumptions, such as that the demand for a new drug will be similar to that of others in its class or that new users will be drawn solely from the currently diagnosed population. These models usually neglect the effect of the new drug on the size of the diagnosed population (i.e., by recruiting patients into care or increasing provider propensity to make the diagnosis), because most organizations feel that they have no adequate method of determining this variable (Reissman, personal communication, 1999). Moreover, the focus of this type of modeling is on the impact of the new drug on pharmaceutical expenditures; it does not usually consider the overall impact of drug use on total medical expenditures (Reissman, personal communication 1999; Schweitzer, 1997).

Medical directors generally recognize the need to better understand demand. In more than one case, the individuals we interviewed pointed to drug manufacturers' increasing use of direct-to-consumer advertising as a significant cause of increased demand, and they mentioned Claritin and Viagra as specific examples of this phenomenon. Several medical directors noted that their organizations had failed to anticipate the demand for new drugs such as Viagra. They also complained that existing risk contracts do not take the possibility of new blockbuster drugs into consideration, leading them to fear the budgetary impact of drugs with wide appeal to patients, particularly those for lifestyle conditions lacking a clearly defined medical diagnosis. Several medical directors also noted that PBMs could play a greater role in demand modeling and forecasting because they have access to large amounts of claims data from which trends could be identified and forecasted.

Our interviews revealed that the level of rigor with which organizations gather information from these sources varies. Oftentimes, the formality of the literature search can depend on the level of controversy or demand for a drug. For instance, one medical director mentioned using a more formal technique for evaluating Viagra than for other drugs because it was considered a "lifestyle drug" and a potential blockbuster. However, even the most formal reviews performed by PBMs appear to be much less scientifically rigorous than a full systematic review or meta-analysis.

How Are Decisions Implemented and the Results Monitored?

All of the organizations we interviewed had a defined process of varying formality for documenting and disseminating their decisions on new pharmaceutical technologies. If the decision is for controlled use, implementing management-control tactics such as developing educational programs requires a major commitment of time and resources. Some of the control tactics may become steps in the implementation process (e.g., developing clinical use guidelines, processes, and educational programs); others may define the implementation plan (e.g., prior authorization required for certain drugs).

The P & T committees in the organizations we interviewed usually included both clinical and administrative staff, and major recommendations typically required management approval. Two of the national plans we surveyed had a separate, formal committee to assess and plan the implementation of coverage decisions regarding new drugs, indications, or control policies; others depended upon the normal management structure to implement new policies and programs.

Every organizational decision has both intended and unintended consequences. Therefore, the monitoring of results is important. A management process as important to a managed care organization as implementing changes in drug benefits or control strategies should be subject to systematic monitoring of the results. For this reason, it was not surprising to find that all of the organizations we interviewed monitored the behavior of physicians and patient drug utilization before and after a major change in policy. Specifically, for shaping behavior, all performed some monitoring of physicians' compliance with formulary and prescribing policy. Similarly, all the PBMs surveyed by Schulman et al. (1996) profiled physicians for compliance with the formulary and all offered programs to educate prescribing physicians regarding formulary issues, including face-to-face visits if necessary. Luce and Brown (1995) found "evidence that the assessments and monitoring of physicians' procedures are modifying physicians' practice patterns."

Our interviews suggest that most organizations have a limited ability to closely monitor the clinical or financial effects of specific pharmaceutical decisions. This is also consistent with Schulman et al. (1996), who, after finding that none of the PBMs they studied tracked the health outcomes of patients and that less than half profiled physicians on cost, concluded that "PBMs are unable to track long-term outcomes and costs of disease. . . and . . . until comprehensive integrated analyses are possible, these organizations will lack the ability to definitively show the effects of their programs." In that study, the employers who engaged PBMs to manage pharmacy benefits were unaware of formulary-selection criteria and generally had no way of monitoring the effects of the PBM on employees' overall health or total costs. Although health plans and medical groups generally reported that they monitored the type and costs of drugs being prescribed, none affirmed having routine processes to assess the overall clinical and financial impact of pharmaceutical technology decisions.

Summary

Variation in locus, timing, rigor, resource intensity, and type of pharmaceutical technology assessment is the rule for managed care organizations. Much of this variation is tied to the type of organization and its perceived needs. In turn, organizational type and perceived needs are closely tied to the organization's available range of contractually determined decision and control options, and the level of controversy around and demand for the drug. Current approaches can result in an adequate response for the decision at hand, but the overall effort is often inappropriately small to

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achieve optimal clinical or financial results, generally because of limitations on resources or skill mix at the managed care organization or because the original questions are drawn in too-narrow terms.

The situation can be improved with standardized methods and better information. The organizations we spoke with all indicated a desire for both. The next section presents a standardized framework and describes methods that can be used successfully within that framework.

3. A Framework and Approaches for Future Practice

Introduction

As detailed above, our review of the literature and interviews revealed that managed care organizations generally lack the institutional structures and processes to accurately assess the probable overall clinical and financial impact of new pharmaceuticals. With several notable exceptions, P&T committees perform pharmaceutical evaluations. These committees are focused on an essential but limited set of issues such as safety, efficacy, and (usually acquisition) cost. They are not charged with broader issues, such as the effects of new pharmaceutical technologies on overall care processes, patient's health outcomes, and the organization's financial viability, and would be ill-prepared to consider them. Moreover, they are sometimes remote from decisionmaking.

Many of the organizations that we interviewed agreed that the evaluation process could be improved. To achieve this improvement, most believed that they needed the following:

- A structured process for assessing pharmaceutical technology that would improve the sharing of information within and across systems, provide a rational basis for decisionmaking, and increase transferability of best practices.
- Unbiased resource(s) to help identify, locate, and evaluate the strength of evidence supporting a pharmaceutical technology relative to its alternatives, as well as information on special features that would affect compliance, associated clinical or administrative costs, and quality of life.
- Reference materials for evaluating pharmaceutical technology, coverage options, and decisionmaking processes, including reports from professional and industry groups, government agencies, proprietary technology assessment organizations, and other sources.
- Timelier, standardized information on the clinical effectiveness, costs, and cost-effectiveness of drugs in real-world settings, relative to alternatives.

The prescriptive portion of this report, which is aimed at managed care organizations interested in improving their evaluative efforts, focuses on the first point. It outlines a structured framework for assessing pharmaceutical technologies. Appendix A and the References section approach the next two points by listing potentially useful reference materials. The last point, the data issues specific to pharmaceutical manufacturers, is beyond the scope of this report.

A Framework for Decisionmaking

The ideal process for making a pharmaceutical coverage decision works within data and budgetary limitations, and is *explicit*—documented, prescribed, standardized; *valid*—uses

legitimate and correct techniques; and *reliable*—produces approximately the same results under identical situations. An *explicit* process helps guard against biases that may be hidden in *ad hoc* processes, and which may vary from decision to decision. A *valid* process will maximize the likelihood of making the correct coverage decision (i.e., the decision most likely to optimize outcomes). A *reliable* process ensures that coverage decisions for similar drugs are similar. With these goals in mind, we combined the comments of our interviewees, findings from the literature, and our own judgment to produce the conceptual framework depicted in Figure 3.1.

The steps should generally be completed in the following sequence:

- Characterize the drug and the disease. Gather information on the drug's relationship to the marketplace (e.g., therapeutic alternatives, clinical need) and on its potential risks and benefits, especially in relation to existing therapies. Gather information on the disease's present and potential future prevalence, and its impact on quality and duration of life, and medical care expenditures. At this stage in the process, the decisionmaker needs to identify the relevant issues, not to verify or quantify this information.
- Characterize the decisionmaking organization. Specify the nature of the organization (e.g., health plan, provider organizations), its structure and contractual obligations, and other factors that affect the extent to which and the means by which it can promote or limit the use of pharmaceuticals.
- Define the decision options. Combine knowledge of the pharmaceutical and the decisionmaking organization to identify the range of available mechanisms for affecting the use of the drug in question.
- Define the analysis needed to make a decision. Define the criteria for determining which drugs will undergo formal analysis, set the appropriate level of resources to devote to the assessment, identify the agent who will perform the assessment (i.e., the make or buy decision), establish the timing of the assessment, and specify the assessment methodology. We group these tasks because they are interrelated. For instance, the degree of rigor applied to the analysis depends upon the level of resources devoted to it and vice versa.

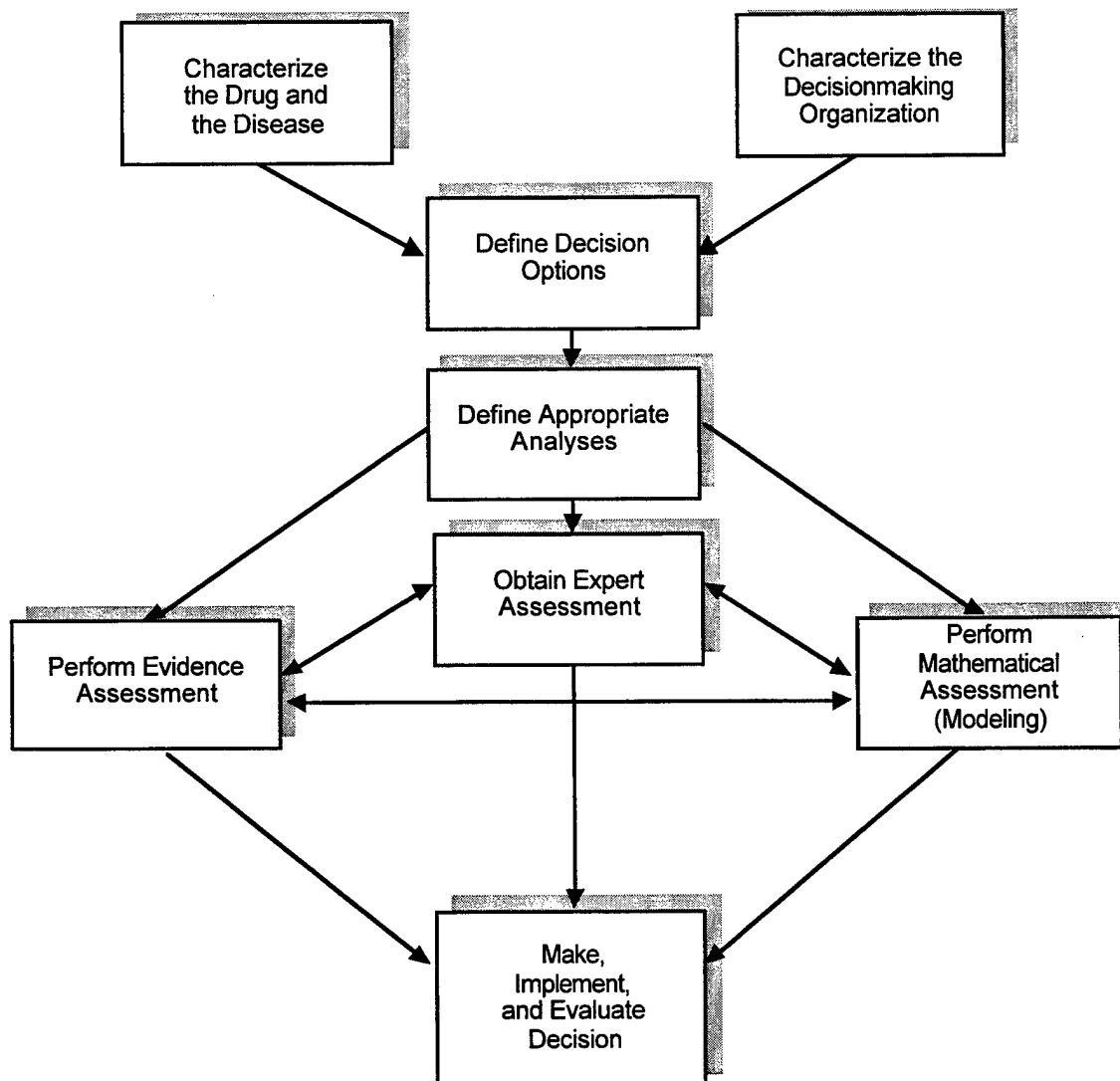


Figure 3.1—The Decisionmaking Framework

- Perform the assessment. In many cases, this will be the most time-consuming step, even though the task should be well understood by the time it is reached. We classify the main relevant methodologies for performing the assessment into three major types. *Expert opinion* encompasses both the usual unstructured consultation and more-formalized consensus methods. *Evidence assessment* can also be conducted with varying degrees of formality and quantitation, but in all cases, it refers to evaluations that rely mainly on studies reported in peer-reviewed literature, industry publications, or scientific meetings. Evidence assessment is distinct from the information gathering that takes place throughout the process in that it moves from identification of issues to evaluation of evidence. *Mathematical assessment* includes evaluations

that attempt to quantify the implications of decision options; it relies on analysis of existing data, with an eye to predicting the effects of a course of action on an outcome of interest.

- Make, implement, and evaluate the decision. Use the results of the assessment to make the decision regarding coverage, controls, and implementation tactics. Operationalize the coverage decision, including disseminating the decision and implementing the controls. Monitor and evaluate the results of the decision by providing mechanisms for assessing outcomes and for periodic or continuous improvement in the coverage decision. While these later steps are crucial to the ultimate value of the evaluation process, they are highly individualized and lie beyond the scope of this report.

Each step is described more fully in the following subsections.

The Steps in the Decisionmaking Process

Characterize the Drug and the Disease

Gathering information to “define” or “profile” the drug under consideration provides the basis for decisionmaking. This step does not explicitly require formal processes and systematic review; however, for consistency over time, the process must be constructed so that similar information is gathered on each product under review. At a minimum, the information gathered should include

- the potential benefits and risks of treatment
- the position of the drug in the current market relative to alternative treatments or to no treatment
- costs associated with its use
- unique characteristics of the drug that would affect an organization’s decision about that drug.

Table 3.1 suggests issues relevant to each of these four categories.

Table 3.1—Characterizing the Drug

I. Basic identification of drug

Purpose: To identify the drug, its common indications, and usage

Issues: Generic name and brand name
Therapeutic class
Indications for use
Mechanism of action
Routes of administration and dosage guidelines
Monitoring criteria

II. Potential benefits and risks

Purpose: To identify the clinical issues concerning the drug in relation to its intended treatment population and to other treatment options

Issues: Effectiveness

- Likely impact on disease morbidity and mortality
- Cure or prevention rates
- Prevalence of contraindications
- Improvement in key disease markers
- Improvement in patient quality of life, physical and social functioning, and satisfaction with care

Untoward effects

- Incidence of serious events
- Reported and potential adverse drug-drug interactions
- Deterioration in patient quality of life, physical and social functioning, and satisfaction with care

Other

- Impact on care process (e.g., effects on outpatient vs. inpatient treatment; increased requirements for laboratory monitoring)
- Impact on total health care expenses (positive or negative)
- Impact on labor outcomes (i.e., patient productivity)

III. Drug position in current market

Purpose: To understand the larger treatment context for a specific condition or disease

Issues:

- FDA approval (existing/pending)
- New or existing therapeutic class
- Competing products or services
- Cost per course of treatment (absolute/relative to other therapies) and per patient per unit time
- Severity of condition treated (life-threatening/chronic/benign)
- Patient-initiated demand
- Likely product life cycle (acceptance/plateau/decline)

Table 3.1—continued

IV. Additional costs

- Purpose:* To understand the total direct costs of drug administration
- Issues:* Special ordering
- Product availability (readily/lottery/other mechanism)
 - Distribution source (manufacturer/wholesaler/single source)
- Handling (shipping/storage/reconstitution)
- Administration
- Packaging (consistent with common prescription sizes/benefit coverage guidelines)
 - Routes and circumstances of administration
 - Monitoring (laboratory/diagnostic testing for efficacy or adverse events)
- Manufacturer's policies (e.g., discounts, rebates, returned goods)

V. Unique characteristics

- Purpose:* To determine whether there is something unique about the drug, or the organization's relationship to it, that should affect a decision
- Issues:* Plan benefit language
- Little evaluation may be needed for clearly excluded drugs
- Uniqueness/dominance of drug in therapeutic class
- Relevance of cost-effectiveness of dominant drug for serious disease
- Nature of demand prior to and after introduction
- From important clients/regulators
 - From providers
 - From patients
- Likelihood of becoming a "blockbuster," or precedent-setting, drug
- Unusually expensive
 - Major impact on cost, quality
 - Precedent-setting for future coverage or practice
-

In contrast, characterizing the disease is, at least initially, a more straightforward, conceptually simple task of listing epidemiological, clinical, and economic parameters. Relevant *epidemiological* parameters include the present and projected future incidence, duration, and prevalence. *Clinical* parameters include the severity and time course of direct and secondary morbidity and mortality, and impacts on functional and health status. *Economic* parameters include the type and intensity of related use of health care.

Characterize the Decisionmaking Organization

The organizational context—structure, philosophy, financial incentives, market position, existing relationships, and the population served—affects decisions about new pharmaceutical technology. Understanding the interaction between an organization and the drug under consideration provides a valuable basis for defining the assessment and decisionmaking process. For example, if important clients, such as major employers, have demanded coverage for a specific drug that appears to be excluded by the benefit-plan language, the organization may decide that a full assessment rather than a simple reiteration of existing policy is necessary. If the drug creates a new class of coverage and is extremely expensive, the organization may decide to include extensive financial modeling in the assessment, as well as to involve other parts of the organization in the decisionmaking process. Many of these organizational issues need to be addressed only periodically; the relevant information can be applied to multiple drug assessments over time. Table 3.2 outlines various issues relevant to this step.

Define Decision Options

Physicians and their patients, not managed care organizations, have direct control over the prescribing and use of pharmaceuticals. However, managed care organizations influence the behavior of physicians and patients through rules, enforcement mechanisms, and financial incentives—mechanisms that define the range of decision options available between the two extreme options of (a) drug exclusion and (b) promotion of unrestricted use. The ability of the service delivery organization to implement these mechanisms depends upon its level of integration,¹² the sophistication of its information-management systems, and the competitiveness of its local market. Some of the more common control mechanisms are as follows:

- **Formularies.** Traditionally used to refer to a list of covered or available drugs, *formulary* now usually refers to a program that includes the list of and procedures for obtaining covered and non-covered drugs under varying circumstances. Formulary programs create these lists and procedures according to the effectiveness, safety, and cost of the covered drugs. Formulary programs vary in the number of covered drugs, the restrictions placed on covered drugs, and the ease with which physicians can obtain coverage for off-formulary drugs.

¹² *Level of integration* reflects how many functions are incorporated into the organization's structure: At a low level, local doctors refer to other practices and pharmacies; at a high level, a large organization such as Kaiser owns facilities and pharmacies and refers only within the organization.

Table 3.2—Characterizing the Decisionmaking Organization

I. Organizational structure

Purpose: To delineate important aspects of the organization that could affect drug coverage

Issues: Type of organization (e.g., health plan, pharmacy benefits management company, medical group, hospital)

Decisionmaking authority for drug coverage (yes/no/shared)

- Locus of responsibility (e.g., medical director/P & T committee)
- Existing evaluation procedures
- Ability to influence decisions in other organizations that affect own organization

II. Institutional characteristics

Purpose: To identify important institutional characteristics that could affect pharmaceutical evaluation

Issues: Organizational philosophy regarding drug coverage/policy/controls

Relative importance of drug coverage/policy/costs/controls

Involvement in managing physician prescribing behavior (e.g., prospective review and/or authorization of specified drugs)

Formulary (yes/no; type: open/closed/tiered)

Cost-sharing features of prescription drug plans

Percent of premium spent on drugs

- Absolute amount
- Direction of change (increasing/decreasing/steady)
- Management goals

III. Financial incentives

Purpose: To understand the financial constraints and incentives under which the organization operates with regard to drug coverage

Issues: Degree to which the organization is at risk for drug costs (fully/partially)

Scope of financial responsibility (e.g., prescription drugs, office-administered drugs, administrative costs)

Extent to which other contracting organizations assume financial responsibility for drug costs

Degree to which existing financial arrangements are relevant to drug assessment, policy, timing, priorities, and control options

Table 3.2—continued

IV. Local health care market

Purpose: To understand the competitive factors at work in the market(s) in which the organization operates

Issues: Overall degree of market competition
 Relative importance of drug benefits/range of drug choices in marketplace
 Relative importance of generosity vs. cost of benefits in the marketplace
 Competitors' relevant drug policy strategies (e.g., early adoption of new drug technologies)
 Total premium and prescription drug costs relative to those of competitors

V. Current relationships with manufacturers

Purpose: To delineate how existing relationships with drug manufactures/vendors will influence organizational policies

Issues: Type of relationships with drug manufacturers and distributors (e.g., exclusive or preferential)
 Contractual obligations
 Degree of dependence on others (e.g., drug manufacturers, PBMs, medical groups, health plans) to finalize or implement drug policy decisions

VI. Population served

Purpose: To describe the demographics of the covered population and identify any special needs

Issues: Overall population demographics (age/sex distribution)
 Type of insurance coverage (e.g., employer-sponsored, Medicare, Medicaid)
 Special subpopulations (e.g., seniors, medically indigent, chronically ill)
 • Drug policy issues specific to these populations
 • Regulatory requirements specific to these populations

- Restrictions on covered drugs take several forms. Dose limits restrict the amount of the drug covered (e.g., limiting coverage of Viagra to a specified number of pills per month). Step-therapy programs ensure that certain therapeutic substitutes are tried before a more expensive and/or toxic drug is prescribed. Limiting medical indications restricts overall use by allowing specific drugs to be used for only particular medical indications (e.g., permitting use of Retin A for acne but not for wrinkles).
- Guidelines outline circumstances under which a drug is recommended for use. To increase physician compliance, guidelines are often developed internally with provider input, but successful implementation still requires substantial resources.
- Prior authorization requires physicians to obtain permission to prescribe a particular drug before prescribing it. This requirement helps to ensure compliance with guidelines, usage

restrictions, and step-therapy programs. Utilization review has similar objectives, but it is used retrospectively to determine whether physicians complied with guidelines.

- Differential co-payments create financial incentives for patients to choose less-expensive drugs over clinical substitutes. For example, generic drugs may require lower co-payments than do brand-name drugs.
- Promulgation and promotion of guidelines or care paths encouraging use of the new drug.

Define the Analysis Needed to Make the Decision

This step encompasses several elements, including defining the criteria for selecting which drugs will undergo formal analysis and deciding upon the timing, type, resource intensiveness, and appropriate methodology for the analysis.

The literature suggests that formal analyses be reserved for *important drugs*, which can be defined as those that will be used by large numbers of patients or have a high cost per course of treatment, a high likelihood of adverse events, controversial uses, or large variations in use across providers (Matuszewski, 1997). Eddy (1989) proposes similar criteria but adds consideration of the expected outcome of the assessment, the potential to influence the use of the technology, and the associated changes in individual and population outcomes. Similarly, Donaldson and Sox (1992) proposed a quantitative framework for priority setting that considered prevalence, morbidity (disease burden), cost, variation in use, and the potential to change outcomes and costs and to inform social and ethical issues. Phelps and Mushlin (1988), who were considering pharmaceutical technology, have suggested using a “back-of-the-envelope” feasibility calculation to determine whether the decision is sensitive to the potential results of a full assessment.

Extending this approach to pharmaceuticals, one might do similar calculations to determine whether a new and highly effective drug might be more cost-effective than less clinically effective existing agents under a plausible range of assumptions. If so, the drug would be better and cheaper, and a decision to adopt it can usually be made without further investigation.

Governmental and professional organizations use criteria for funding technology assessments that could be adapted for use for setting assessment priorities. The U.K. Medical Research Council considers the importance of the disease, proposed methodology of assessment, timeliness, generalizability, compatibility, and value for money (Harper, Townsend, and Buxton, 1998). The National Institutes of Health Office of Medical Applications of Research (OMAR) uses medical importance, scientific controversy amenable to consensus research, availability of data, ability to be objectively evaluated, and appropriateness of timing of the assessment (Eddy, 1989).

Issues of the staffing, timing, and the methodological rigor of a drug assessment should vary not only by the nature of the outcomes of most interest but also by organizational situation—its legal/regulatory requirements, existing benefit structures, coverage preferences among similar drugs, competitive environment (i.e., the influence of its decisions on competitor or client behavior), the *a priori* range of possible clinical and financial outcomes from adoption, and availability of resources. Therefore, we touch only briefly on these topics. Other considerations include the similarity of the assessment in question to available previous assessments, and the availability of in-house staff or outside consultants to perform the assessments. Timing issues include determining when in chronological time or in the life cycle of the drug to perform an assessment or re-assessment, and the amount of time to devote to it.

Perhaps the most important of these decisions is the choice of methodology for the final evaluation. Which evaluation methods are appropriate to technology assessment vary with the researcher (Garber, 1994; Matuszewski, 1997; Goodman, 1998). We find it useful to classify the most relevant methods into three groups: evidence assessment, expert opinion, and mathematical assessment.

Evidence Assessment. Until recently, *evidence assessment* meant that a scientist who collected evidence in what might be characterized as a nonsystematic manner—such as searching only one library database and not supplementing that search by contacting experts (see the “Perform the Assessment” subsection below for ways to do a search systematically)—would then summarize the results in narrative form. This type of informal review usually will take place in the early stages of the decisionmaking process. Although useful, such reviews are idiosyncratic, mix opinion with evidence, and both collect and summarize evidence in a non-reproducible way. The evidence-based medicine movement, which emphasizes data-driven care, has developed better means of evaluating evidence. Managed care decisionmakers are likely to concentrate on the usual clinical evidence for assessing pharmaceuticals: completed scientific studies.¹³ This evidence is best obtained and summarized by a *full evidence assessment*, here defined as a systematic review. To qualify as a systematic review, an evidence assessment must comprehensively collect, sift, classify, and summarize the existing knowledge either qualitatively or quantitatively, using meta-analytic techniques (Sackett et al., 1997).¹⁴ If, as is often the case, available studies do not provide

¹³ NOTE: evidence assessment can include, for example, the secondary analysis of patient databases.

¹⁴ Some would say that the standards of the evidence-based medicine movement require an unreasonably comprehensive approach because of the low returns to a very extensive, compared to merely extensive, effort (e.g., looking at the informal literature in non-Western languages).

adequate information for a targeted evidence report, decisionmakers should extend available information using expert or mathematical assessments.¹⁵

Evidence assessment can be most useful when addressing a focused question supported by high-quality evidence; however, the requirements for thoroughness and reproducibility can be taxing if performed to the highest standard. Fortunately, rapidly increasing numbers of useful systematic reviews can be found through routine searches of the medical literature, as well as by contacting sponsors such as the Cochrane Collaboration, an international nonprofit organization (www.cochrane.org), and the Agency for Healthcare Research and Quality (AHRQ; formerly the Agency for Health Care Policy and Research, AHCPR), which sponsors 12 Evidence-Based Practice Centers across the United States (www.ahrq.gov/clinic/epc).

Expert Assessment. *Expert assessment* has been used to refer to the common practice of asking for the opinion of an informed expert or two. This simple approach should be reserved for straightforward decisions, such as a medical director choosing to adopt a close substitute. It is too narrowly based, idiosyncratic, and irreproducible for decisions about important new technologies. Rather, expert assessment for significant new pharmaceutical technologies is best obtained from a group process that draws upon a wide range of direct knowledge and experience.

Expert consensus methods are an appropriate means of decision support when the scientific literature contains few high-quality research studies and a valid research synthesis cannot be conducted—a situation that often occurs during the early or “emerging” phase of a technology but that also occurs when it is necessary to generalize to specific patient groups and clinical situations that are not directly addressed even when the scientific literature is well developed. However, in all cases, it is important to remember that consensus development is a process for making policy decisions, not a scientific method for creating new knowledge (Phelps, 1993).

Mathematical Models. *Mathematical models* represent the decision to be made in quantitative terms and that must predict the outcomes of alternatives, often using the results of evidence and expert assessments as inputs. More generally, models are decisionmaking aids that represent processes in physical, graphical, or mathematical terms. Well-constructed models expose “structural relationships among key variables” (Stokey and Zeckhauser, 1978). Models are uniquely able to reduce uncertainty by using these relationships to predict consequences of alternative strategies and are thus particularly useful when data are incomplete or fragmented. For example, they can be used for identifying the effects of a drug on the overall continuum of care when only clinical data on a subset of that care (e.g., the acute effectiveness of a drug that shortens flare-ups of

¹⁵ For instance, most studies will not consider the particular population or cost structure under consideration.

a chronic disease) are available. In addition, models are useful for translating the findings of other assessments into results that are meaningful for a specific organization.

Mathematical models are particularly suited for describing the likely effect of new drugs under various control mechanisms, in part because the key outcomes of pharmaceutical use (e.g., improved health, expenditures) lend themselves to these approaches (Austin and Boxerman, 1995). Three types of mathematical models are particularly relevant to drug assessment: cost-outcome analysis, decision analysis, and demand assessment.

Cost-Outcome Analysis. Only this assessment method simultaneously quantifies both the costs and benefits of a decision.¹⁶ It is especially useful when adoption of new pharmaceutical technology is expected to severely strain a tight budget. In this context, the result of a cost-outcome analysis is usually expressed as the ratio of the costs of the decision made (e.g., add the pharmaceutical to the formulary) to benefit of the decision (e.g., life-years saved). Cost-outcome analysis can be divided into three categories.¹⁷ *Cost-effectiveness analysis* (CEA) estimates the cost of each unit of clinical improvement on similar outcomes (e.g., life-years saved). *Cost-utility analysis* converts similar and dissimilar outcomes to the common metric of *utility*, or total net perceived value of present and future health. *Cost-benefit analysis* (CBA), which converts all costs and benefits to a monetary value, is unpopular in the healthcare setting because of the technical and ethical barriers to placing a monetary value on health outcomes.

The results of cost-outcome analysis should not be the only consideration when making coverage decisions, because they could point to politically untenable coverage decisions (Eddy, 1991). Additionally, the results of a cost-outcome analysis always require interpretation. Individual drugs or alternative courses of action are at least as effective and no more costly than alternative strategies, or are less effective and more costly (O'Brien et al., 1997). When the decision to be made is clear, a formal cost-outcome analysis can add value only by quantifying the likely impact of the policy to be adopted. However, the optimal course of action is less clear when one of the alternatives is more effective and more costly, or less effective and less costly.

Finally, we note that cost-outcome analyses can simplify to cost-minimization analyses when outcomes are similar. When evaluating close substitutes, an assumption of similar outcomes may be reasonable and one might start with a cost-minimization analysis. However, this is usually inappropriate when considering a significant new pharmaceutical, because only simultaneous

¹⁶ We use the term *cost-outcome analysis* in order to avoid the confusion that can arise from the common practice of using *cost-effectiveness analysis*, not only for what we refer to as cost-effectiveness analysis, but to subsume cost-utility and cost-benefit analysis as well.

¹⁷ There is some variation in the specific definitions of *cost-outcome analysis* provided across different sources. For this report, we adopt the convention described.

consideration of cost and outcomes illuminates the possibility that a more expensive alternative represents a prudent investment.

Decision Analysis. In pharmaceutical assessment, the benefits of a strategy in a specific circumstance must be estimated. *Decision analysis* is a mathematical method of estimating likely consequences of an action when the evidence is insufficient to directly support decisionmaking. Sometimes incorporating data on costs (Haddix et al., 1996), decision analyses generally evaluate how a decision affects health outcomes (Sox, Blatt, and Higgins, 1988; Richardson and Detsky, 1995a, b; Pauker and Kassirer, 1987). They are especially explicit because they develop a decision tree (see "Decision Analysis" subsection), which shows the pathways from each decision point to all possible outcomes, the probability that each outcome could occur, and the expected result of a decision, which combines pathway and probability.

Demand Assessment. Whereas cost-outcome assessments and decision analyses are usually performed to determine the outcome of a decision in a controlled environment, such as the impact of beta-blockers when used by all eligible patients, that use, which, in turn, depends on providers prescribing it, must be understood and reliably predicted. *Demand assessment* investigates the number of people likely to take beta-blockers under each coverage scenario. This type of analysis is an important component of cost analyses, resource planning, and benefits measurements. Given the characteristics and actions of providers, patients, payers, service delivery organizations, and the drug (Schweitzer, 1997), demand models predict pharmaceutical use (or realized demand). Pharmaceutical use is too complex to model in its entirety, but it can be described by models that account for drug initiation, dosage, and duration. The most useful models focus on the choices or sequence of choices relevant to the managerial decision at hand. For example, a health plan may be particularly interested in modeling the initiation of treatment if a new drug is likely to recruit patients into treatment for a specific condition; however, it may be less concerned about modeling compliance if the duration of use is brief, the side effects are minimal, and the benefits are high.

Perform the Assessment

A managed care organization may choose to use one or, more likely, a combination of the above analytic modalities.

Evidence Assessment. If performing a full evidence assessment, or systematic review, the MCO will engage in a multi-step process in which all relevant clinical evidence is collected into a systematic review that summarizes the knowledge about a clinical area and identifies gaps in the literature. It is completely adequate only when it examines *all* of the relevant clinical evidence systematically and reproducibly.

Those conducting definitive systematic reviews should consult an experienced medical librarian who is familiar with the techniques developed by the consensus of experts participating in the Cochrane Collaboration and others rather than relying on a simple MedLine search, which is likely to miss many relevant articles, including randomized clinical trials (*The Cochrane Methods Handbook*, 1998; Dickersin, Scherer, and Lefebvre, 1994). A full effort would ideally include searches of other databases, the non-English literature, and the so-called gray literature of conference proceedings, and reports to and from government. All of these sources have been shown to increase yields and should be covered to avoid bias (Counsell, 1997; Egger and Smith, 1998; Egger et al., 1997). Searching through important sources and registries by hand for mis- or un-indexed material should be considered as well.

An adequate search process often results in the identification of a large number of potential sources, which must be reduced to the truly useful by a reproducible process that clearly delineates inclusion and exclusion criteria. In the Southern California Evidence Based Practice Center, we follow the common practice of generating criteria to apply sequentially to the lists of titles, abstracts, and articles to determine which to review at each successive step in the winnowing process (The Cochrane Library, 1999). Of course, such an extensive effort is not always appropriate or possible. Even when the intent is not to be definitive, a systematic and reproducible approach addressing the most important databases and other sources is most likely to uncover the most important information.

To assess the quality of the evidence, the evidence must first be categorized according to a hierarchy of quality, such as that of the widely used Canadian Task Force system. This system classifies study designs into (I) randomized controlled trial; (II-1) nonrandomized controlled trial; (II-2) well-designed cohort or case-control study; (II-3) multiple time-series studies with or without the intervention; and (IV) expert opinion (Canadian Task Force on the Periodic Health Examination, 1979). Once classified, the quality of each individual study needs to be assessed according to the strength of the design and the execution of that design. Weaker classes of studies and weaker studies within classes may be removed from further consideration or deleted in sensitivity analyses to assess their impact.¹⁸

After quality assessment, studies need to be organized into clinically sensible groups that are comparable. Even for an identical clinical question, randomized clinical trials will differ in some subtle and some not-so-subtle ways, and it is necessary to determine which studies are sufficiently similar so that a qualitatively or quantitatively pooled result has meaning. The determination of *clinical sensibility* is primarily a clinical task and requires input from experienced clinicians. This

¹⁸ The quality assessment of studies and the organization of those studies into homogeneous subgroups are two different processes.

issue of dealing with “clinical heterogeneity”—ensuring that a literature review is not criticized for “combining apples with oranges”—cannot be underestimated (Mulrow, Langhorne, and Grimshaw, 1997).

Finally, the evidence is summarized, often in evidence tables of studies and characteristics. If the studies are few or heterogeneous, the summary may be restricted to qualitative conclusions, such as “the superiority of the new method has not been established” or “formal economic analyses are not available, but the new drug will enable treatment to be done on an outpatient basis rather than in the hospital.” Otherwise, applying statistical pooling or meta-analysis techniques will generally provide the most information. Meta-analysis aggregates the results of multiple studies, thereby increasing sample size and allowing more statistically powerful conclusions regarding a common treatment or intervention effect across studies. However, meta-analysis cannot overcome poor study quality and can produce deceptive results when based on poor-quality data. Qualitative systematic reviews pose little risk in this regard.

Expert Opinion. Using formal approaches to obtain *expert opinion* generally involves capturing and synthesizing the opinion of a broad-based, unbiased panel informed by objective information representing all sides of an issue (Brook, 1994). The information exchange usually begins with materials delivered to the panel and usually includes a face-to-face meeting, which may be public (Kanouse et al., 1989). Most often, the evaluators will also organize some form of interaction or deliberations, which are usually structured and/or controlled by a facilitator. Finally, the evaluator should use an explicit means of aggregating judgments to identify consensus (Fink et al., 1984). While the best method of aggregation is not clear, mathematical approaches combining panelists' scores have the advantage of being quantitatively reportable, and thus are preferable to non-quantitative approaches. The scoring process is often iterative, with feedback of combined scores to participants and sometimes further discussions prior to re-scoring (Brook et al., 1986).

High-quality expert assessments can be resource-intensive: preparing materials, selecting the panel, and choosing methods for scoring and reporting can all be substantial undertakings. In some cases, these costs can be avoided by taking advantage of the private or public efforts of others, as long as the implications of the composition of the panel, the completeness and timeliness of the information considered, and the approach to aggregating panel judgments are understood. Alternatively, a limited effort could include the more important elements of a formal process by choosing a few (more than one or two) experts, giving them the evidence in advance, and ensuring that all participate in generating a consensus.

Mathematical Assessment. A decisionmaker may choose to utilize mathematical assessments instead of, or in addition to, formal expert opinion and evidence assessment.¹⁹ Several decisions must be made in performing a mathematical analysis to quantify the relationship between the costs and benefits of a policy (Haddix et al., 1996):

- *Define the Perspective of the Analysis.* In the context of this report, the *perspective of the analysis* will normally be the health plan. However, for certain applications, other perspectives may be included: for example, the perspective of the employer-purchaser in including lost productivity or the perspective of society in including remote health effects (i.e., after the patient changes plans or jobs) for a government purchaser or when attempting to characterize all likely social impacts.
- *Define the Time Frame of Concern.* The choice of *time frame* generally includes all points at which relevant costs or benefits might accrue. For example, some benefits of a drug that prevents pregnancy cannot be realized for at least nine months after its introduction.
- *Define the Coverage Options to Be Compared.* The choice of *decision options* (and, hence, coverage options) to be compared is critical to the usefulness of the model. For example, an analysis comparing the candidate treatment to a policy of no treatment will be of little practical use when some level of treatment is the status quo standard of care (Drummond et al., 1997).
- *Define and Estimate the Costs of Each Option.* When defining and estimating *costs*, an accurate result depends on considering all relevant direct and indirect costs (Luce and Elixhauser, 1990).²⁰
- *Define and Estimate the Benefits of Each Option.* To define and estimate a benefit requires additional data. Cost-effectiveness analyses often rely on simple clinical measures.²¹ For cost-utility analyses, one has to address the more daunting task of estimating the utility (e.g., value) of different health states and length of life, but the outcomes are generalizable across different types of interventions. Methods for utility estimation include direct estimation using techniques such as standard gamble, time trade-off, rating scales, and willingness-to-pay or indirect measurement from measures of health-related quality of life such as the quality of well-being

¹⁹ Some expert opinion and/or evidence assessment is necessary to build the models, but decisionmakers may either choose not to or not be able to carry these assessments to the point at which they directly affect decisionmaking.

²⁰ Our colleague Steven Garber points out that making decisions for society that favor the rich might be avoided by defining *value for all persons* according to the willingness-to-pay of persons with the median income. However, this may require an assumption that preferences are ordered by income, and may simply be moving the problem down the income scale.

²¹ That is, for cost-effectiveness analysis in the narrow sense used in this report.

index (Haddix et al., 1996; Gold et al., 1996).²² Often, the evaluator will use the results of these utility assessments to weight or discount life expectancy to create an estimate of the net total utility, generally expressed as the equivalent in years of perfect health or quality-adjusted life years (QALYs). For instance, if living one year with severe chronic pain is equivalent to living six months with no chronic pain, then one year of living with severe chronic pain has the value of 0.5 quality-adjusted life year. However, the evaluator can choose to use other similar (e.g., healthy-year equivalents) or simpler (e.g., disability-free years) units. For cost-benefit analyses, the evaluator has to take the additional step of converting outcomes to dollar equivalents. The available approaches include the human capital approach of valuing a year of life saved as the net present value of a person's economic output during that year or calculating a value from the premium paid to workers in risky occupations. All of these approaches are controversial in medical applications for a variety of reasons, including perceived equity issues of valuing different individuals' lives differently.

- *Perform Sensitivity Analysis.* Because the result of a cost-outcome analysis is a single ratio, traditional statistical significance tests cannot be used to quantify uncertainty. Rather, evaluators quantify the impact of uncertainty through *sensitivity analysis*, which involves varying the model assumptions (e.g., percent of antibiotic failures with oral treatment for a specified condition) over a reasonable range in order to illustrate the effects of uncertainty on the results of the analysis. One's confidence in the model's conclusions should depend on how well they hold up to reasonable variations in these inputs.

As mentioned in the preceding subsection, "Mathematical Models," the common final step of a cost-outcome analysis is interpreting the resulting cost-to-benefit ratio. For example, Figure 3.2 illustrates the nine categories into which strategies may fall when they are evaluated by the criteria of incremental costs and incremental effectiveness over an alternative. It is a modified version of the matrix of costs and benefits devised by O'Brien et al. (1997). Three cells (labeled Acept) characterize strategies that are at least as effective and no more costly than the point of comparison and should be adopted. Similarly, three cells (labeled Reject) characterize strategies that are no more effective and at least as costly and therefore should be rejected. However, the optimal course of action for strategies falling in the remaining three cells (labeled Judgment) is unclear, because

²² None of these methods is a gold standard. For instance, equating the value of an outcome with how much someone would pay to achieve it (willingness-to-pay) may create a bias toward outcomes favored by the wealthy (Drummond et al., 1997). Similarly, asking persons to trade quality for time alive may create a bias toward outcomes favored by healthier people, who anticipate having more healthy life-years left (Drummond et al., 1997).

	Incremental Effectiveness			
Incremental Cost		More	Same	Less
	More	<i>J</i>	<i>R</i>	<i>R</i>
	Same	<i>A</i>	<i>J</i>	<i>R</i>
	Less	<i>A</i>	<i>A</i>	<i>J</i>

Figure 3.2—Cost-Effectiveness Grid

these cells indicate that strategies are less effective and less costly, similarly effective and similarly costly, or more effective and more costly.

A fuller analysis may illuminate the correct decision. Often, however, decisions will have to be made on other grounds or, for more expensive and more effective interventions, be based on whether the strategy represents a reasonable investment. However, no set threshold exists for the ratio at which a strategy can be recommended. Some authors have asserted that strategies costing less than \$20,000/QALY (in 1992 Canadian dollars) are quite cost-effective, that strategies costing between \$20,000 and \$100,000/QALY are reasonable, and that those costing over \$100,000 are suspect (Laupacis et al., 1992). It is sometimes possible, and usually useful, to place the recommendation in context by including a league table, which shows similarly constructed cost-outcomes assessments for other interventions that have and have not been adopted by this or other organizations,²³ particularly after an organization has a history of conducting such analyses. Including one's own analysis in the table allows for ready comparisons and acts as a check for internal consistency in analysis and decisionmaking.

Decision Analysis. To obtain estimates of effectiveness for cost-outcome analysis or for direct comparison of strategies, evaluators often use decision analysis. The steps in a decision analysis are as follows: (1) define the strategies under consideration and the time horizon, (2) define the model according to the strategies and time frame, (3) translate the consequences into a relevant metric, and (4) perform sensitivity analysis. The first, third, and fourth steps are similar to those for cost-outcome analysis; these steps are not described here. The second step involves defining the appropriate model. As noted above, the model usually used in decision analysis is the decision tree, because it provides an explicit graphical explanation of trade-offs between the risks and benefits of different strategies, thereby justifying coverage decisions. Figure 3.3 illustrates this point with a simple example of a decision tree.

The analysis of the tree follows a patient from left to right. At each node, an event occurs (i.e., either a decision or a chance happening) that sends the patient along a branch to the right.

²³ The term "league table" originated in tables of British soccer-league standings.

For instance, the issue may be whether to cover beta-blockers after a heart attack. If the organization covers beta-blockers, this model indicates that one of two events will occur with some probability: the patient will both be eligible to take beta-blockers (that is, have clinical indications for taking them) and take the beta-blockers, or not. If the patient does not take beta-blockers, then he or she has some increased probability of experiencing the outcome of interest, another heart attack. Using this tree, the evaluator “works back” from the outcomes at the far right to calculate the relative value of each represented decision strategy from the probabilities along each path. The expected result of each strategy is the weighted sum of all the possible outcomes at the end of all possible paths for that strategy; the weight for each outcome is equal to the overall probability of that outcome as defined by the tree.

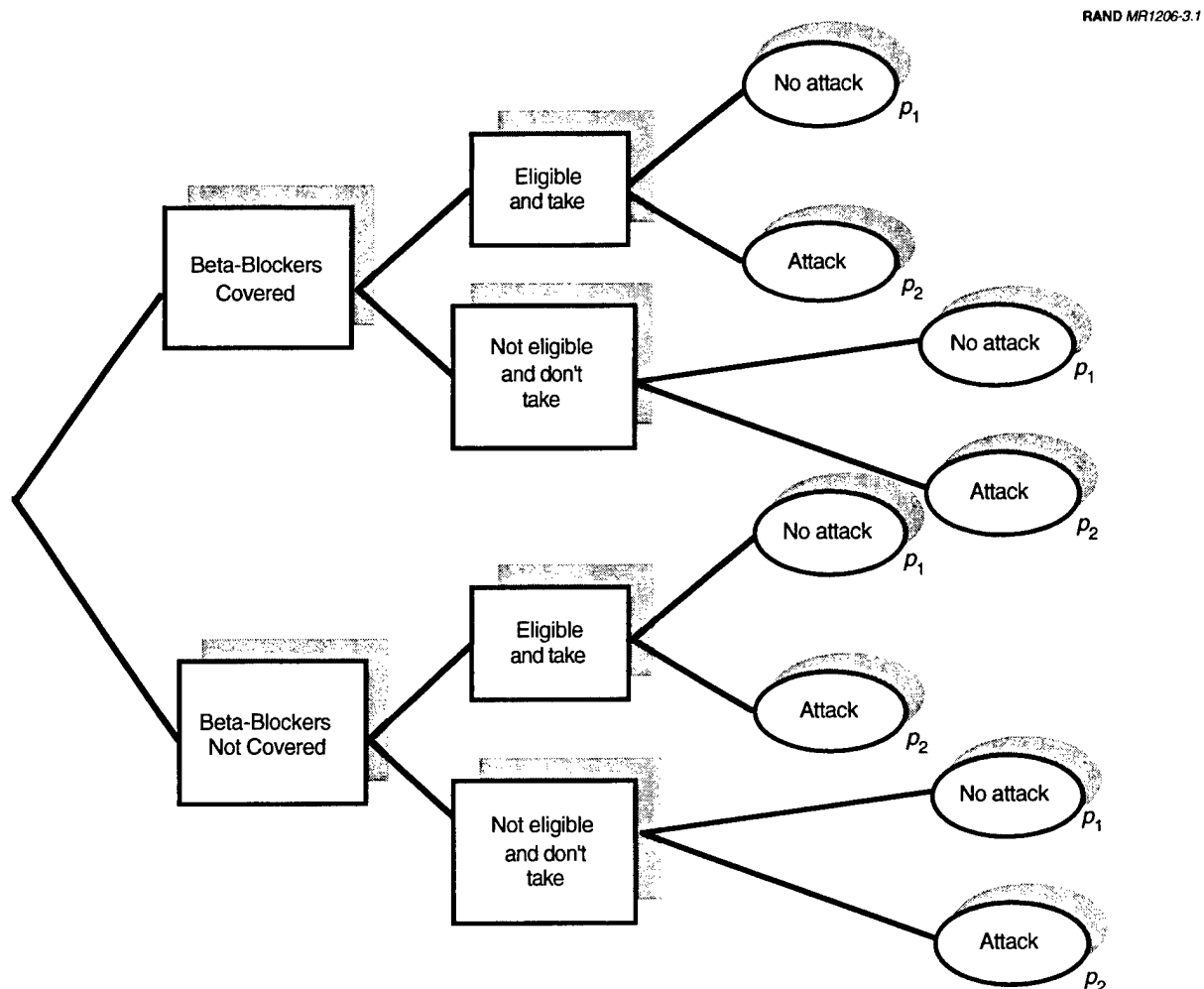


Figure 3.3—Example of a Decision Tree

In the beta-blocker example, the outcome could simply be the probability of a second heart attack, or it could be converted into a metric such as survival. When the same decision is made

repeatedly over time—say, to consider third as well as second heart attacks—the model can be modified to be iterative, or what is known as a Markov process model (Pauker and Kassirer, 1987).

Demand Assessments. Standards for assessing the clinical demand for, or actual use of, pharmaceuticals are less well developed than decision analyses. For example, in the decision tree above, demand assessment would include estimation of the likelihood that eligible patients are prescribed, and take, beta-blockers, as well as the more subtle possibility that use of a pharmaceutical may lead to the identification of more candidates. In the past, simple models based on disease-prevalence and clinical criteria were the standard for predicting use, and such models are still appropriate for rough estimation. However, this approach has failed historically in determining physician manpower and hospital-bed requirements, and more recently has failed to predict the use of “lifestyle drugs” and drugs that are advertised directly to consumers (Feldstein, 1988). Clearly, serious demand-assessment efforts need to be more sophisticated.

One approach to formulating models that are more adequate is to conceptualize pharmaceutical demand in terms of stocks and flows. *Stocks* are the number of users of the drug in question among the population of covered lives; *flows* are any additions to or subtractions from the number of users during a given period. Seen in this way, use of a particular drug during any period of time can be calculated from three pieces of information: (1) the number of people on treatment within a given period of time (the “stock” in the prior period plus the net flow [change in number of users]), (2) dosage, and (3) duration of use. Thus, demand assessment is complex because of the need to account for all of the components of “realized demand,” or pharmaceutical use (initiation, dosage, and duration).

Steps Common to All Models. Although the steps in constructing a model can vary, four factors are nearly always relevant.

The first is identifying the decisionmakers whose choices influence demand. These decisionmakers can be one of four sets of actors: (1) physicians only, the key actors in emergent conditions; (2) physicians and patients, when choice of treatment is more discretionary; (3) patients only, when compliance and duration are being considered; and (4) pharmacists, when issues of substitution and compliance with drug-management programs (e.g., disease-management, step-therapy protocols) are key considerations.

The second issue is specifying those choices that are actually to be modeled. Examples include the patient’s decision to seek care for a condition or the physician’s decision to prescribe a particular drug.

The third issue is defining the set of alternatives that the decisionmakers face. For example, if there is interest in the decision to initiate drug therapy, the choice set may be no treatment and treating with currently available drugs.

The fourth issue is determining the characteristics of the decisionmakers and the attributes of the choice-set factors that cause them to choose one alternative over the others (Train, 1986). Examples include the demographic and clinical characteristics of the patients and the specialty of the physicians.

At this point, the goal is to formulate the impact of the control mechanism on the demand—for example, the extent to which prior-authorization requirements for certain drugs discourage use by increasing time requirements and other difficulties in prescribing. A demand model will be most useful when this factor can be ascertained. If it cannot, the model can be used to estimate use but not how organizational choices influence use.

Make a Decision

The steps in the process outlined above can inform a decision, but they cannot *make* a decision. It is usually too difficult for a single analysis to incorporate all relevant considerations, such as the administrative burden of adopting a new pharmaceutical or an organizational interest in pursuing a particular strategic behavior. Even when a model includes all of the important factors, it may not point to a clear decision. For example, the model may predict a number of dissimilar outcomes that it can be difficult to aggregate into an overall summary score.

In such cases, judgment must be used to determine the relative importance of each outcome (e.g., if promoting use of a drug may be predicted to result in increases in both appropriate and inappropriate use, which is more important?). Moreover, instituting innovations may have strategic implications for the organization that may mean that existing practices will have to be disrupted, affecting provider morale, patient convenience, etc. Therefore, deciding to accept or reject a new pharmaceutical technology can raise non-analytical questions of organizational and social values, such as how much should be invested to obtain a particular outcome and what technologies or services should be sacrificed to obtain that outcome.

In the next section, we look at how to apply the framework described above. Both thorough and abbreviated approaches are presented to ensure that the most important information is obtained on each product.

4. Applying the Framework Practically

The decisionmaking framework described in Section 3 provides a "road map" for pharmaceutical technology assessments. It is not an unvarying recipe for how to make decisions about pharmaceutical technologies. Each organization must tailor its approach according to its own priorities and the information and resources that are available. However, consistent application of this framework (or a modified version of it) will expose hidden biases, reduce the risk of illogical or poorly thought-through decisions, and position the organization to reap the rewards of responding to patient and purchaser needs in a fiscally and medically responsible way. Use of a comprehensive framework will achieve these benefits by providing an objective and repeatable process for analyzing promising new pharmaceuticals. Compared to less structured approaches, the results should be more defensible to internal and external clients, less dependent on the involvement of particular individuals, and better able to support comparisons across specific situations and time periods.

Decisionmakers hardly need to be reminded of the barriers in applying this framework to real-world situations (Matuszewski, 1997):

- a failure to align organizational incentives to do an evaluation
- lack of evidence or inconsistent evidence upon which to base analyses
- lack of agreement on how to perform an assessment under a particular circumstance
- inadequate financial or human resources.

The rational yet practical decisionmaker must devise strategies for working within these confines. Thus, a central task for the decisionmaker is to determine which evaluations and which steps of those evaluations need greater or lesser attention. In some circumstances, the lack of human resources may lead the decisionmaker to buy (rather than make) an analysis, or to improve local capabilities. In others, the decisionmaker must devise a resource-sparing means of implementing a structured evaluation process.

A first step to evaluation is realizing that, in the context of an ongoing technology assessment effort, many of the tasks outlined in Section 3 need not be resource-intensive. For example, if the characteristics of the decisionmaking organization are fairly static, they need not be regenerated with each new assessment. Rather, the evaluator could make what could be essentially a one-time effort to create a data file to address the issues outlined in Table 3.2, relying largely on internal information. Alternatively, a more extensive but seldom necessary approach would involve profiling alternative organizational structures. In any case, with periodic updates, this generic file could contribute to the assessment process for many drugs.

Similarly, by drawing from the organization's strategy and philosophy toward drug management in general, the decisionmaker or evaluator could identify a generic list of decision

options. For most drugs, the decisionmaker would then need to consider only the existing list or small amendments to it. However, decisionmakers should always be alert to the possibility that they are considering an important drug (i.e., those true advances with the potential to increase the effectiveness or efficiency of care, or to create new classes of care) that may merit modification of existing rules, even if such modification requires shifting procedures or benefit structures.

Characterizing the drug also need not be resource-intensive in all situations. A first cut at the issues surrounding the drug might be derived from the manufacturer's publications, FDA reports, peer-reviewed articles including formal or informal reviews, and the decisionmaker's own experience with the manufacturer and similar drugs. Because this step calls for the identification of issues rather than a formal evaluation of evidence, a documented but relatively simple search for information may suffice. Since the evidence gathering that takes place throughout the process will provide further information about the drug, that information can be used to augment the characterization of the drug subsequently.

Choosing the type and level of analysis needed to make a decision will also be subject to constraints on time, resources, and skills. Because the results of one lead naturally to the next, evidence assessment should be considered first, then expert assessment, and, finally, mathematical assessment. Evidence assessments will be most useful and possibly sufficient when considering a focused clinical question for which there are at least several good studies. When the literature does not provide adequate information, as is often the case, the decisionmaker should seek to extend the usefulness of existing information and experience through expert or mathematical assessment. Which of these two alternative methods to use depends upon the amount of time and staff available, and upon the recognition that the resulting information for decisionmaking will vary greatly according to the choice made (e.g., cost/life year versus greater than 50% agreement by experts). Expert assessments can be faster, but are arguably less explicit and do not generally provide quantitative results. Consider a situation in which the literature indicates that the drug has higher efficacy and costs less than its substitute in certain circumstances, but does not provide pertinent information about the values of these quantities. In this case, an expert assessment may be appropriate but a cost-outcome assessment may be more useful.

Although performing a full evidence assessment may not be necessary or possible in a given situation, the underlying principles discussed in Section 3 should guide the process. For example, evidence assessment should at least include information from the authoritative Cochrane Collaboration database or other sources for systematic reviews. If an adequate evidence report is not available, it is often possible to perform systematic searches of literature databases (as opposed to convenience searches), and at least some assessment of the strength of the evidence uncovered (preferably by multiple readers). When an expert assessment is appropriate and there are few or no

recent studies addressing the specific question at hand, the decisionmaker should, at a minimum, seek opinions from multiple experts with diverse backgrounds and perspectives, ideally after allowing for a review of the evidence and an informed discussion among them.

Similarly, while mathematical models are best developed using formal methods with sensitivity analyses, limited ("back of the envelope") calculations can provide important insights. For example, parameter estimates and results arising from such an approach may be so clear as to make more-complete analysis very unlikely to move a new treatment out of the Accept or Reject region of Figure 3.2. In all cases, such an exercise provides guidance on the level of rigor required for a more formal mathematical assessment, and simply creating a schematic for an explicit mathematical model (e.g., a decision tree) can be useful in helping to identify key relationships and in providing grounds for discussion between experts (Roberts and Klein, 1984). Moreover, the shell of a model might be used to investigate whether the optimal policy changes under extreme values absent the intention or possibility of determining best estimates for parameters,.

Finally, while it may be appropriate to omit some steps entirely in certain circumstances, evaluators will want to consider at least abbreviated approaches to working through each step of the framework. For reference, Table 4.1 summarizes both thorough and abbreviated approaches.

Table 4.1—Thorough and Abbreviated Approaches to Technology Assessment

Approach Type	Step	Thorough Approach	Abbreviated Approach
Evidence Assessment	<i>Collect evidence</i>	With the assistance of a professional librarian, search multiple library databases in all languages, as well as the industry literature, and identify unpublished studies.	Search only a single English database—e.g., Medline—for a limited range of publication years.
	<i>Sift through evidence</i>	Develop an explicit, reproducible coding scheme for rejection and acceptance of literature for inclusion in review, and for extraction of data. Use multiple readers.	Allow for a "miscellaneous" rejection code. Use a single reader to decide on inclusion/exclusion and for data extraction.
	<i>Classify evidence by quality</i>	Develop an explicit scheme for valuing evidence. For example, rank evidence using the five classifications of the Canadian Task Force system, and quality-score studies using a validated instrument. Use multiple reviewers.	Rank evidence using five or fewer levels (e.g., Excellent, Good, Fair) or do not quality-score studies. Use a single reviewer.
	<i>Summarize evidence</i>	Perform a meta-analysis and write a full report including evidence tables.	Write an abbreviated report or give an oral presentation (e.g., at the quarterly P&T meeting) without meta-analysis—i.e., perform a qualitative analysis only.
Expert Assessment	<i>Select experts</i>	Select a diverse set of about twelve experts from multiple disciplines and professional affiliations.	Maintain a list of contacts in various fields and select at least three experts who represent only a few disciplines or affiliations.
	<i>Provide background to experts</i>	Perform a literature review (or full evidence assessment) and provide to experts before soliciting opinion.	Give a brief presentation at beginning of face-to-face (or teleconference) meeting. If no meeting, provide abbreviated material before soliciting opinion.
	<i>Solicit opinion</i>	Collect written responses and distribute a summary of responses to the experts. Follow-up with a mediated, face-to-face discussion.	Collect only written responses or collect only face-to-face responses with no follow-up.
	<i>Aggregate judgments</i>	Use an explicit, reproducible method for summarizing findings. For example, statistically summarize responses to numeric questions.	Provide narrative of the responses.

Table 4.1—continued

Approach Type	Step	Thorough Approach	Abbreviated Approach
Mathematical Assessment			
Cost-Outcome and Decision Analysis	<i>Define perspective</i>	Use the health plan's perspective.	Take the perspective required by the choices made below. For example, estimates of cost from the literature usually take the societal perspective.
	<i>Define time frame of concern</i>	Consider the entire horizon of possible effects (including secondary or indirect effects).	Use best guesses about downstream effects.
	<i>Define coverage options to be compared</i>	Accurately characterize the full range of decision options.	Develop stylized descriptions of the most-promising and estimable options.
	<i>Define and estimate costs of each option (for Cost-Outcome only)</i>	Include both direct and indirect costs (including downstream costs), with estimates based on an evidence assessment or reliable internal information where available.	Estimate direct, immediate costs based on informal evidence or expert review or conjecture. May rely on best guesses about indirect and downstream costs.
	<i>Define and estimate benefits of each option</i>	Include both direct and indirect benefits (including downstream benefits) with estimates based on an evidence assessment or reliable internal information where available.	Estimate direct, immediate benefits based on informal evidence or expert review or conjecture. May rely on best guesses about indirect and downstream benefits.
	<i>Perform sensitivity analysis</i>	Fully characterize the robustness of the results by varying the above estimates over any conceivably relevant range.	Explore the robustness of the results to only a few interesting alternative estimates.

Table 4.1—continued

Approach Type	Step	Thorough Approach	Abbreviated Approach
Demand Analysis	Identify relevant decisionmakers and corresponding decisions	Consider entire sequence of decisions involved in determining initiation and duration of use.	Limit focus to one or two key actors—usually, physicians and patients—using best guesses about the influence of other actors on use.
	Characterize decision elements • Universe of alternative treatment • Key decisionmakers • Relevant drug attributes • Decisionmaker characteristics	Obtain information from medical records, supplemented with epidemiological data, representative surveys of patients and physicians, and existing literature where appropriate.	Rely on secondary data sources, interviews, or focus groups with patients and physicians. Formulate "best guesses" about effect of unmeasured elements on use.
	Incorporate elements into demand models	Specify and estimate econometric models with patient-level data. Use resulting parameters in predicting impact of new drug. Validate predictions through comparisons with take-up rates ^a resulting from earlier introductions of new drugs.	Use informally obtained information combined with "best guesses" to create back-of-the-envelope models under alternative sets of assumptions. Use earlier introductions of related drugs to gauge effects.

^aTake-up rates are how quickly consumers and providers adopt a new drug.

Summary

In summary, we have provided a decisionmaking framework in response to the need for better evaluations of new pharmaceutical technologies by managed care organizations. Use of the framework will not create evidence. Instead, it should stimulate decision analyses that are broader, more explicit, more efficient, more reproducible, and more relevant than those now being performed. Similarly, while it will not increase resources, it should stimulate skill-building and an explicit discussion of the trade-offs between the rigor of an evaluation and budgetary and data constraints. Finally, we hope that it will assist in implementing a systematic analytic process for pharmaceutical technology assessment that should ultimately improve the health of the populations under care and the effectiveness of the organizations that serve them.

Appendix A: Annotated Bibliography

Pharmaceuticals in Healthcare

Schulman KA, Rubeinstein LE, Abernethy DR, Seils DM, Sulmasy DP. The effect of pharmaceutical benefits managers: is it being evaluated? *Ann Intern Med.* May 1996;124(10):906-913.

The authors summarize the history and current role of pharmaceutical benefits managers, and identify their contribution to health care delivery, as well as their limitations.

Schweitzer SO. *Pharmaceutical Economics and Policy.* New York, NY: Oxford University Press; 1997.

An overview of the economics of drug manufacturing, use, promotion, and regulation in the United States and abroad, this book contains an interesting discussion of the forces driving increasing expenditures on pharmaceuticals and of the role of pharmaceuticals in the health production process from an economic perspective.

Current Practices

Dubinsky M, Ferguson JH. Analysis of the National Institutes of Health Medicare coverage assessment. *Int J Technol Assess Health Care.* 1990;6:480-488.

The authors report the results of a study designed to measure the level of agreement between the assessment performed by the National Institutes of Health (NIH) and that of the Office of Health Technology Assessment (OHTA). Because OHTA adopts NIH conclusions in 93% of the cases, it appears that a significant proportion of coverage decisions at the national level rely on expert opinion rather than on scientific evidence.

Luce BR, Brown RE. The use of technology assessment by hospitals, health maintenance organizations, and third-party payers in the United States. *Int J Technol Assess Health Care.* 1995;11(1):79-92.

Through a series of structured in-depth interviews with various decisionmakers, this survey attempts to determine the reliance on technology assessment in hospitals, health maintenance organizations (HMOs), and third-party payers.

Lyles A, Luce BR, Rentz AM. Managed care pharmacy, socioeconomic assessments and drug adoption decisions. *Soc Sci Med.* 1997;45(4):511-521.

The authors report on a telephone survey of 50 managed care plans in the United States. The survey determined the plan's formulary type, use of assessment methodologies, the drug coverage approval process, the decisionmakers within the organization, the sources used in the assessments, and the decisionmakers' attitude toward assessments.

Mather DB, Sullivan SD, Augenstein D, Fullerton DS, Atherly D. Incorporating clinical outcomes and economic consequences into drug formulary decisions: a practical approach. *Am J Managed Care*. 1999;5(3): 277-285.

This article describes an evidence-based formulary adoption process used by a large managed care organization. The process is unique in that it requires drug manufacturers to compile and submit clinical and economic data from published and unpublished sources prior to review and to create models that the plan can use to forecast health outcomes and costs of care associated with use of the drug.

Steiner C, Powe NR, Anderson GF, Das A. The review process used by U.S. Health care plans to evaluate new medical technology for coverage. *JGIM*. May 1996;11:294-302.

The authors conducted a survey of 231 physicians at private health plans. The sample covered 66% and 72% of the HMO and indemnity beneficiaries, respectively, in the United States. The survey demonstrated that final coverage decisions for medical technology are not uniform from plan to plan, are difficult to predict, and differ from assessments done by the medical scientific community. Different health plans have different review processes, confer different authority on the medical director, have different timing for making decisions, and view sources and evidence differently.

Steiner CA, Powe NR, Anderson GF, Das A. Technology coverage decisions by health care plans and considerations by medical directors. *Med Care*. 1997;35(5): 472-489.

This survey of private health care plans in the United States demonstrates considerable variability in whether a given laser technology would be covered. Clinical, economic, and regulatory issues appear to dominate the decisionmaking processes of medical directors.

Weingart SN. Acquiring advanced technology: decision-making strategies at twelve medical centers. *Int J Technol Assess Health Care*. 1993;9(4):530-538.

This paper reports on a survey designed to describe the decisionmaking strategies regarding the acquisition of technology in 12 major medical centers. Although exemplary models exist, the technology assessment process at most institutions is described as "political," "informal," or "ad hoc."

Overview of Technology Assessment

Garber AM. Can technology assessment control health spending? *Health Aff*. Summer 1994;115-126.

Garber summarizes the different approaches to technology assessment, including cost-effectiveness analysis, appropriateness evaluation (a formal group technique to elicit expert opinion), and evaluation of strength of evidence (requires scientifically rigorous proof of effectiveness). He further identifies the potential barriers to technology assessment.

Goodman CS. *TA101: Introduction to Health Care Technology Assessment*, Washington, D.C.: National Information Center on Health Services Research & Health Care Technology, National Library of Medicine; January 1998.
http://www.nlm.nih.gov/nichsr/ta101/ta101_c1.htm

This report contains a comprehensive introduction to technology assessment, with special reference to health care.

Matuszewski KA. A primer on the assessment of medical technologies. *Pharm Pract Manage Q.* January 1997:53-65.

This article covers the basics of technology assessment, including what it is, who does it, how it is done (perspectives, essential tools, qualities of a good assessment). The author also notes common problems encountered in executing a technology assessment.

Choosing What to Assess

Eddy D. Selecting technologies for assessment. *Int J Technol Assess Health Care.* 1989;5:485-501.

The focus of this article is on setting priorities in choosing technologies to assess. The author reviews the qualitative criteria given by agencies in priority setting. He suggests a quantitative method that is essentially a decision analytic approach to priority setting.

Eddy D. *A Manual on Assessing Health Practices and Designing Practice Policies: The Explicit Approach*. Philadelphia, Penn: American College of Physicians; 1992.

Provides an overview of the author's approach to explicit analysis of evidence, estimation of outcome, calculation of costs, and assessment of preferences.

Harper G, Townsend J, Buxton M. The preliminary economic evaluation of health technologies for the prioritization of health technology assessments: a discussion. *Int J Technol Assess Health Care.* 1998;14(4):652-662.

The authors review the existing methods for priority setting in technology assessment and suggest elements of an ideal priority-setting process.

Evidence Assessment

Berlin JA, Antman EM. Advantages and limitations of meta-analytic regressions of clinical trials data. *Online J Curr Clin Trials.* 4 June 1994; Doc. No. 124.

This publication discusses the methodology and appropriateness of meta-regression, which has become an increasingly common technique through which to both account for and understand heterogeneity between studies in a meta-analysis.

Berlin JA. Invited commentary: benefits of heterogeneity in meta-analysis of data from epidemiologic studies. *Am J Epidemiol.* 1995;142(4):383-387.

This author defines heterogeneity in the meta-analysis setting. Generally, heterogeneity is seen as an unfortunate complication in a meta-analysis because it may deter the analyst from combining studies. Berlin discusses how heterogeneity benefits a meta-analysis.

Borzak S, Ridker PM. Discordance between meta-analyses and large-scale randomized, controlled trials. *Ann Intern Med.* 1995;123:873-877.

This article discusses the strengths and weaknesses of meta-analysis. The authors also compare meta-analytic results with those of large randomized-controlled trials, and consider the settings in which a meta-analysis may not be definitive, and a large trial is necessary to answer a particular clinical question.

The Cochrane Library, *The Cochrane Methods Handbook*, 1999;Issue 1. Vista, Calif.: Update Software (www.cochrane.org).

The Cochrane Collaboration is an international nonprofit organization dedicated to "preparing, maintaining and promoting the accessibility of systematic reviews of the effects of health care interventions." The first Center was established in Oxford, England, in October 1992. Since then, more than a dozen Centers have opened around the world. In particular, the Cochrane Collaboration maintains a library of systematic reviews whose abstracts can be viewed at no cost on the Web, and whose contents can be obtained for a modest fee by an individual or library. In addition, the Collaboration provides materials to teach individuals how to conduct high-quality systematic reviews and meta-analyses.

Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Ann Intern Med.* 1997;126:376-380.

This article is the first in a series in the *Annals of Internal Medicine* on systematic reviews. It defines a systematic review and meta-analysis, and contrasts the systematic approach with that of a narrative review, as well as discussing the past and future promise of systematic reviews.

Cook DJ, Sackett D, Spitzer WO. Methodologic guidelines for systematic reviews of randomized control trials in health care from the Potsdam Consultation on Meta-analysis. *J Clin Epidemiol.* 1995;48:167-171.

This article provides guidelines for the conducting of a meta-analysis. In particular, it argues that similar to a randomized controlled trial, a meta-analysis should be based on an a priori protocol, and the authors discuss what elements should be defined in that protocol.

Cooper H, Hedges LV, eds. *The Handbook of Research Synthesis*. New York: Russell Sage Foundation; 1994.

This book provides guidance on all stages of a literature synthesis, from the question formulation, to study gathering, to the pooling and presentation of results. The chapters are written by different authors, but common examples run throughout the text. The book is not written from the perspective of medical applications, but contains primarily examples from education and psychology.

Counsell C. Formulating questions and locating primary studies for inclusion in systematic reviews. *Ann Intern Med.* 1997;127(5):380-387.

This article is another in the *Annals of Internal Medicine* series on systematic reviews, and focuses on the formulation of the question, and how to conduct a systematic, unbiased, and comprehensive search of the literature.

Egger M, Smith GD, Phillips AN. Meta-analysis: principles and procedures. *BMJ*. 1997;315:1533-1537.

This article is one of a series in *BMJ* of articles on methods and interpretation of meta-analysis. It introduces the basic steps in a meta-analysis for the nontechnical reader.

Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-634.

This article is another in the *BMJ* series. It discusses the use of funnel plots, in which each study's effect size is plotted versus the study's sample size. These plots may be useful in detecting bias in meta-analyses.

Egger M, Smith GD. Bias in location and selection of studies. *BMJ*. 1998;316:61-66.

This article is another in the *BMJ* series. It discusses the primary data-gathering step in a systematic review or meta-analysis: identifying studies. In particular, it addresses publication bias, and the bias that may be introduced by the exclusion of articles not published in English.

Egger M, Zellweger-Zahner T, Schneider M, Junker C, Antes G. Language bias in randomized controlled trials in English and German. *Lancet*. 1997;350:326-329.

This article concludes that an author is more likely to publish statistically significant results from a randomized controlled trial in an English-language journal, and thus bias may result if a systematic review is restricted to studies published in English-language journals.

Hedges LV, Olkin I. *Statistical Methods for Meta-analysis*. New York: Academic Press, Inc.; 1985.

This book is the standard reference for statistical methods in meta-analysis. The text is technical. It contains several data examples for the motivation of particular techniques.

Laird NM, Mosteller F. Some statistical methods for combining experimental results. *Int J Technol Assess Health Care*. 1990;6:5-30.

In this article, the authors define the three basic meta-analytic pooling models: equal effects, fixed effects, and random effects. They apply these models in a variety of settings including the calculation of a pooled proportion, and odds ratio. This introduces the technical issues of pooling studies.

Lau J, Ioannidis PA, Schmidt CH. Quantitative synthesis in systematic reviews. *Ann Intern Med*. 1997;127:820-826.

This article is another in the *Annals of Internal Medicine* series on meta-analysis. It explains basic meta-analysis methods including pooling data and meta-regression, and is a good introduction for the nontechnical reader.

Moher D, Jadad AR, Nichol G, Penman M, Tugwell P, Walsh S. Assessing the quality of randomized controlled trials: an annotated bibliography of scales and checklists. *Control Clin Trials*. 1995;16:62-73.

This article presents an annotated bibliography of twenty-five scales and nine checklists that have been developed to assess the quality of randomized controlled trials.

Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, Tugwell P, Klassen TP. Does the quality of reports of randomized trials affect estimates of intervention efficacy reported in meta-analyses? *Lancet*. 1998;352:609-613.

The authors discuss the possible relationship between study quality and treatment effect. In addition, they provide a good reference list to other publications on study quality.

Mulrow C, Langhorne P, Grimshaw J. Integrating heterogeneous pieces of evidence in systematic reviews. *Ann Intern Med*. 1997;127:989-995.

This article is another in the *Annals of Internal Medicine* series on systematic reviews, and focuses on three topics: (1) how reviewers can classify heterogeneous evidence; (2) what factors complicate integration of such evidence; and (3) what strategies can be used to integrate such evidence.

Oxman AD, Cook DJ, Guyatt GH. Evidence-Based Medicine Working Group. Users' guide to the medical literature. VI. How to use an overview. *JAMA*. 1994;272(17):1367-1371.

This article is one in the *JAMA Users' Guide* series and discusses how to read and use a systematic review or meta-analysis. As compared with other guideline publications, this document is written from the perspective of a clinician caring for individual patients, rather than from a population-based perspective.

Sackett DL, Richardson WS, Rosenberg W, Haynes RB. *Evidence-based Medicine*. New York: Churchill Livingstone Inc.; 1997.

This text defines evidence-based medicine and explains clearly how to apply its key principles. The book is written for the clinician. It gives useful examples of how to apply evidence-based medicine in one's own clinical practice.

U.S. Preventive Services Task Force. *Guide to Clinical Preventive Services*. 2nd ed. Baltimore, Md.: Williams and Wilkins; 1996.

This report gives examples of categorizing evidence on the efficacy of preventive services via an evidence hierarchy.

Expert Assessment

Brook RH, *The RAND/UCLA Appropriateness Method*. Reprinted from McCormick KA, Moore SR, and Siegel RA. *Methodology Perspectives*, Rockville, Md.: Public Health Service, U.S. Department of Health and Human Services; 1994:59-70. AHCRR publication 95-0009. (Also available as RAND reprint RP-395.)

This document describes the criteria and methods used in the development of the RAND/UCLA Appropriateness Method.

Coulter I, Adams A, Shekelle P. Impact of varying panel membership on ratings of appropriateness in consensus panels: a comparison of multi- and single disciplinary panel. *Health Serv Res*. 1995;30:4:577-591.

This study demonstrated that the composition of a panel influences the ratings of various medical indications. In addition, it was found that those who use a given procedure are more likely to rate it as appropriate.

Ferguson JH. *Technology Transfer: Consensus and Participation: The NIH Consensus Development Program.* Oakbrook Terrace, Ill.: The Joint Commission on Accreditation of Healthcare Organizations; July 1995. Publication 1070-3241.

This document describes the goals of the NIH Consensus Development Conferences and attempts to assess the impact of the conferences. The Office of Medical Applications Research has conducted many studies on the impact of the consensus conferences and, thus far, studies have shown minimal recognition of the NIH program or conferences.

Leape LL, Park RE, Kahan JP, Brook RH. Group judgments of appropriateness: the effect of panel composition. *Qual Assur Health Care.* 1992;4(2):151-159.

In this study, the authors compared the ratings of appropriateness for the use of carotid endarterectomy between an all-surgical panel and a multispecialty panel. It was found that the surgical panel rated more indications appropriate and fewer indications inappropriate than the multispecialty panel.

McGlynn EA, Kosecoff J, Brook RH. Format and conduct of consensus development conferences: multinational comparison. *Int J Technol Assess Health Care.* 1990;6:450-469.

This document compares the process by which consensus conferences are conducted in the United States, Canada, Denmark, Finland, the Netherlands, Norway, Sweden, Switzerland, and the United Kingdom. Although the model of NIH has been used extensively in other countries, it has never been shown to produce replicable results or to be preferable to other models.

Pearson SD, Margolis CZ, Davis S, Schreier LK, Sokol HN, Gottlieb LK. Is consensus reproducible? A study of an algorithmic guidelines development process. *Med Care.* 1995;33(6):643-660.

The objective of this study was to evaluate the reproducibility of a consensus guideline development process across different groups of physicians in a health maintenance organization. The authors demonstrate that physician panels using a simplified literature support and consensus process may produce guidelines that vary.

Phelps CE. The methodologic foundations of studies for the appropriateness of medical care. *New Engl J Med.* 1993;329(17):1241-1245.

This author discusses how methods used to study appropriateness can lead to biased estimates of the rates of inappropriate treatment and that these rates may differ markedly from the true rates. The overall value and credibility of methods to assess the appropriateness of medical interventions cannot be determined until studies estimate the sensitivity and specificity of this "diagnostic test."

Phelps CE, Mushlin AI. Focusing technology assessment using medical decision theory. *Med Decis Making.* Oct-Dec 1988;8(4):279-289.

The authors describe a hurdle approach to assessments of diagnostic technology. The first hurdle calculates the cost-effectiveness ratio of using the technology assuming that it is perfectly accurate. If the technology is worthy under that assumption, then further analysis should be performed.

Shekelle PG, Kahan JP, Bernstein SJ, Leape LL, Kamberg CJ, Park RE. The reproducibility of a method to identify the overuse and underuse of medical procedures. *New Engl J Med.* 1998;338:1888-1895.

The authors conducted a scientifically rigorous test of the reproducibility of the RAND/UCLA Appropriateness Method and found that when the method is used to measure appropriateness rates in a single population, precise estimates are not possible. At best, in a single population, the Appropriateness Method can estimate whether the proportion of cases with overuse is small or large. By extension, in making decisions for individual patients, the Appropriateness Method does not have sufficient reproducibility to justify its use as a gold standard of appropriateness.

Wortman PM, Smyth JM, Langenbrunner JC, Yeaton WH. Consensus among experts and research synthesis: a comparison of methods. *Int J Technol Assess Health Care.* 1998;14(1):109-122.

The authors find a positive correlation between consensus panels and systematic review and synthesis within the context of assessing carotid endarterectomy. The authors go on to state: "consensus methods may be more appropriate during the early or 'emerging' phase of the intervention when there are few high-quality research studies and a viable research synthesis cannot be conducted. As the intervention develops and sufficient research studies accumulate, research synthesis would seem more appropriate."

Mathematical Assessment

Hogarth RM, Makridakis S. Forecasting and planning: an evaluation. *Manage Sci.* 1981;27(2):115-138.

Reviews the psychological literature on human judgment abilities and the value of simple quantitative models in overcoming errors in judgment.

Stokey E, Zeckhauser R. *A Primer for Policy Analysis.* New York: Norton; 1978.

This classic book is intended primarily as guide for public-sector decisionmakers. However, this book contains chapters on modeling approaches that are relevant for health care decisionmakers, such as decision analysis, simulation, Markov models, discounting, and linear programming. This book is technical, although the authors claim that readers need training beyond college algebra. This book has many useful examples.

Cost-Outcome Analysis

Brown M, Fintor L. Cost-effectiveness of breast cancer screening: preliminary results of a systematic review of the literature. *Breast Cancer Res Treat.* 1993;25(2):113-118.

The authors review 16 studies of breast cancer screening and find large differences in the reported cost-effectiveness of screening. The authors identify the different assumptions leading to the disparate conclusions made in two of these studies.

Drummond MF, Richardson WS, O'Brien JB, Levine M. User's guide to the medical literature: XIII. How to use an article on economic analysis of clinical practice, A. are the results of the study valid? *JAMA*. May 21, 1997;277(19):1552-1557.

This is the first of two articles (see O'Brien et al., 1997) written for clinicians who turn to cost-outcome analysis to assess treatment for a specific patient. Although the perspective is not that of the medical director, the discussion is an excellent introduction, contains many references, and identifies the potential problems with cost-outcome analyses.

Eddy D. Oregon's methods: did cost-effectiveness analysis fail? *JAMA*. 1991;266:2135-2141.

The author reviews Oregon's attempted practice of ranking health care interventions by their ratio of cost to effect. He discusses the political environment and its implications for the impact of cost-effectiveness studies.

Gage BF, Carinalli AB, Albers GW, Owens DK. Cost-effectiveness of warfarin and aspirin for prophylaxis of stroke in patients with nonvalvular atrial fibrillation. *JAMA*. 1995;274(23):1839-1845.

This article provides an example of cost-effectiveness research using clinical trial data and decision analysis. The authors examine the cost-effectiveness of treatment with warfarin, aspirin, or no treatment for the prevention of stroke. The authors estimate the probability of stroke, hemorrhage, and death using published clinical trial evidence, and perform a decision analysis to evaluate the three treatment options.

Gold MR, Siegel JE, Russell LB, Weinstein MC. *Cost-Effectiveness in Health and Medicine: A Report of the US Public Health Service*, New York: Oxford University Press; 1996.

This book reports the findings of an expert panel convened by the U.S. Public Health service to study cost-outcome analyses. It contains a review of the foundations, the current practices, and the current shortcomings/controversies of cost-outcome analyses. The book further suggests a standardized method that had been previously lacking. The findings of the panel are widely accepted as best practices for cost-outcome analyses. One assumption of the book that will make strict application to a specific health plan difficult is that the panel recommends a societal perspective, as opposed to a payer perspective, in performing these analyses.

Haddix AC, Teusch SM, Shaffer PA, Dunet DO. *Prevention Effectiveness: A Guide to Decision Analysis and Economic Evaluation for the Prevention Effectiveness Activity Epidemiology Program Office, Centers for Disease Control and Prevention*. New York: Oxford University Press; 1996.

This book contains an easy-to-follow description of how to perform decision analysis and cost-effectiveness analysis as suggested by a Centers for Disease Control and Prevention course. It includes several useful examples and references.

Laupacis A, Feeny D, Detsky A, Tugwell P. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economical evaluations. *Can Med Assn J*. February 15, 1992; 146(4):473-481.

The authors suggest a grading scheme for economic evaluations of health care strategies. The authors grade the evidence and methods used in studies, as well as the ratio of cost to outcome. They recommend grading based on, among other criteria, the ratio of cost to quality adjusted life year.

Luce B, Elixhauser A. Estimating costs in the economic evaluation of medical technologies. *Int J Technol Assess Health Care*. 1990;6:57-75.

The authors explain the foundations of cost estimation, list the common errors made, and provide a list of costs to consider.

O'Brien BJ, Heyland D, Richardson WS, Levine M, Drummond MF. User's guide to the medical literature: XIII. How to use an article on economic analysis of clinical practice. B. What are the results and will they help me in caring for my patients? *JAMA*. June 11, 1997;277(22):1802-1806.

This is the second of two articles (see Drummond, 1997) written for clinicians who turn to cost-outcome analysis to assess treatment for a specific patient. As with Drummond, the perspective is not that of the medical director, but the discussion is an excellent introduction, contains many references, and identifies the potential problems with cost-outcome analyses.

Russell LB, Gold MR, Seigel JE, Daniels N, Weinstein MC, for the Panel on Cost-Effectiveness in Health and Medicine. The role of cost-effectiveness analysis in health and medicine. *JAMA*. 1996; 276(14):1172-1177.

This article is the first in a three part series that summarizes the findings of the Panel on Cost-Effectiveness in Health and Medicine convened by the US Public Health Service. The findings of the panel are detailed in Gold, 1996.

Sloan F, ed. *Valuing Health Care: Costs, Benefits, and Effectiveness of Pharmaceuticals and Other Medical Technologies*. New York: Cambridge University Press; 1995.

With contributions from several well-known economic analysts, the book reviews the foundations of cost-outcome analysis, the current uses of cost-outcome analysis, and recommends best practices.

Tucker AW, Haddix AC, Bresee JS, Holman RC, Parashar UD, Glass RI. Cost-effectiveness analysis of a rotavirus immunization program for the United States. *JAMA*. 1998;279(17):1371-1376.

An example of cost-effectiveness research using decision analysis. The authors examine the cost-effectiveness of a US rotavirus immunization program. The authors used a decision tree to estimate the impact of the proposed program.

Decision Analysis

Beck J, Pauker S. The Markov process in medical prognosis. *Med Decis Making*. 1983;3:411-458.

This article gives a nontechnical introduction to Markov processes and the assumptions of these models.

Haddix AC, Teusch SM, Shaffer PA, Dunet DO. *Prevention Effectiveness: A Guide to Decision Analysis and Economic Evaluation for the Prevention Effectiveness Activity Epidemiology Program Office, Centers for Disease Control and Prevention*. New York: Oxford University Press; 1996.

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Law A, Kelton W. *Simulation Modeling and Analysis*. 2nd ed. New York: McGraw-Hill; 1991.

This text serves as a reference for how to perform and analyze the results of simulation analyses. The book is written for persons with a basic familiarity with probability, statistics, and computer programming. Examples in the book are drawn from a wide range of managerial scenarios.

Pauker SG, Kassirer JP. Decision analysis. *New Engl J Med*. 1987;316(5):250-258.

The authors describe decision analysis to physicians. The focus is on clinical decisionmaking for the individual. The discussion is quite dated, but nicely introduces decision analysis and Markov processes.

Richardson SW, Detsky AS. User's guide to the medical literature: VII. how to use a clinical decision analysis, A. are the results of the study valid? *JAMA*. April 26, 1995;273(16):1292-1295.

This is the first of two articles (see Richardson, May 1995) written for clinicians who turn to decision analytic studies to assess treatment for a specific patient. Although the perspective is not of the medical director, the discussion is an excellent introduction, contains many references, and identifies the potential problems with decision analysis.

Richardson SW, Detsky AS. User's guide to the medical literature: VII. how to use a clinical decision analysis, B. what are the results and will they help me in caring for my patients? *JAMA*. May 24-31, 1995;273(20):1610-1613.

This is the second of two articles (see Richardson, April 1995) written for clinicians who turn to decision analytic studies to assess treatment for a specific patient. Although the perspective is not of the medical director, the discussion is an excellent introduction, contains many references, and identifies the potential problems with decision analysis.

Sox HC, Jr., Blatt MA, Higgins MC, Marton KL. *Medical Decision Making*. Boston, Mass: Butterworth-Heinemann; 1988.

The book is written to introduce medical practitioners to decision analysis. The book also contains an introduction to cost-outcome analysis.

Weinstein M, Fineberg HV. *Clinical Decision Analysis*. Philadelphia, Penn.: WB Saunders Company; 1980.

A classic text that walks the reader carefully through the logic and perspective of decision analysis.

Demand Modeling

Duan N, Manning WG, Morris CN, Newhouse JP. A comparison of alternative models for the demand for medical care. *J Bus Econ Stat*. 1983;1(2):115-126.

A classic but technical article about the use of econometric models to estimate demand for medical care. The framework presented in the model is useful for modeling behavior, such as initiation of pharmaceutical therapy and dosage decisions.

Green PE, Krieger AM. An application of a product positioning model to pharmaceutical products. *Marketing Sci.* 1992;11(2):117-132.

Kontzalis P. Identification of key attributes, gap analysis, and simulation techniques in forecasting market potential of ethical pharmaceutical products. *Int J Forecasting.* 1992;8:243-249.

These two articles lay out a process for forecasting demand for pharmaceuticals through a process of primary data collection, modeling, and simulation. The articles are from the perspective of drug manufacturers. However, the general approach is useful for the service delivery organizations as well. The decisionmakers considered in these studies are hospital dietitians and physicians, respectively.

Waldo D. Estimating the cost of the Medicare outpatient drug benefit. *Health Care Financing Rev.* 1994;15(3):103-112.

An example of a "back of the envelope" model used to produce cost estimates for the Clinton Administration's health reform initiative. The author draws parameters from a range of sources and performs sensitivity analysis under different demand scenarios.

Primary Data Collection for Demand Analysis

McQuarrie EF. *The Market Research Tool Box: A Concise Guide for Beginners.* Thousand Oaks, Calif.: Sage Publications; 1996.

This book introduces managers to a range of marketing research methods. The author discusses the value of marketing research data for informing business decisions. The book is intended as a background text rather than a "how-to" guide. The author includes suggested readings, and the examples are intended to be relevant to managers selling expensive, high-tech products but also inform decisions faced by medical directors and other health care managers.

Salant P, Dillman DA. *How to Conduct Your Own Survey.* New York: John Wiley and Sons; 1994.

The authors present an applied approach to developing telephone and mail surveys. The book is intended for professionals with no training in survey research. This book offers systematic instructions on everything from question and questionnaire design to budgeting. A strength of this book is the many practical examples.

Templeton JF. *The Focus Group.* Chicago, Ill.: Probus Publishing; 1994.

A practical guide to organizing and conducting focus groups and analyzing resulting data. This book contains sample schedules, interview guides, and final reports. This book offers advice on being an "ideal" client, dealing with common problems, and choosing panelists.

Appendix B: Interview Questionnaire

DEFINITION STATEMENTS:

For this effort, we want to separate consideration of "routine" and "revolutionary" pharmacological advances.

- *Routine* is defined as an incremental improvement in diagnosis or management of a condition that is currently handled using similar approaches. Examples might be new formulation of an existing drug or a new drug with a profile similar to that of an existing drug.
- *Revolutionary* involves a change in the paradigm for diagnosis or management. It may include the development of medical treatment for a disease formerly managed surgically (and vice versa), a new drug which is substantially *different* in potency or mode of administration or action, and introduction or extension of drug therapy to persons who were formerly treated expectantly or by nonmedical means.

In addition, we want to separate consideration of "medical necessity" and "coverage" decisions.

- For this purpose, *medical necessity* involves decisions regarding/identified with a putative clinical need.
- *Coverage* will refer to decisions intended to apply to larger numbers of yet unidentified patients.

THE QUESTIONNAIRE

A. WHAT'S DONE NOW IN YOUR ORGANIZATION

- In regard to emerging pharmaceuticals or new indications for existing drugs, does your organization make rules and/or decisions internally?(Y / N) probe for how they are made...
 - a. National vs. local
 - b. Plan vs. PBM
 - c. Plan vs. Medical Group
 - d. Coverage
 - e. Indications for use
 - f. Medical necessity
 - g. Level of coverage (co-payment) for drug
 - h. Formulary inclusion
- For those areas where you make rules and/or decisions, do you have policies and procedures in place and/or a structured process for considering and making decisions?
 - a. Coverage (Y / N)
 - b. Indications for use (Y / N)
 - c. Medical necessity (Y / N)
 - d. Formulary inclusion (Y / N)

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- Which of the following methods are employed by the agent who performs your technology assessment:

(Elicit distinctions in procedures for *Medical Necessity* vs. *Coverage* decisions and for *Routine* vs. *Revolutionary* innovations.)

a. Expert Judgment

- Formal (consensus or guideline panel, e.g., Delphi)
(Yes No Don't know/Unfamiliar term)
- Informal (individual or usual committee, e.g., P & T
Or expert opinion)
(Yes No Don't know/Unfamiliar term)

b. Review of evidence

- Formal
 - Literature synthesis
(Yes No Don't know/Unfamiliar term)
 - Meta-analysis
(Yes No Don't know/Unfamiliar term)
 - Other
(Yes No Don't know/Unfamiliar term)
- Informal
 - Casual literature review
(Yes No Don't know/Unfamiliar term)
 - Other
(Yes No Don't know/Unfamiliar term)

c. Modeling

- Formal
 - Decision analysis
(Yes No Don't know/Unfamiliar term)
 - Cost-effectiveness/Cost-benefit analysis
(Yes No Don't know/Unfamiliar term)

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- Marketing models
(Yes No Don't know/Unfamiliar term)
- Other
(Yes No Don't know/Unfamiliar term)
- Informal
 - Ad hoc
(Yes No Don't know/Unfamiliar term)
 - Back of the envelope
(Yes No Don't know/Unfamiliar term)
 - Other
(Yes No Don't know/Unfamiliar term)
- Who performs the technology assessment for your organization? _____

If the assessment is performed by another agent, do you have a structured process to participate in those decisions?

5. How does your organization decide on when to review an emerging drug or new indications for use or to what drugs the rules should be applied? Solicit examples for illustration purposes.
- a. Coverage
 - b. How and when it's covered (prior auth / indications for use – when it's medically necessary/special benefit structure / formulary preference)
 - c. If drugs fall into certain categories, are they treated differently?
 - Drugs you have to have – needed to treat illness and injury
 - Drugs you would like to have but there are existing / already approved less expensive alternatives
 - Drugs that are lifestyle focused
 - Preventive health care drugs with only long-term positive impact
6. How does your organization learn about emerging drugs, classes of drugs, or new indications for use?
- a. What mechanism is there for learning about emerging drugs in the pipeline
 - Where – from what sources – do you learn about emerging drugs?
 - Is there a formal mechanism for surveillance.
 - b. What mechanism is there for learning about new indications for use?
 - Where – from what sources – do you learn about new indications for use?
 - Is there a formal mechanism for surveillance?

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7. What information do you use to generate your decision rules?

Ask if they are willing to share hard copies of the information, process flows, etc.

- a. What sources of information / guidance are useful in decisionmaking (including specific names of reference materials they recommend)
- b. Role of HCFA coverage / State Medicaid coverage
- c. Role of competitors approach / coverage
- d. Role of consumer request or direct-to-consumer advertising

8. How are the rules applied and monitored (e.g., indications for use)?

- a. By whom are the rules applied
- b. How is the effect of the rules measured

B. WHAT'S MISSING TO IMPROVE THE PROCESS

1. What would you like to have that you don't have to support the processes we just discussed?

- a. Literature
- b. Educational Programs
- c. Processes
- d. Models – financial and clinical impact
- e. Reference materials

Given that this project is to produce a reference document for medical directors or decisionmakers, what would you suggest would be useful to include in the document?

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