

# Usefulness of Economic Evaluation Data in Systematic Reviews of Evidence



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## **Usefulness of Economic Evaluation Data in Systematic Reviews of Evidence**

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This report is based on research conducted by The Johns Hopkins University Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2007-10061-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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## Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To improve the scientific rigor of these evidence reports, AHRQ supports empiric research by the EPCs to help understand or improve complex methodologic issues in systematic reviews. These methods research projects are intended to contribute to the research base in and be used to improve the science of systematic reviews. They are not intended to be guidance to the EPC program, although may be considered by EPCs along with other scientific research when determining EPC program methods guidance.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The reports undergo peer review prior to their release as a final report.

We welcome comments on this Methods Research Project. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by email to [epc@ahrq.hhs.gov](mailto:epc@ahrq.hhs.gov).

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# Usefulness of Economic Evaluation Data in Systematic Reviews of Evidence

## Structured Abstract

**Background:** Systematic reviews play an important role in improving understanding of the comparative effectiveness of medical interventions, but economic data have not usually been included despite their importance in determining the value of interventions. This paper addresses the usefulness of incorporating economic evaluation data into systematic reviews of medical interventions.

**Methods:** A consensus process including outside experts was used to develop a conceptual framework for including economic evidence alongside systematic reviews, and to define tradeoffs in presenting economic data. The framework was based on five questions: (1) Why are stakeholders interested in economic evaluation data? (2) When should economic evaluation data be requested in a systematic review? (3) Who is interested in economic evaluation data? (4) What economic evidence is of interest? and (5) How should the economic evaluation be conducted?

**Results:** Decisions about inclusion of economic data in systematic reviews should be based on the magnitude of the incremental cost, magnitude of the incremental effect, and the probability that economic evidence will change a decision. Economic data should be given a high priority when evidence indicates a small effect at a high level of expenditure with a high probability of influencing a decision. All stakeholders (including public and private insurers) should be interested in economic data and the perspectives of patients, providers, and manufacturers because patients and providers together determine the demand for care and manufacturers determine the supply. Economic data are of interest for decisions at many levels, including decisions about approval and monitoring of services, formulary inclusion, insurance coverage, reimbursement rate, preferred practice guideline, technology adoption or nonadoption, or clinical management. Economic data of interest include information that contributes directly to cost-effectiveness analyses, as well as data on productivity changes related to a disease or its treatment, basic price data, and data on responses to price changes. When it is appropriate to include economic data in a systematic review, it may be sufficient to review available economic analyses, but it may be necessary to perform a new economic evaluation if previous evaluations are inadequate (absent, low quality, or very heterogeneous) or if important new data are available.

**Conclusion:** The approach to gathering economic data alongside a systematic review of evidence will be governed by the decision context and the need for a new economic evaluation consistent with the other findings of the systematic review.

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# Introduction

## Aims of This Report

The United States has placed a strong focus on comparative effectiveness research in recent decisions about research funding. A logical conclusion based on this focus is that incremental (i.e., relative) effectiveness will be used more frequently as a criterion for making clinical decisions than it has been in the past. It may also lead to greater use of incremental effectiveness (and cost) data to make decisions about the availability of new technologies and reimbursement for the use of these technologies. A potential next step is to incorporate cost and other economic outcome information alongside the effectiveness data so that cost-effectiveness could inform policymaking in selected situations in which costs are particularly important to stakeholders. Some experts have recommended integrating cost or economic evaluation data routinely in the United States health care policy process.<sup>1,2</sup> The United States has the opportunity to build on the experience of other countries (e.g., the United Kingdom and Australia) to determine the most appropriate way to address such recommendations. This report has two aims, as described below.

### **Aim 1: To Provide a Framework for Including Economic Data Alongside Systematic Reviews**

The first aim is to develop a conceptual framework for deciding when economic outcomes could provide policy-relevant information when included in systematic reviews of clinical outcomes. This is not the first document to do so. In the last of a series of works on grading of recommendations, the authors began a discussion about including resource use (a key input into costs and other economic considerations) in the grading of recommendations.<sup>3</sup> When deciding on what to include in an economic evaluation component of a systematic review, the analyst needs a frame of reference. This report provides a conceptual framework that can guide the choice of perspective, the target or reference populations, and the assessment of generalizability. The framework also demonstrates how the interaction of these choices has important implications for the conduct of the analysis. The framework was developed by a multidisciplinary team that developed a draft framework and shared that framework with experts in cost-effectiveness analysis and public policy who reviewed and provided feedback before the framework was finalized.

### **Aim 2: To Define Tradeoffs in Presenting Economic Data**

The second aim of this report is to define tradeoffs between incorporating previously completed “off-the-shelf” evaluations from the published or grey literature into systematic reviews, versus performing an explicit independent economic evaluation as part of a systematic review. The evaluation of the tradeoffs between the choices is based on theoretical and conceptual arguments, the availability of data, and nature of expected results.

## Background

Many health care policymakers in the United States would like to make more use of economic data in reviewing new and existing medical interventions.<sup>4-8</sup> Although much work is being done to evaluate the comparative effectiveness of medical interventions<sup>9, 10</sup> even this technique is not used extensively in policymaking. The United States has fallen behind international best practices in using economic data in the comparison of medical interventions for the purposes of policymaking.<sup>4-6</sup> Systematic reviews of evidence offer opportunities to increase the use of economic data in the health policy process.

Among the systematic reviews that have been conducted recently, there is great inconsistency in whether economic evidence is collected alongside clinical research data, the quality of the data collected, and the methods used to collect the data. In many cases, clinical research data may be sufficient for making decisions about adopting interventions. However, we need to explore and define better the information that is needed to guide those who are in charge of making requests for systematic reviews of evidence. More information is needed about: (a) when economic data might add to decisionmaking on top of the efficacy/effectiveness data presented in typical systematic reviews, and (b) if economic data are helpful, what methods should be used to include this information. Such information could guide future calls for systematic reviews of evidence.

More information on best approaches for the inclusion of economic data alongside systematic reviews of clinical evidence will also benefit those responsible for producing systematic reviews. Producers of reviews are put in a position to interpret and give input on the requests that are being made and are asked a variety of questions in relation to the aim and outcome of a particular review. It is just as important for those who are responsible for producing systematic reviews to understand the boundaries and implications of what is being requested and how collected information can be used to guide their efforts.

At present, many systematic reviews of evidence do not include economic evidence. Even if efforts are made to review the economic evidence, economic evidence often is insufficient to treat it in the same way that meta-analytic techniques can be applied to other pieces of evidence. Further, some economic evidence concerns primary data while other economic evidence is derived from more or less standardized and protocol-based approaches based on mathematical modeling. Investigators involved in performing systematic reviews need better guidance for making requests for economic evidence alongside other systematic reviews of evidence, with careful definitions of terms.

# Methods

To provide guidance on when to ask for specific types of economic evidence alongside other information that is being gathered in a systematic review of a medical intervention, we obtained input from members of the interdisciplinary project team and outside experts (including health economists and those having experience with systematic reviews in different countries). The discussion began with an attempt to determine how widely we wanted to define the term “economic evidence.” After deciding that our operational definition of economic evidence was wider than simply “cost-effectiveness” or even “economic evaluation,” we began by defining stakeholders and decision situations. As we progressed, it became clear that answers to the questions we were posing would best be structured pragmatically and in touch with the real life settings as answers to a series of questions that are raised in the systematic review process. The questions addressed the appropriate occasions, places, people, and methods for gathering economic evidence alongside other evidence with the same level of rigor as in a systematic review of evidence. The elements of economic evidence that are the most important to request depend on the stakeholders involved and the decisionmaking context.

A schematic diagram is shown in Figure 1 that conveys the different concepts that are used to motivate the appropriate collection of economic data alongside systematic reviews. The conceptual model provides a short heading for each of the five questions that were the focus of consideration after the model was developed. Extended versions of the questions and further justification for each question are provided below:

- Why are stakeholders interested in economic evaluation data? This is the most logical starting point for discussion. Without a clear sense of the need for reviews that include economic data, the remainder of the discussion is somewhat superfluous.
- When should economic evaluation data be requested in a systematic review? Having identified the reason for interest, the next logical step is to identify the particular situations in which reviews with economic data are useful.
- Who is interested in economic evaluation data? To a degree, this is framed by the why and when questions, but it is important to clearly identify stakeholders who would be interested in the questions.
- What economic evidence is of interest? Given the large number of different types of economic evidence, it is critical to identify what types of data are useful, having established the reasons for interest, situations in which stakeholders are interested, and identity of those stakeholders.
- How should the economic evaluation be conducted? Specifying the method to be used is extremely important, given the range of options for analysis, the range of recommendations about analysis, and the constraints on resources, even after deciding on the importance of a specific type of evidence.

Prior to answering the questions, we provide definitions for several terms (Table 1). Economic evaluation involves an entire logical process and set of analytic steps that involve economic and epidemiological data. Our assumption is that those planning reviews will, in some cases, want to review the original economic data, and in other cases want to review the results of previous economic evaluations. We provide structure for thinking about both situations.

# Results

## Decisionmaking Contexts—Why Are Stakeholders Interested in Economic Evaluation Data?

Decisionmaking contexts for pharmaceuticals begin with regulatory approval of new drugs or devices on safety grounds. Other decisionmaking contexts start with a choice of a manufacturer to develop a new device or the choice of a practice to develop a new intervention. They also include decisions to cover specific services and decisions on how much to reimburse for specific services. At health care facilities, adoption or nonadoption and utilization decisions will be driven by economic criteria, i.e., profit maximization. Health care providers will focus primarily on utilization decisions. Patients are interested in the utilization of specific interventions or treatments to improve their health. We are interested in economic data alongside a systematic review of evidence to place the effectiveness in context of the resources that are required to achieve it so that individuals, organizations, and society can decide whether to make the investment or not.

While contexts are frequently changing and being modified by new alternatives that are available in the market and new budget constraints, we can summarize decisionmaking contexts as follows.

- **Approval and monitoring:** This type of decision is at the level of a regulatory body responsible for ensuring patient safety. Such decisions are most frequently for safety and do not involve economic criteria.
- **Formulary inclusion:** Formulary inclusion focuses on coverage of pharmaceutical products and may be at the level of the third-party payer (public or private) or the level of a hospital. The formulary decision may be a decision to include or exclude but may also be a decision about the tier on which to place a particular item, i.e., most favorable coverage or less favorable coverage for consumers. This decision requires economic data, ideally on cost-effectiveness and the price elasticity of demand for the product in question, as well as the price elasticity of demand for complements and substitutes.
- **Insurance coverage decision:** Insurance coverage decisions are separate from formulary decisions because insurance coverage decisions include far more than only pharmaceutical products. Formulary decisions can be only about whether something should be on the formulary list, but also can be to place an item on a particular formulary tier. Insurance coverage decisions are about whether something should be paid for by the insurer. In addition, insurers make decisions about how much to pay for services; these are reimbursement decisions that can create incentives for use of the items or treatment options. Such decisions call for data on cost-effectiveness, the price elasticity of the service or product in question, and the cross-price elasticity of substitutes and complements. These types of data are useful in making insurance coverage decisions and in allowing insurers to anticipate how the change in coverage will impact predicted expenditures and, ultimately, premiums.

- **Reimbursement rate:** The reimbursement rate focuses on the amount that will be paid to the providers of care or the facilities in which the providers operate. This type of decision is usually made along with the decisions about whether a new technology or procedure should be covered and what the patient will be expected to pay out of pocket to generate an entire system of incentives. This clearly involves an entire set of economic data on incentives and potentially on cost-effectiveness if the desire is to direct consumers and providers to use specific treatments.
- **Preferred practice guideline:** Preferred practice guidelines are often developed by professional associations, but could be developed by other bodies within the health care system. These guidelines are often outside of the context of economic constraints, and focus more on patient well-being or more narrowly defined patient health.
- **Technology or nonadoption:** Decisions about technology or nonadoption are being made at the level of the provider. Decisions may be made by a large health care facility. Large facilities may choose to adopt multiple technologies, and the economics are especially important for portfolios of technology. Decisions also may be influenced by the relationship between a physician's office and any facilities with which the practice is associated if the facility already has the technology.
- **Clinical Management:** Clinical management refers to the physician-patient dyad decisionmaking about specific services to use to address medical issues that a patient faces. A subset of this is treatment adherence that reflects decisions made by the patient and perhaps the patient's family. Decisions to continue to use and follow the directions for use of specific medical interventions (e.g., the appropriate use of eye drops to reduce intraocular pressure for patients with glaucoma) are at least partially based on economic criteria. Whether the physician typically asks about economic issues or the patients feel comfortable sharing economic issues with the physician are issues that require empirical analysis.

More than one decisionmaking context may be relevant to any specific stakeholder. For example, although the adherence issue most directly involves the patient, the family, and consumer organizations, all stakeholders should be interested in adherence as it usually will affect the economics and the outcomes. Similarly, while the patient is most directly involved in the adherence decisionmaking context, the patient will have an interest in coverage decisions and the amount that will be reimbursed. These different decisionmaking considerations can be applied to pharmaceutical products, imaging devices, or any other type of medical intervention.

## **When Should Economic Evaluation Data Be Requested in a Systematic Review?**

The health economist focused on efficiency and making decisions under perfect information might say that economic evaluation data should always be included when a systematic review is being performed to help stakeholders make informed decisions. As long as there is a decision that could be made or changed based on the review, it is never too late to consider inclusion of economic data. Frequently, however, the resources available do not allow for all data to be integrated into a systematic review.

Several criteria can be used to determine whether or not to request inclusion of economic evidence in a systematic review of a medical intervention. These include the expected incremental cost of the intervention, the expected incremental efficacy of the intervention, and the likelihood that the magnitude of expenditures will affect decisions about use of an intervention. While a reason for any review is, in part, to determine just how large the incremental costs and incremental effects are, policymakers are likely to have prior beliefs about what the expected incremental values are. If policymakers do not have prior beliefs themselves, consultation with experts can help to provide insight on the expected changes that can then be used to motivate, in part, the need to gather economic data alongside a systematic review of effectiveness.

Part of the last consideration is whether the intervention fits within the budget of the decisionmakers. The consideration can also be a function of the politics of the situation. In some cases, such as the only treatment for an otherwise fatal condition, the cost-effectiveness result is not likely to make a difference in treatment decisions. This does not mean that economics will not be important at all. Decisionmakers and those requesting systematic reviews of evidence should carefully distinguish between not asking for any economic evidence and simply not asking for data to be gathered, summarized, and analyzed at the level of rigor of a systematic review.

Each of the three criteria mentioned above can be dichotomized for simplicity: high or low incremental cost, large or small incremental effect, and a high or low probability that the magnitude of the expenditure will affect the decision.

The magnitude of incremental costs and effects are quantitative measures. The issue of whether the magnitude of the expenditure will affect the decision is a subjective issue. The subjective issue can be guided by thinking about several issues. First, how local is the decision? The more local the decision, the greater the limits on resources and the more likely that decisionmakers will be cognizant of the resource limitations and be interested in cost data. Second, how many options exist for the target patient population? Is there only one option or are there multiple effective options? In cases with a single effective option, the magnitude of expenditures is likely to play a less important role in the decisionmaking process, although this may be changing. A national decision for a new biologic agent that would be the *only* effective treatment for a particular type of cancer would be unlikely to focus primarily on the magnitude of expenditures. In contrast, a decision at a community health center about another new medication for hyperlipidemia would likely be heavily influenced by the magnitude of expenditures. The assumption is that the community health center (particularly, since its board includes community representation) would be concerned about either a societal perspective, or the perspective of their patients who do not necessarily have full insurance.

We choose to ignore the situations in which an intervention is associated with a negative incremental cost and a positive incremental effect relative to the current best practice. In that case, the new alternative would be said to dominate the status quo. While there is no guarantee that the more effective and less expensive treatment option will be chosen, there is little economic question here. If it is unclear whether the new option is both more effective and less expensive, but this outcome is expected, then economic data alongside a systematic review can be very useful. However, if the cost differential is certain, there is little reason to collect economic data alongside a systematic review of the effectiveness. One example of a dominant technology is influenza vaccination for specific high risk target populations. In this case, economic data alongside a systematic review could be useful to direct policy, but that is only the

case because of the need to demonstrate the favorable economic outcome alongside the clinical outcome. Another issue with one alternative that dominates another is the possibility of different interpretations regarding dominance when different time horizons are used. Time horizons are the time periods that are relevant to different decisionmakers; not every decisionmaker will care about the same amount of time. The savings for the dominant alternative may materialize as downstream financial savings many years in the future while the decisionmaker is more focused on short-term results. In that case, the decisionmaker may want to treat the assessment of the importance of cost data using the nondominant discussion below.

We also ignore the situation in which there is a positive incremental cost and a negative incremental effect of a new intervention. This would be dominated by the status quo. These types of interventions are never likely to be adopted, so there is little opportunity for change from the status quo.

Our primary focus is on situations in which a new treatment alternative is more effective and more expensive. We could address similar issues about situations in which new interventions are less expensive and less effective. However, in the United States, while such interventions may be cost-effective, they rarely get much attention.

Table 2 focuses on decisions about interventions or technologies that are more effective and more expensive than the status quo. The information presented is for making intuitive arguments based on relative costs. We do not claim to define the exact threshold for when a cost or an effect becomes “large” rather than small. The key is to interpret the results within the context of the decision at hand. When we use the terms cost and effect we are focusing on incremental costs and effects—how much more expensive than the status quo (assuming that we would be willing and able to continue to invest in the status quo) and how much more effective than the status quo. The most appropriate time for gathering data alongside a systematic review for effectiveness is when there is a question regarding the value of the treatment or intervention. This may occur regardless of how large the incremental effects are. It is also important to recall that the purpose of this document is to detail when to collect economic data alongside the effectiveness review and not to decide when to conduct an effectiveness review. That decision has already been made in the context of the discussion in this document.

In deciding whether to ask for economic evidence alongside other evidence in a systematic review, we are focusing primarily on short-term costs and primarily budgetary (or financial) costs rather than economic opportunity costs. We have chosen to do this as many decisionmakers, despite the scientific recommendations about decisionmaking, focus on such costs rather than all long-term costs. However, this is a loose definition and may be adapted by specific decisionmakers. Some decisionmakers will be interested in focusing on all of society’s opportunity costs while others will be focused only on budgetary financial costs. While most of the focus is on short-term effects, specific decisionmakers may focus on long-term present value. We are not trying to discourage following the scientific recommendation to consider societal long-term costs, but we are trying to offer pragmatic suggestions about how to gather useful economic data alongside a systematic evidence review.

Table 2 has two rows for which the result is relatively “obvious.” The first is the case of a low incremental cost, a large incremental beneficial effect, and a low probability of the economic evidence changing the decision. In that case, there is a low priority on economic data. Despite the low priority, a decisionmaker may want to know something about the supporting economic evidence. In that case, the evidence does not have to be gathered and analyzed with the precision and detail of a systematic review of evidence. In contrast, if the expected incremental costs are

high, the expected incremental beneficial effect is small, and the economic evidence has a high probability of changing the decision, then it would be logical to ask for data gathered with the rigor of a systematic review of evidence.

In the other six boxes we offer some guidance, placing a high priority on the expected costs while paying attention to the probability of changing the policy decision. For example, if the incremental costs are low, the incremental effect is small and there is a low probability of changing the decision, it would be less appropriate to ask for economic evidence treated with the rigor of a systematic review. In contrast, if the incremental costs are high, the incremental beneficial effect is small, and the probability of changing the decision is low, it might be a more appropriate but not absolutely necessary time to ask for economic evidence. It is a high priority to ask for a full review of economic evidence when expected incremental costs are high with a small incremental effect and a high probability of changing the decision. When expected incremental costs are low with a small incremental effect and a high probability of changing the decision, it may still be a medium priority to ask for a review of the economic evidence. Although low incremental costs with a large incremental effect and a low probability of changing the outcome suggests a very low priority for reviewing economic evidence, the priority also is low when the incremental costs are high with a large incremental effect and a low probability of changing the outcome. Finally, when the incremental cost is high and the incremental effect is large with a high probability of changing the decision, it may not be absolutely necessary to request a detailed review of economic evidence, but it seems reasonable to assign at least medium priority to including economic evidence in the review.

The analysis requiring economic data prior to the systematic review is somewhat complicated; the highest quality data may not be found until the review is conducted. To make a decision prior to the conduct of the systematic review, preferred sources of data would include prior reviews, surveillance data, and financial cost data, although they may be a subset of all data that will be used for analysis.

## **Stakeholders—Who Is Interested in Economic Evaluation Data?**

Health care policy and medical care decisionmaking potentially involve a large number of different parties or stakeholders. While the scientific recommendation is generally to perform an analysis from the societal perspective, very few stakeholders actually use this perspective when they are making a decision. The societal perspective, considering all benefits and all costs incurred, is appropriate for making optimal economic decisions for an entire economy. The difficulty is that a good outcome for the economy as a whole does not guarantee a favorable outcome for specific stakeholders, and some specific stakeholders (e.g., a private payer) should not be expected to consider the entire societal perspective. When the societal perspective suggests a positive outcome, but individual stakeholders are not convinced it is good for them, there is no obvious way to make transfers between stakeholders to facilitate turning the situation into a win-win situation for all concerned.

Stakeholders include governmental agencies. At the federal level, stakeholders include the Food and Drug Administration (FDA), the Centers for Medicare and Medicaid Services, and federally qualified community health centers. At the state level, stakeholders include health

departments, and Medicaid administrators. Other stakeholders include private insurers, manufacturers, health care providers, health care facilities (such as hospitals, ambulatory surgery centers, group practices, etc.), employers, and patients and their families.

Most stakeholders will be worried about their own “bottom line.” Later, when we link data elements to specific decisionmaking contexts for specific stakeholders, this will be apparent. However, all stakeholders (even public and private insurers) should be interested in the perspective of the patient, the provider, and any relevant manufacturers because the patients and providers together determine the demand for care and the manufacturers are integral to determining the supply of specific types of care. It is critical to recognize that economic evidence that supports the adoption or nonadoption of a new technology or new intervention from one stakeholder’s perspective will not necessarily support adoption or nonadoption from all perspectives. Ultimately, no matter what incentives are created by the insurers or other health care payers, unless the adoption or nonadoption of a new intervention or treatment makes economic and clinical sense to the providers, patients, facilities and relevant manufacturers, the new intervention or treatment will not be implemented successfully.

Employers have a role in the process by providing benefits that may include health insurance, which may be self-financed. In light of the health care reform bill passed in 2010, employers will continue to have a stake in and concern about issues related to the productivity of their workers and sick time. Employers also will continue to have a direct role in the insurance process.

Society is a perspective that is often used for analyses. This perspective is intended to capture all costs and all effects. This is a useful theoretical construct and helps to indicate when there is a potential gain in economic efficiency. This perspective does not, however, show specific stakeholders what they stand to gain or lose based on a particular implementation of a new treatment alternative or change in policy. Taking a societal perspective can help to emphasize long-term costs and benefits. Thus, it is useful to consider the stakeholders who make up society in addition to considering the effect on the entire economy. In many cases, multiple stakeholders will be interested, and the data that are located may have to be modified to be relevant to specific stakeholders. Even when using less than a societal perspective, it is important to realize that for accountability any stakeholder should be aware of how decisions will affect other perspectives. Economic theory suggests that decisionmakers generally only look at their own well being or profit when making decisions. Recognizing that terms like “payer” or “regulator” can refer to many different individuals and organizations, we summarize the stakeholders with the following terms.

- **Regulator:** In the United States, the FDA is not allowed to use economic data to determine whether a drug should be approved for use, although the FDA does evaluate the economic data that manufacturers intend to provide to consumers who may be interested in this evidence. In other countries, there may be other regulatory bodies that are interested in economic evidence. These may be interested in systematic reviews of effectiveness to determine whether to approve a new drug or device. The data on summary costs and unit prices would provide information for understanding the budgetary implications of the regulatory decision or could influence a decision if cost-effectiveness were part of the regulatory process. Other regulators (such as those in charge of certificate of need programs) are much more interested in economic data.
- **Private Third-Party Payer:** In the United States, this would primarily be private health insurance companies or other types of private insurance companies that pay for medical

care expenditures such as car insurance companies. Employers may also be direct third-party payers if the employers are self-insured. Third-party payers use varying levels of managed care techniques. A small number of third-party payers are also providers (e.g., traditional staff model health maintenance organizations), and in this case the combined interests must be considered. In other countries, the list would be almost exactly the same. A systematic review of effectiveness would be of interest in deciding whether to cover a technology—making sure only to cover those that are effective or perhaps as effective as existing technologies. The data on summary costs and unit prices would help in understanding the budget impact and how to set reimbursement and coverage policy. A third-party payer’s perspective diverges from society’s perspective for a number of reasons, including the fact that many long-term benefits to society will not accrue to private third-party payers when enrollees switch payers ever three to five years. With respect to the term “private third-party payers,” it is also useful to note situations in which the employer is ultimately the payer and the insurer plays only an administrative role.

- **Public Third-Party Payer:** In the United States, the two largest third-party public payers are Medicare (a federal program with some variation in payment level by region of the country) and Medicaid (a federal state partnership program with much more variation). There are other public third-party payers but these are much smaller than either Medicare or Medicaid. The interest in systematic reviews of effectiveness and in the economic data is similar to those of a private third-party payer. There are many other government payers: the Department of Defense, the Department of Veterans Affairs, CHAMPUS, and the coverage for government employees. These would have their own interests although they are all part of the government perspective. The interests of the government when insuring its employees are likely to be similar to the interests of private third-party payers. However, the government does have different types of oversight to be concerned about as the expenditures on employees are a matter of public record and public discourse in ways that the expenditures for employees of private employers are not.
- **Public Health Planner:** This would include local, state, and federal agencies. At the local level, this would most likely be a health department. The same would be true at the state level. At the federal level, public health planning is done within the Centers for Disease Control and Prevention and the Health Resources and Services Administration within the Department of Health and Human Services. A public health planner would be interested in effectiveness to ensure that public resources are used for only the most effective interventions. Accompanying data on summary cost and unit prices would allow the planner to assess whether the new intervention fits within the available budget.
- **Provider:** This is not meant to be only physicians. This would include physicians, nurse practitioners, complementary and alternative care providers, and any individuals or groups of individuals who are part of the system of providing care. Providers are interested in their own well being and the interests of their patients. This is a key distinction from facilities which are listed below. Even providers driven by a profit motive would like to provide the most effective care. Their interest in data related to costs is most likely related to the expense of providing services rather than the expenditures necessary to use services.
- **Facility:** Facilities include hospitals, nursing homes, ambulatory surgery facilities, community health centers, and others. The key is that there are multiple individuals, and

the decisionmaker's job is to make the best decision on behalf of the organization rather than on behalf of himself or herself. Facilities have interests similar to the providers.

- **Employer:** In the United States (which has consistently, although not always, had a relatively low unemployment rate), employers have a variety of interests in the health care system. Not all employers offer health insurance. Those who do are certainly interested in the health care system and changes in technology or interventions. Self-insured employers will experience financial costs directly. Employers who purchase insurance from a third-party payer are interested in new technologies and interventions because changes will affect the premium that must be paid and the incentives that will be offered to employees. Even outside the insurance issues, employers are interested in changes in technology and interventions because they affect workers' absenteeism and level of productivity when at work. Employers might have interests similar to payers. They also may be interested in the adoption or nonadoption of certain technologies or interventions within a workplace which would make their interests more similar to a facility or provider.
- **Manufacturer:** Manufacturers of pharmaceutical products and medical devices are interested in economic evidence that will determine the incentives for providers to prescribe and consumers to use the products of the manufacturers. Manufacturers are most likely to pursue effective products. The prices would help manufacturers to make appropriate profit maximizing decision. If the market would not bear a price that would be necessary to make a new product profitable, it will not be produced. There are many businesses in addition to the actual manufacturers of products who could be very interested in the economic data alongside systematic reviews of evidence of effectiveness.
- **Patients/Families/Consumers:** Patients are interested in economic evidence for their own and their families' decisionmaking purposes. Families are interested in economic evidence when they are required to make specific medical decisions on behalf of patients in their families, or when they have to make decisions about how to provide long-term care for family members. Finally, consumers in this case may refer to people who make decisions about the use of health care services outside of a doctor-patient relationship. Consumers want to use only effective interventions and are interested in the financial (out-of-pocket) and opportunity cost implications as they affect consumers' budgets and the value of consumers' insurance products.

We will not list society as a stakeholder because society is ultimately made up of all the other stakeholders and all economic evidence is of interest when an analyst is trying to present a societal perspective.

## **Economic Components—What Economic Evidence Is of Interest?**

The economic measures that are included cover a broad range of items that can be grouped into three categories.

- Demand for care

- **Time:** The demand for care depends on the time required to travel to, wait for, receive, and return from receiving medical care. Time is valuable. These data could be found in a time and motion study, a cost-outcome analysis, or a study of the demand as a function of time.
- **Distance:** The demand for care also is affected by distance, where distance is separate from the time required to receive medical care because the cost of traveling different distances will vary because of different public transit fares or different amounts of mileage costs in a personal car. These data are likely to be found in the same types of studies as time data because time and distance often are correlated.
- **Price of the innovation:** A new technology or procedure will have a specific price attached to it that will affect the demand for the technology or innovation. The price may be the result of market equilibrium (e.g., rehabilitation services that are not covered by a third-party payer) or the result of incentives provided by a third-party payer. The price can change over time, but it is difficult to anticipate exactly how and when the price will change. These would likely have to be projected from existing data on other products.
- **Price sensitivity:** Consumer demand will depend not only on the initial price but on how much the price is likely to change and the accompanying changes in the quantity demanded. The relationship between the percentage change in price and the percentage change in quantity is referred to by the term “**elasticity**.” Many empirical studies focus on elasticity.
- **Substitutes and complements:** Patient demand will be determined not only by the monetary, time, and travel costs of the good but also by what other goods and services are available that may be substitutes for or complementary to the procedure or technology in question. In addition to studies focusing on own-price sensitivity, at least some studies also focus on cross-price sensitivity and could yield insight on what are substitutes and complements and how these will be affected by a new product.
- **Willingness to pay:** This reflects the patient’s valuation of a good or service. In contrast to markets that do not involve third-party payers, the willingness to pay for medical care does not correspond directly with demand and measures of consumer surplus as patients do not have to pay the entire cost of the treatment when they are insured. However, when conducting economic evaluations, particularly cost-benefit analyses, the willingness to pay is a key component of the analysis. Typically there are few studies of willingness to pay, although these studies are becoming more common as cost-benefit analysis is becoming at least somewhat more popular.
- **Absenteeism/Presenteeism:** Absenteeism is time missed from work. This could lead to a loss of income. Even if a patient has sufficient sick leave not to lose income, there may still be a psychological loss of purpose. If the condition persists for a sufficient time, the patient will eventually lose his or her job. Presenteeism is a term used to reflect a lack of productivity compared with some optimum when the patient is at work while ill. This may bring a psychological cost to employees who believe that they should always be highly productive but is unlikely to result in an immediate loss of income. The avoidance of both absenteeism and presenteeism is a benefit of good health. The desire to achieve the benefits of good health leads to a derived demand for health care. Thus, absenteeism and presenteeism can be used as measures

- of burden in cost-effectiveness or cost-benefit analyses, and can be used to understand the derived demand for health care. The absenteeism and presenteeism associated with many conditions and treatments is being studied around the world.<sup>11</sup>
- Supply of care
    - **Economies of scale:** Suppliers of care and suppliers of the technology will be interested in whether there are opportunities to supply a product at a lower average cost as the quantity of production increases. Much research has been done to examine economies of scale in health care markets.
    - **Changes in efficiency over time:** Suppliers of care and suppliers of the technology will be interested in whether there is a learning curve that will be associated with greater efficiency in service provision over time. These types of data are interesting, but very few studies are done to compare efficiency over time.
    - **Return on investment in innovation:** Decisions on whether to adopt a new technology or implement a new procedure ultimately will be based on whether the return on investment will be higher than what could be achieved by other uses of the resources that are being invested. These data, particularly for an individual organization, are rarely found in the literature.
  - Summary measures of equity and efficiency
    - **Cost of illness:** A measure of the expected lifetime costs of the onset of a condition.
    - **Burden of disease:** A measure of the costs (and possibly quality of life and potential years of life lost) attributable to a condition within a year.
    - **Quality of life:** A broad measure that is often, but not always, combined with costs in assessing the impact on a person's functioning and well-being.
    - **Budget impact:** A type of model that reflects only monetary outcomes—usually for a specific organization.
    - **Incremental cost-effectiveness (cost-utility) ratio:** An analysis comparing the extra costs with the extra value obtained from an intervention, procedure, or technology. Cost-utility analysis includes a particular valuation of quality of life.
    - **Net-benefit:** The result of a cost-benefit analysis in which all outcomes (including life and health) are valued in dollars.
    - **Disparities:** Various measures of differences in outcomes among subsets of a population. These may be driven by heterogeneous outcomes related to patient characteristics or to system characteristics. While most systematic evidence reviews are aimed at pharmaceuticals or other types of treatment for individual patients, it is also worth considering system-wide effects and interventions.

Table 3 summarizes the economic evidence elements of greatest interest to specific stakeholders in specific decision contexts—thus linking the who, what, why, and when questions addressed above. The stakeholders' considerations are not necessarily limited to what is in the boxes, but these are considered the most important. For example, a manufacturer faced with a reimbursement rate only needs supply-oriented data to indicate how much to produce to make a profit maximizing decision. When data are unavailable, a common practice is to rely on expert opinion or to attempt to find data on similar products in other markets. We will elaborate on Table 3 using the stakeholder as the organizing principle, thus discussing a stakeholder's interest in different decisionmaking contexts.

Regulators' involvement is primarily at the point of approval and monitoring. At this stage, the regulators could have an interest in all economic measures. This could involve approval for any use at all, approval for a particular use, or approval of expansion of a facility or purchase of a new technology. For some decisions, there is not necessarily any economic input. For other decisions, economic inputs of all types might be useful.

Public and private third-party payers have similar interests. At the stages of approval and monitoring, formulary decisions, and insurance coverage, the third-party payers could take an interest in summary measures (to indicate how important the health problem is and how efficient a new treatment or monitoring system is) and demand figures. The demand figures assume that at the stage of formulary inclusion and insurance coverage, the third-party payer is a price taker. However, there is a separate decisionmaking context for a reimbursement level. At this stage, the third-party payer would be more interested in knowing about data on the supply of the product of service to make sure that reimbursement levels are set so that profits are not economically unreasonable.

Public health planners are most likely involved in two decision-making contexts—approval and monitoring and technology adoption or nonadoption. In the context of approval and monitoring, a public health planner could be interested in all economic measures. In the context of technology adoption or nonadoption, the key would be summary measures that indicate economic efficiency of the new treatment.

Health care professionals are likely to be interested in nearly all decisionmaking contexts—we have excluded technology adoption or nonadoption assuming that these decisions occur at a higher level. For clinical management, the most important factors are supply and demand factors. For preferred practice guidelines, the summary measures are of greatest interest. Summary measures of economic efficiency are also important to all the other decisionmaking contexts. Demand is more important for contexts that will dictate consumer incentives. Supply is likely more important in contexts that affect incentives for providers.

Other stakeholders would tend to be interested in economic data similar to those discussed so far. A key is that in some cases, self-interest of decisionmaking (as suggested by economic theory) would lead to more of a focus on a narrow range of measures—like consumers primarily being interested in demand and manufacturers being interested specifically in either supply or demand depending on the context.

While only a small number of stakeholders have been listed as being directly interested in cost-effectiveness, this requires some clarification. Many of the stakeholders are likely to be interested in whether a new treatment alternative is deemed to be cost-effective in comparison with other interventions. However, not all stakeholders will make their decisions primarily based on cost-effectiveness. Some stakeholders will make decisions based on other economic data about comparisons of the effectiveness of a new treatment with extant treatments and responses to changes in economic incentives.

## **How Should the Economic Evaluation Be Conducted? Should the Economic Evaluation Be a Summary of Existing Evaluations or New Evaluations With Inputs Consistent With the Remainder of the Systematic Review?**

In general, the preferred choice is to perform a new analysis (essentially redoing a state-of-the-art cost-effectiveness analysis) so that the inputs to the model are consistent with the results of the systematic review of evidence and the results are applicable to the question to which the systematic review is addressed. In such cases, a review will help to identify key parameters for the economic model, and reciprocally the new economic model will help to identify important issues for the review. However, this is not always feasible, and the many tradeoffs that exist will be discussed below. In addition to discussing a number of interesting tradeoffs, we will also discuss the options of conducting the economic evaluation alongside the systematic review or conducting the two sequentially.

Those commissioning and planning systematic reviews must consider several issues and tradeoffs when addressing the issue of whether to perform a new economic evaluation that is consistent with the findings from the systematic review or whether to simply review the economic data that exist. Of course, the first issue is the quality of existing economic studies. The tradeoffs include: the feasibility in terms of cost, time, and the need for expertise; the applicability of the existing literature to the question at hand; the internal and external validity of the results; the quality and credibility of the analyses; and the transparency of the analyses.

Performing an analysis *de novo* will, by definition, be more costly. To conduct a *de novo* analysis, all the steps that would have to be performed for a review of extant data will have to be performed anyway. With highly constrained financial resources, the argument for reviewing existing findings would be fairly strong. The possibility of performing a *de novo* analysis may be more feasible if it is possible to seek more resources for the economic evaluation after the main review of evidence is complete. Limited resources could also be an argument, then, for a sequential analysis.

Similar to the need for more money to conduct an analysis *de novo*, there is also a need for more time, and time may not always be available. In this case, the time available deadline will play a role in determining whether a sequential analysis would even be possible. If there is a fixed timeline for the completion of the project and that timeline is short, then a sequential analysis is not likely possible. On net, if there is a relatively long timeline, it would be preferred to perform a *de novo* analysis.

A review of extant studies could be completed without the need for expertise on performing economic evaluations. Rather, the research group would need only the expertise to interpret the results. The need for more expertise may be closely related to the need for more resources. The expertise may be unattainable if the expertise is not available internally for the decisionmaker or there are insufficient resources to hire an external collaborator.

Another consideration is whether the findings that exist in the literature are sufficiently applicable to the current decision situation. This is a standard research question. The existing literature may not be applicable to the decision at hand if it is old, if it deals with a different target population, comparison, or outcome, if it is from a different health care system, or if it is from efficacy rather than effectiveness studies. Cost-effectiveness should ideally be based on effectiveness studies so that the results come from situations that are as close to real world

situations as possible. Differences in one of these criteria may leave the analyst concerned but willing to use extant results. However, differences in more than one of these criteria would suggest that the option of a review of existing literature would not be ideal.

The issues of internal and external validity and the quality of the studies are closely related (although there are certainly more criteria for the quality of the study than the internal and external validity). Higher quality extant results (based on any metric) will reduce the need for a de novo analysis.

The credibility of an analysis depends on both the quality and the certainty of the results. The goal is to maximize the credibility. Certainty is a function of both the statistical certainty of model parameters like effectiveness and the degree to which the qualitative nature of the results changes when parameters that do not have statistical uncertainty per se are varied across a reasonable range. In some cases, credibility would be maximized by using de novo results that are consistent with the review being conducted. In other cases, the credibility would be maximized by interpreting separate old results rather than combining multiple studies. This criterion does not always favor either de novo or a review of existing analyses.

The transparency is likely to be higher if existing results are presented and interpreted instead of being reviewed and synthesized in a de novo analysis. However, de novo analyses can also be transparent or nontransparent. The goal is to maximize transparency for the decisionmaker and for those affected by the decisions that result from the analysis. This criterion does not favor either the review or de novo in analysis in all cases.

When there are sufficient monetary resources in the short-run, or the sequential option is available, the time is not too short for a de novo analysis, and the expertise is available, a de novo analysis is a real possibility. Further, when the extant data are sufficiently applicable to the current decision situation, there is sufficient internal and external validity, and the extant studies are of sufficient quality, a simple review would be a real possibility. In this case, when both choices are realistic, several criteria can be used to guide the thinking of those commissioning and planning a review with the intent of including economic data.

- No pre-existing full economic evaluation relevant in the context of the systematic review;
- Substantial differences in the previous economic evaluation in terms of data used, methods and resulting findings;
- Substantial new evidence or evidence with decreased statistical variation regarding the cost or effectiveness since the most recent economic evaluation;
- Prior economic evaluations not based on the most up-to-date data on effectiveness rather than efficacy.

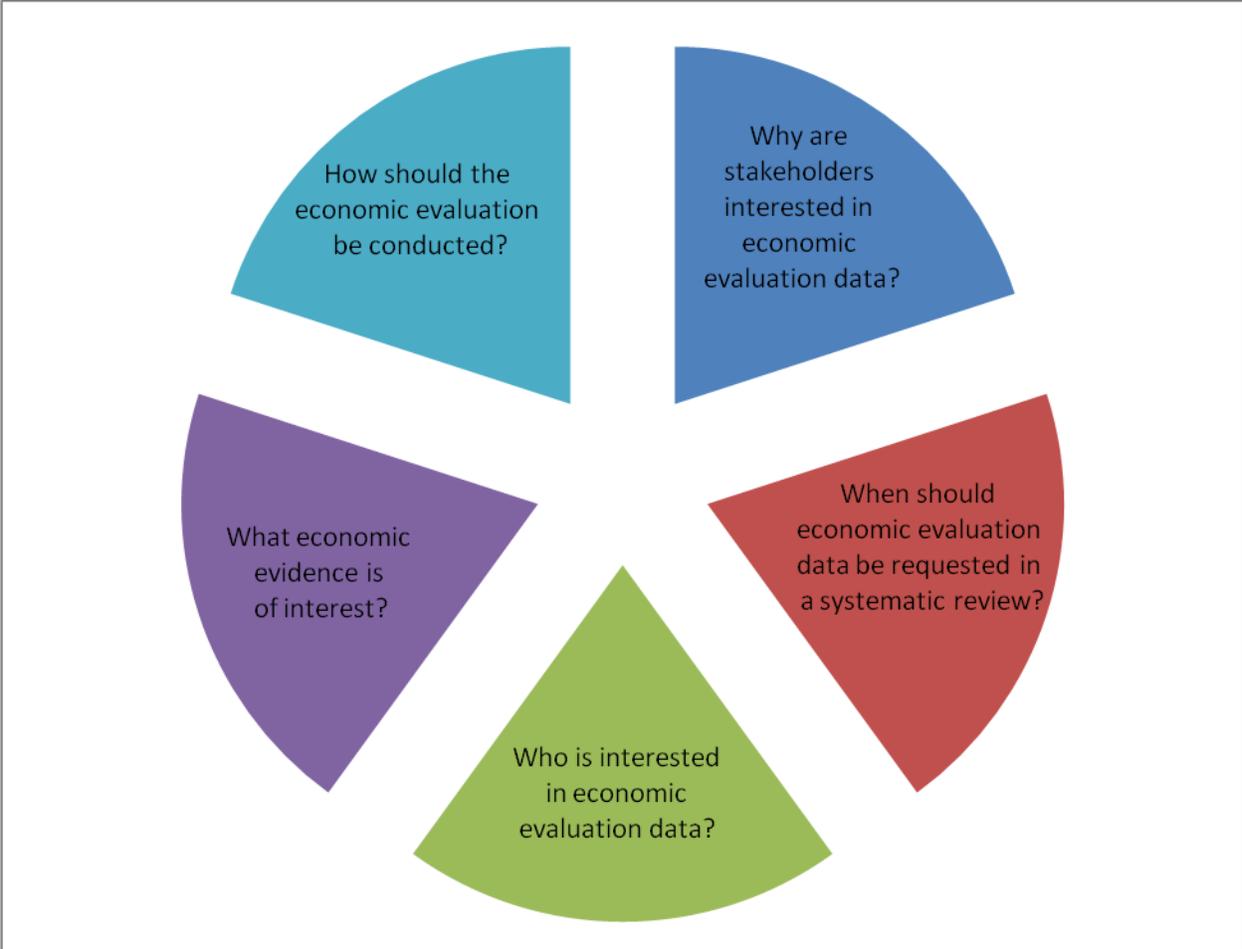
While the quality of the existing economic evidence is not always known prior to the conduct of the systematic review, another reason for conducting an original economic evaluation using results of the systematic review of evidence is if the quality of the prior evaluations was relatively poor. The criteria on which to judge the quality of studies is discussed in a separate document.<sup>12</sup>

## Discussion

The answers to the questions we addressed will provide critical guidance to those who are in a position to request systematic reviews that may include economic evidence and that may involve new economic evaluations consistent with the summary findings of effectiveness. Our results can help decisionmakers who have characterized the decisions they face to prioritize the economic evaluation data relative to clinical research data in the systematic review process. Stakeholders span the health and medical care system ranging from regulators to manufacturers, to providers, to patients. The decision contexts range from approval and monitoring to clinical management. In answering the question about when economic evaluation data should be collected and reviewed, we have dichotomized three criteria: the magnitude of the positive incremental cost, the magnitude of the positive incremental effect, and the magnitude of the perceived probability that the economic evidence will change the decision. In only one of eight combinations is high priority suggested: a small effect at a high cost with a high probability of influencing the result. In contrast, a very low priority is given to collecting such data when the incremental costs are low, the incremental effect is high, and the probability of impacting the decision is low. The situations in which it may be less important to gather data alongside systematic review are not necessarily situations in which all economic data are useless. Stakeholders will have to decide on what economic data are important in these situations as this particular report focuses only on what to collect alongside systematic reviews. A new full evaluation consistent with the results of a systematic review is most useful if there had been no previous full economic evaluation, if there were previous analyses with highly heterogeneous results, or if there were new cost or clinical data.

Systematic reviews may play a role in bringing economic data into the policy process.<sup>13</sup> These reviews play a role in determining the comparative effectiveness of medical interventions and are critical for developing clinical practice guidelines, efficacy-based coverage decisions, and general health policy.<sup>14-17</sup> The processes of searching for and summarizing studies illustrating clinical efficacy and effectiveness have been streamlined in the United States and elsewhere.<sup>18, 19</sup> This report should help to do the same for economic data along with several other recent reports.<sup>20, 21</sup> This report may also stimulate interest in assessing the extent to which published economic studies actually address the questions being raised in the systematic review of important clinical interventions. The circumstances of a health policy decision that are motivating a systematic review of evidence as viewed by the stakeholder requesting the systematic review may warrant that priority be given to collection, systematic review of, and analysis with primary economic data.

**Figure 1. Concepts motivating the collection of economic evaluation data alongside systematic reviews**



**Table 1. Definitions**

<b>Term</b>	<b>Definition</b>
Economic evidence	A term used to refer to either pieces of economic data (like costs, price elasticities, etc.) or the results of economic evaluation modeling.
Original economic data	Data that were measured and reported in an earlier study. The data could include costs, price elasticities, willingness to pay values, etc.
Original economic evaluations	Economic evaluations that combine data that may be new to the evaluation as well as data from previous studies and that lead to a result like a net benefit, cost-utility ratio, or cost-effectiveness ratio comparing two alternative treatments and not simply comparing one with a placebo.

**Table 2. Criteria to guide when to ask for economic evidence in a systematic review**

<b>Expected Incremental Cost</b>	<b>Expected Incremental Effect</b>	<b>Will Economic Evidence Change Decision?</b>	<b>Priority for Asking for Economic Evidence</b>
Low	Small	Low Probability	Low Priority
Low	Small	High Probability	Medium Priority
Low	Large	Low Probability	Very Low Priority
Low	Large	High Probability	Low Priority
High	Small	Low Probability	Medium Priority
High	Small	High Probability	High Priority
High	Large	Low Probability	Low Priority
High	Large	High Probability	Medium Priority

**Table 3. Most critical data elements for specific stakeholders in specific decision contexts**

<i>Decision Contexts</i>	<i>Stakeholders</i>									
	<b>Regulator<sup>a</sup></b>	<b>Private Third-Party Payer<sup>b</sup></b>	<b>Public Third-Party Payer<sup>c</sup></b>	<b>Public Health Planner<sup>d</sup></b>	<b>Health Care Professional<sup>e</sup></b>	<b>Health Care Facility<sup>f</sup></b>	<b>Employer</b>	<b>Manufacturer</b>	<b>Patient/Family/Consumer Groups</b>	<b>Research<sup>g</sup></b>
<b>Approval &amp; Monitoring</b>	All Measures	Summary Measures & Demand	Summary Measures & Demand	All Measures	Summary Measures & Supply	All Measures	All Measures	Summary Measures & Supply	Summary Measures & Demand	Dictated by purpose of research, including the specific stakeholder and specific decision context of interest
<b>Formulary Inclusion</b>	X	Summary Measures & Demand	Summary Measures & Demand	X	Summary Measures & Demand	Summary Measures & Demand	Summary Measures & Demand	Summary Measures & Supply	Demand	
<b>Insurance Coverage</b>	X	Summary Measures & Demand	Summary Measures & Demand	X	Summary Measures & Demand	Summary Measures & Demand	Summary Measures & Demand	Demand	Demand	
<b>Reimbursement Rate</b>	X	Supply	Supply	X	Summary Measures & Supply	Summary Measures & Supply	X	Supply	X	
<b>Preferred Practice Guideline</b>	X	X	X	X	Summary Measures	Summary Measures	Summary Measures	Summary Measures	Summary Measures	
<b>Technology or Nonadoption</b>	X	X	X	Summary Measures	X	Summary Measures & Supply	Summary Measures	Summary Measures	Summary Measures	
<b>Clinical Management</b>	X	X	X	X	Supply & Demand	All Measures	Demand	Demand	Demand	

Note: X indicates that a particular decisionmaker is unlikely to have decisionmaking capacity for a particular decisionmaking context.

<sup>a</sup>In the United States this could be the Food and Drug Administration

<sup>b</sup>This includes fee-for-service plans and managed care organizations that may only pay for care or may hire health care providers

<sup>c</sup>This includes Medicare (Federal) and Medicaid (with State-level variation)

<sup>d</sup>An example would be a local public health department considering

<sup>e</sup>Includes physicians, nurse practitioners, health care educators and others

<sup>f</sup>Facilities can be both public and private organizations and include hospital, nursing homes, ambulatory surgery centers, and others

<sup>g</sup>Researchers and research funding agencies. The research interest will largely overlap with a specific perspective for which the research is funded.

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