FORMAT FOR FORMULARY SUBMISSIONS

VERSION 2.0

A Format for Submission of Clinical and Economic Data in Support of Formulary Consideration by Health Care Systems in the United States

FMCP Foundation for Managed Care Pharmacy

AMCP Academy of Managed Care Pharmacy

ACKNOWLEDGEMENTS

The Academy of Managed Care Pharmacy (AMCP) and the Foundation for Managed Care Pharmacy (FMCP) gratefully acknowledge the contributions of many individuals who have devoted much time, expertise and commitment in the preparation of this valuable pharmacy tool.

Version 1.0 of AMCP's *Format for Formulary Submissions*, published in October 2000 was the culmination of nearly three years of mostly voluntary collaboration between talented authors experienced in the challenges presented by the complex task of appropriate formulary decision making: Joseph A. Gricar, MS, Regional Outcomes Research Manager, Pharmacia Corporation; Paul Langley, PhD, 3M Pharmaceuticals; Bryan R. Luce, PhD, MBA, CEO & Senior Research Leader, MEDTAP International, Inc.; C. Alan Lyles, PhD, MPH, BS Pharm, Associate Professor, University of Baltimore; and Sean D. Sullivan, PhD, Professor & Director, Pharmaceutical Outcomes Research and Policy Program, University of Washington Department of Pharmacy.

The *Format* would not have come about without the pioneering work of Dwight S. "Pete" Fullerton, PhD, RPh, and the pharmacy services staff at Regence BlueShield; as well as Dell B. Mather, PharmD, RPh, Senior Director, Pharmacotherapy Assessment and Policy, Prime Therapeutics, Inc. Their efforts in improving the evidentiary requirements for rational drug selection in managed care organizations served as a practical basis for evaluating the items considered for inclusion in this document. These guidelines have benefited directly and indirectly from their efforts.

By the Spring of 2002, efforts to have the *Format* process adopted by health systems and the pharmaceutical industry had progressed to the point that most of the major pharmaceutical companies were preparing product dossiers based on the AMCP *Format* at the request of numerous national managed health care systems, pharmacy benefit management companies, the Department of Defense, and a few hospitals and state Medicaid agencies. At this time, FMCP looked to Dr. Sean Sullivan to lead efforts to revise the *Format* by consolidating and addressing the hundreds of comments received since the *Format's* publication from pharmacists and other health care professionals representing managed health care systems, academia, and the pharmaceutical industry. The Academy and Foundation are deeply indebted to Dr. Sullivan for his continuing passionate support for the *Format* and his tireless devotion to evidence-based decision-making.

In addition to drawing on the expertise of most of the authors of Version 1.0, Dr. Sullivan was well served by members of the *Format* Revision Committee who acted as an expert review panel. We are indebted for the sage advice and constructive comments given by: Kerri Chitwood-Dagner, PharmD, BS Pharm, National Pharmacy Director, Great-West Life; Joseph A. Gricar, MS, Regional Outcomes Research Manager, Pharmacia Corporation; Dell Mather, PharmD, BS Pharm, Senior Director, Pharmacotherapy Assessment and Policy, Prime Therapeutics, Inc.; Marsha Moore, MD, MBA, Senior Vice President, Medical Affairs, AdvancePCS; Pete Penna, PharmD, Partner, Formulary Resources, LLC; and Nancy E. Stalker, PharmD, Vice President of Pharmacy Services, BlueShield of California.

The Academy and the Foundation are deeply indebted to Pete Penna, Partner, Formulary Resources, LLC, for his diligent work as FMCP Program Director for the *Format* from May 2001 to April 2002. The broad acceptance and rapid adoption of the *Format* process by health care systems and pharmaceutical manufacturers is directly attributable to his many years of experience in pharmacy benefit management, his meticulous attention to detail, and his continuing commitment to evidence-based decision-making as a fundamental requirement for improving patient health outcomes.

BACKGROUND

The Academy of Managed Care Pharmacy (AMCP) published the *Format for Formulary Submissions* in October 2000. The AMCP Leadership and its members were motivated to develop these Guidelines by a growing need to ensure that any increased utilization of medications, biopharmaceuticals and vaccine products was appropriate and that newer products would bring added clinical and economic value to covered populations. To satisfy this need, the Academy recognized that it had to provide its members with the means to (1) promote the concept of combining efficacy, safety, effectiveness, and economic evaluation for the formulary decision-making process, (2) provide a consistent and direct means for manufacturers to supply information directly to health systems in order to support use of their products, and (3) break down cost silos and emphasize that simple acquisition cost reduction IS NOT the best approach to controlling overall health care expenditures.

Since publication of the AMCP *Format*, The Foundation for Managed Care Pharmacy (FMCP) has spearheaded an initiative to market its usage. This effort has included presentations and forums at AMCP and other professional organization's national meetings and conferences, articles in newsletters, peer-reviewed and lay literature, and numerous seminars designed to train health system pharmacists and pharmaceutical industry personnel on the appropriate use of the *Format.* Consequently, the *Format* has garnered nationwide publicity and attracted considerable attention, both positive and negative. Nevertheless, adoption of the *Format* process by health systems and the pharmaceutical industry has exceeded AMCP's and FMCP's expectations. Over the past two years a growing grassroots network has developed among health systems stimulating adoption initially by managed health care systems and PBMs and, most recently, by hospitals, integrated health care systems, state Medicaid agencies, and the Department of Defense. As adoption of the *Format* has spread, manufacturers have begun to standardize the framework within which they present population-specific data.

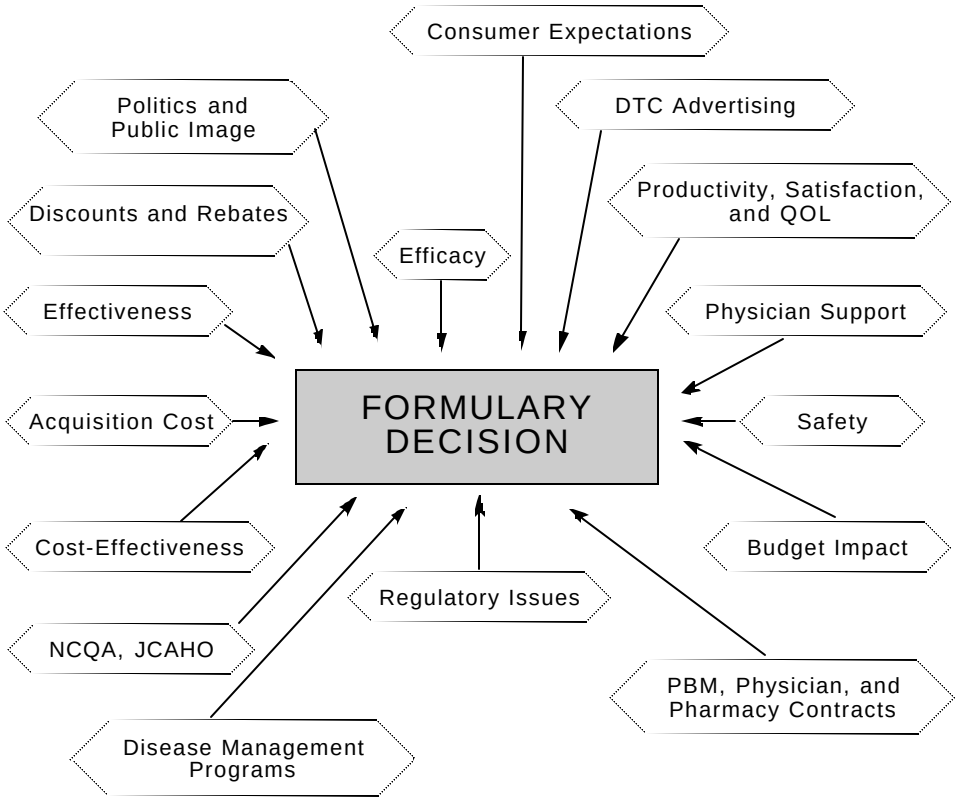
The *Format's* process is designed to maintain a high standard of objectivity to achieve two important goals. First, it is intended to improve the timeliness, scope, quality and relevance of information available to a health system's evaluators and ultimately to its P&T Committees. **However, health systems should not expect that its use would lower their drug expenditures.** A distinguishing feature of the *Format* is its use as an Unsolicited Request from a health system to a manufacturer for all possible clinical and economic information necessary to assess the overall clinical utility and value that a product brings to a specific patient population and health care system. In response to this Unsolicited Request, manufacturers are asked to submit all possible published and unpublished studies and information regarding both FDA-approved indications and anticipated off-label uses of the product. Therefore, this request improves access to material that has been difficult to obtain in the past. It also enables manufacturers to submit such data within regulatory constraints mandated by the Food and Drug Administration (FDA). While no explicit FDA guidance regarding unsolicited requests exists, FDA officials have repeatedly stated their intention to issue such guidance in the future. In the meantime, FDA officials have very clearly stated their position that they have responsibility for (1) assuring that requests for off-label product information are truly unsolicited and unprompted, (2) assuring that the information provided is not false or misleading, and (3) assuring that the response is specific to the requestor.

Health care professionals and health care systems worldwide are challenged daily to set priorities in an environment where demand for health care services outweighs the supply of resources allocated to finance it. In the absence of widely accepted models

BACKGROUND
continued

for legitimate and fair priority setting in health care, health care professionals must rely on the best available evidence to reach consensus about what constitutes a fair allocation of resources to meet competing health care needs. For example, formulary decision-making is frequently conducted under uncertain conditions due to the variability of available evidence on safety, effectiveness, and appropriateness of particular interventions. Gibson, et.al. state, "In the absence of consensus on guiding principles, the problem of priority setting becomes one of procedural justice — legitimate institutions using fair processes."[1] By improving the timeliness, scope, quality and relevance of information available to P&T Committees, the *Format* strengthens the ability of health care systems to assess the impact of a particular product.

Figure 1



[1] Gibson JL, Martin DK, Singer PA. Priority setting for new technologies in medicine: A transdisciplinary study. *BMC Health Services Research*. 2002. 2:14. 18 July 2002.

BACKGROUND
continued

Further, by assessing the health system impact of using a product, the data requested can improve the P&T Committee's ability to assess the effects of formulary alternatives on clinical outcomes and economic consequences for the entire health system. However, this information still must be weighed in the context of other values such as equity, social justice, the health of individuals as against communities, the "rule of rescue," and democratic decision making.[1, 2, 3] In addition, health care system priorities will be influenced by numerous other factors as represented in Figure 1.

Second, the *Format* will streamline the data acquisition and review process for health system staff pharmacists. By clearly specifying the standards of evidence implicit in the existing formulary process, the submission guidelines furnish pharmaceutical manufacturers with consistent direction concerning the nature and format of information that is expected. In addition, the standardized format allows clinical staff to formally evaluate the completeness of submissions received and to easily add the results of the health system's literature reviews and analysis. **Importantly, manufacturers should understand that submission of information in the format recommended does not guarantee approval of their product for formulary listing.** Discussion about, and subsequent receipt of, a dossier should be seen as a process to improve the quality and format of information provided, but not as a formula for approval.

Effective formulary deliberations require accurate, complete product dossiers best developed by manufacturers in partnership with health systems. Therefore, implementation of the *Format* calls for resource commitments by both health systems and manufacturers and a shared vision of the requirements to facilitate the collaboration necessary between the health system and manufacturers to support drug product evaluation.

Successful implementation of the *Format* process by a health system will include:

a) Human, technical (IT) and financial resources to support the process within the plan including support of senior management and the P&T Committee;

b) A commitment by all staff to make it work;

c) Clear communication of *Format* requirements to pharmaceutical industry representatives;

d) Health system pharmacy staff training in interpreting and integrating the data presented into the formulary process; and

e) Accessibility to health system staff by industry representatives for presentations on data and economic models.

Part of a health system's use of the *Format* includes critical appraisal of the data supplied by manufacturers prior to its submission to the P&T Committee. In addition to a critical evaluation of the clinical information, the review should include an evaluation of the economic data by one trained in pharmacoeconomics. In order to evaluate the health economics information, health systems can use one of many published tools [see for example, guidelines for authors and peer reviewers reported in the *British Medical Journal, Drummond and Jefferson, 1996 (see Appendix A)*], which provide a checklist for health systems as a consistent measure of the quality and comprehensiveness of the report.

---

[2] Daniels N. Four unsolved rationing problems. Hastings Center Report. 1994, 24:27–29.

[3] Richardson J and McKie J. The rule of rescue. Working paper #112 (2000). Centre for Health Program Evaluation, Health Economics Unit, Monash University, Australia. http://chpe.buseco.monash.edu.au/pubs/wp112.pdf.

BACKGROUND
continued

Using the *Format*, the pharmaceutical industry will have the opportunity to justify the price of a new agent in terms of its overall value to the health system. In addition, industry scientists and consultants, using a reasonable scientific framework, will have the opportunity to provide additional information (e.g., adherence data, patient satisfaction, indirect and non-medical cost impacts) to demonstrate the broad value of their products when compared to usual treatments. Therefore, manufacturers have increased responsibility for providing relevant clinical data and economic impact information. The economic data called for must be broadly applicable to a health system's population and address the system-wide impact of formulary changes on both clinical outcomes and resource utilization and costs. The *Format* does not specify methods for economic evaluation. It is the submitter's responsibility to utilize appropriate techniques and data sources.

In response to similar requirements for reimbursement, pricing and formulary listing in Australia, Canada, the United Kingdom and other countries[4, 5, 6] pharmaceutical manufacturers are already submitting comprehensive reports on the effectiveness, safety and cost-impact of their products. The AMCP *Format's* requirements mirror these requests by requiring manufacturers to provide product dossiers that contain sufficient detail to give transparency to the analytical methods. However, the *Format* provides considerable flexibility. The formalized system suggested in AMCP's *Format* should be seen as a dynamic, rather than static, process. It is anticipated that increased standardization of information will lead to progressive improvement in the quality of submissions over time and provide health system pharmacists with data often unavailable in the past.

AMCP is not a standard setting organization. Therefore, the Academy has always viewed the *Format* as a template or guide, not a mandate or standard. As such, it does not claim to establish a standard of practice for managed care pharmacy. It is up to individual health care systems to decide how they will implement the *Format* and how they will operate their formulary review processes. For example, a health system may require dossiers for only new molecular entities. Another may require dossiers for all new products at launch and for existing products through their annual therapeutic class reviews. Others may choose to provide exceptions to the submission requirements for certain drug classes such as orphan drug products, chemotherapy agents and HIV/AIDS drugs. Ideally, products should only be considered for formulary review when the manufacturer can submit a complete dossier. Realistically, following an unsolicited request from a health system, manufacturers should make every attempt to submit a complete dossier. When evidence is missing, the manufacturer should provide the health system with a detailed explanation of what evidence is missing and a plan that addresses this deficiency within a specific time limit. If a dossier is not submitted following a health system's unsolicited request, the health system should reserve the right either to refuse to consider the product for formulary admission or to exercise other available options regarding the product's benefit status that are in keeping with its formulary and drug benefit management policies and procedures.

[4] Guidelines for the Pharmaceutical Industry on Preparation of Submissions to the Pharmaceutical Benefits Advisory Committee: including major submissions involving economic analyses. Australia. 1995 and 2000. http://www.health.gov.au/pbs/pubs/pharmpac/gusubpac.htm and http://www.health.gov.au/pbs/pubs/pharmpac/interim/.

[5] Guidelines for Economic Evaluation of Pharmaceuticals. Canada, 1997. http://www.ccohta.ca/entry_e.html.

[6] National Institute for Clinical Excellence. Great Britain. http://www.nice.org.uk.

BACKGROUND
continued

The steady increase in the number of health systems adopting the *Format* have strengthened AMCP's and FMCP's conviction that this process represents the best opportunity for organizations to effectively implement a standardized and fair process for the evaluation of medications to determine how a specific product will impact overall health care delivery within their population. Therefore, the Academy and Foundation will continue to encourage the use of the *Format* as an essential tool to support product evaluation and selection with clinical outcomes as the most important consideration while avoiding the use of low acquisition cost and rebates as the *PRIMARY* basis for selection. While cost considerations, under certain circumstances, may be relevant reasons for limits, in practice they tend to be highly controversial and contested. The recent backlash against managed care can be readily attributable to an American culture that is unwilling to accept limits. Writing in *Health Affairs* in 1998, Daniels and Sabin state "To change that culture requires a concerted effort at education, and education requires openness about the rationales for managed care plan's decisions."[7] By adhering to careful and thoughtful decision-making processes that provide the rationales for limits, health care systems will be able to show, over time, that "arguably fair decisions are being made and that those making them have established a procedure we should view as legitimate."[3] AMCP and FMCP believe that the *Format* is a tool that will help health systems establish a record of commitment to rational decision-making thus gaining the confidence of patients, clinicians, and members. The AMCP *Format for Formulary Submissions* is an essential tool to evaluate medications, but requires thoughtful consideration as it is used.

Since publication of the *Format*, AMCP and FMCP have continuously sought input from pharmaceutical manufacturers and health system pharmacists through various venues in order to improve and clarify the process. Version 2.0 is the first attempt to address users comments and concerns. Current and potential users of the *Format* will find that the Contents sections of the guidelines have not changed substantially. Our revision efforts in these sections were focused on providing additional clarity and making the document more user-friendly and understandable. We have attempted to address major areas of concern expressed by health system pharmacists and the pharmaceutical industry over the past two years in the following section — **Response to Comments**. We firmly believe that our efforts will result in more widespread acceptance and that grassroots efforts will lead to an ever-expanding network of adopters of the *Format* process. FMCP will continue its efforts to train health system pharmacists and pharmaceutical industry personnel on the appropriate use of the *Format*. The Foundation also assumes that further refinement of the *Format* will be necessary. To that end, FMCP staff will continue to solicit and catalog comments from users and potential users of the *Format.* In addition, FMCP is sponsoring formal research to critically evaluate the *Format* process to address ongoing concerns and to determine, among other things, its impact on health system's decision-making processes and on the pharmaceutical industry. Comments and ideas are always welcome and should be directed to Richard Fry, FMCP Director of Programs, (703) 683-8416, ext 345 or at rfry@fmcpnet.org.

[7] Daniels N, Sabin JE. The ethics of accountability in managed care reform. *Health Affairs*. 1998: 17(5): 50–64.

TABLE OF CONTENTS

[– –] Formulary Submission Guidelines (Health care systems should personalize the guidelines by inserting their organization's name wherever [– –] appears in the document).

OVERVIEW

HEALTH SYSTEM GUIDELINES FOR MANUFACTURERS (Evidentiary Requirements for Formulary Submission Dossiers)

continued on the next page

TABLE OF CONTENTS

continued

OVERVIEW

FOUNDATION OF A SOUND FORMULARY SYSTEM

Rational product adoption decisions employing clinical, economic, and humanistic data are built on the foundation of a sound formulary system. Pharmaceutical, biological and vaccine products should be subjected to a rigorous clinical review (and periodic re-review) based on evidence from the clinical literature. Evidence-based assessment of product efficacy, safety, effectiveness and cost-effectiveness provide the foundation for this review.

These precepts are affirmed by the National Committee for Quality Assurance (NCQA) managed care organization accreditation standard Procedures for Pharmaceutical Management and by the *Principles of a Sound Drug Formulary System*[15] developed and endorsed in August 2000 by AMCP and the Alliance of Community Health Plans, the American Medical Association, the American Society of Health-System Pharmacists, the Department of Veterans Affairs, Pharmacy Benefit Management Strategic Healthcare Group, the National Business Coalition on Health and the U.S. Pharmacopeia. *(See Appendix B)*

The goal of the [– –] formulary review process is to provide a quality pharmaceutical benefit determined through an evidence-based decision-making process taking into account the reality of constrained health care budgets. Where feasible, product comparisons should be made relative to existing competitor products as well as to placebo. For products with similar safety and efficacy profiles, decisions may be made primarily on net acquisition cost unless reasonable product value or other program efficiency arguments made by the manufacturer can be supported with pharmacoeconomic evidence. In other words, good economics does not make up for questionable clinical value.

THE ROLE OF FORMULARY SUBMISSION GUIDELINES

Formulary submission guidelines support the informed selection of pharmaceuticals, biologicals and vaccines by:

a) standardizing and communicating product and supporting program information requirements;

b) projecting their impact on both the organization and its enrolled patient population; and

c) making evidence and rationale supporting all choice(s) more clear and evaluable by [– –] decision makers.

These submission guidelines are intended to support an emphasis away from the *product price/rebate* approach often utilized for formulary decisions to one that emphasizes formulary decision-making based on evidence of clinical benefit, i.e. relative efficacy, safety and effectiveness and then total cost and health impact. Simply stated, manufacturers are asked to provide evidence of the clinical and economic value of their products for health system members — in terms of clinical benefits (efficacy and effectiveness), safety, health outcomes and overall economic impact. These guidelines emphasize that, while cost-benefit analysis and economic modeling are important elements in the value equation, they follow the principle clinical concerns of safety and efficacy. Importantly, manufacturers should understand that submission of information in the format recommended herein does not guarantee approval of their product for listing.

OVERVIEW

continued

These guidelines are intended to offer a clear, shared vision of the requirements to facilitate the collaboration necessary between [– –] and manufacturers to support drug product evaluation. Recognizing that manufacturers may not have all the requested information for, especially, new products, this document describes the minimum information requirements necessary to support a comprehensive assessment of the proposed product.

> ***The Food and Drug Administration (FDA) and pharmaceutical manufacturers have generally regarded this Format as a detailed unsolicited request for information to support formulary evaluation by [...] clinical pharmacists. This request has enabled manufacturers to submit such data within existing regulatory constraints of the Food and Drug Administration.***

GUIDELINES OVERVIEW

A complete formulary submission dossier for pharmaceutical, biological and vaccine products should include the following sections:

1. Disease and Product Information
2. Supporting Clinical and Economic Information
3. Cost-effectiveness and Budget Impact Model Report
4. Product Value and Overall Cost
5. Supporting Information: Reprints, Bibliography, Checklist, Electronic Media and Appendices

CONTENT

These guidelines are not intended to restrict the content, presentation of data and the research methods of studies that comprise the dossier. Rather, they are intended to specify evidentiary requirements for product review. However in preparation of the evidence, the approach and methodology adopted by the manufacturer and the techniques employed should be consistent with the formulary evaluation objectives of [– –]. It is recommended that the manufacturer consult with [– –] representatives to determine appropriate sources for data and to agree on specific requirements and model assumptions. *(See page 6 — Agenda for Pre-Submission Meeting)*

STANDARDS OF CARE AND DATA SOURCE

[...] recognizes that clinical development programs are designed, in large part, to meet regulatory requirements. When feasible, manufacturers are encouraged to consider the broader clinical and payer audience who require evidence on new drugs. For example, trial designs might be modified to reflect comparators of interest to [– –]. Furthermore, economic evaluations should be capable of reflecting the characteristics of the treatment environment of [– –]. Analyses based on clinical trials alone or data from other health systems or PBMs may be insufficient unless the manufacturer shows them to be directly applicable to [– –] membership. The manufacturer should focus on patterns of medical services provided directly by reasonable peer organizations. In some cases, there may be differences of opinion as to what constitutes appropriate standards of care. This should be resolved with [– –] prior to submission.

OVERVIEW

continued

DISCLOSURE OF POTENTIAL REPORTING BIAS

To minimize the potential for bias in formulary submissions, manufacturers should follow generally-accepted rules of scientific conduct and reporting of clinical and economic evaluation data.[2, 3] At a minimum, the following should be disclosed for economic evaluation studies, budget impact models and authors of the submission dossier:

1. Identify all investigators/authors and give the details of their affiliations.
2. All financial or contractual relations that might impact the independence of the investigators/authors.

RECOMMENDED FORMULARY SUBMISSION PROCESS

New Products

The following steps are recommended for the submission of new drug products:

Step 1: Manufacturers should keep [– –] clinical pharmacy staff informed of the status of drugs in their pipeline. Both parties should identify specific contacts to ensure efficient communication.

Approximately 6 months prior to product launch, the [– –] pharmacy staff will issue a formal Unsolicited Request letter that contains a copy of the formulary submission requirements. The letter will be directed to the appropriate company employee who can engage in health professional-to-health professional communication, in compliance with FDA regulations on provision of label and off-label information.

Step 2: Following submission of the Unsolicited Request, [– –] pharmacy staff and manufacturer representatives may schedule an initial pre-submission meeting to establish a deadline for dossier submission based on the anticipated review date, and to discuss other pertinent issues such as commercial-in-confidence data, economic model assumptions, availability of spreadsheet models, etc. *(See page 6 — Agenda for Pre-Submission Meeting).*

Step 3: At least 2 months prior to the product review, the manufacturer will present one (1) paper copy and one (1) electronic copy of the submission dossier to [– –].

Step 4: The [– –] clinical staff assigned to the product will review the submission. Based on the initial review, the manufacturer may be asked to clarify certain points or submit additional information before a formulary monograph is prepared by [– –] staff for P&T review.

Step 5: The designated clinical pharmacists will prepare a detailed summary (monograph) for the P&T review. The summary presents an overview of all data, and the principal arguments for and against listing the product on formulary, and any conditions that may apply.

Step 6: As soon as possible, [– –] staff will inform the manufacturer of the P&T Committee's recommendation. Upon request, staff may provide the manufacturer with the rationale for a product's denial or restriction as well as guidance for reconsideration or appeal.

OVERVIEW

continued

NOTE: *Establishment of a formal appeals process is at the discretion of individual health care systems. Public entities, such as state Medicaid agencies, the Department of Defense or the Veterans Administration may be required by state or Federal law to have formal appeals processes in place to deal with denials related to formulary decisions.*

AGENDA FOR PRE-SUBMISSION MEETING

This meeting(s) should take place at least 4-to-6 months before the actual date of anticipated product review to allow time for the manufacturer to gather the necessary data for [– –]. This meeting will also serve as a forum to discuss the consequences of missing information deemed necessary by [– –]. This agenda can serve as a discussion guide to ensure that [...] and the manufacturer address relevant topics. On-going communication between [...] should occur as deemed necessary.

The representatives for the manufacturer should provide a copy of, and be prepared to discuss, the following at the first meeting(s):

a) List of intended indications

b) Summary of studies to be included in the formulary submission. This will include:
   - Clinical trials (experimental and non-experimental)
   - Outcomes studies
   - Meta analysis
   - Retrospective studies
   - Economic and budget impact models

c) Use of comparator products and their appropriateness

d) A general description of how the cost and outcomes impact assessments will be developed. This should include:
   - List of data sources (studies, databases, etc.),
   - Discussion of incorporation of health system data,
   - Discussion of conversion of efficacy to effectiveness for both drug and comparators,
   - Approach to modeling the health care environment of [– –],
   - Discuss level of patient switching and impact on overall costs,
   - Assumptions and suggested approach for determining patient characteristics for switching.

e) Summary of anticipated studies to be completed within 1–3 years

f) A filled out submission checklist

OVERVIEW continued

PERIODIC REVIEW OF THERAPEUTIC CLASSES AND REQUESTS FOR UPDATED DOSSIERS WHEN COMPETITOR PRODUCTS ARE BEING REVIEWED

Periodically, [– –] will undertake reviews of all drugs in each therapeutic class, including drugs currently listed and those that are non-formulary. Manufacturers may be asked to update their product dossiers with the most recent clinical data and economic modeling information. If required by [– –], this request will be made through issuance of a separate Unsolicited Request letter.

In addition, when a new competitor product is being reviewed, [– –] may ask manufacturers for an updated dossier for products with the same or very similar clinical profiles. In each case, manufacturers will be given as much notice as possible.

NOTE: *Health care systems may choose to delete this section on annual review if their current P&T Committee procedures do not include a regular therapeutic class review.*

ROLE AND RESPONSIBILITIES OF [– –]

[– –] clinical pharmacists welcome the opportunity to meet with manufacturers to review dossier submission requirements and to discuss data and analyses. As stated previously, [– –] should provide the manufacturer with timely information regarding product submission and evaluation such as:

- A dossier submission deadline;
- Anticipated date of initial product review or re-evaluation;
- General demographic information to assist in development of economic analyses, if feasible;
- Notification of additional information or data clarification requirements;
- The P&T Committee's recommendation.

By submitting this request [– –] recognizes that confidential information may be provided. [– –] recognizes the need to respect and honor commercial-in-confidence information and may be willing to sign necessary confidentiality agreements under agreed circumstances.[16]

As noted throughout this document, the success of the formulary submission process depends on an active collaboration between [– –] and the pharmaceutical industry.

THE FORMULARY SUBMISSION DOSSIER

Manufacturers should complete their formulary submission dossiers using this *Format* to integrate the relevant published and unpublished data evaluating the efficacy, safety, economic impact, and other medical outcomes associated with the use of their product. Sections 1–4 should be completed and presented in the order listed. Compliance with this standardized reporting format allows for efficient review and facilitates the use of provided information by decision makers. Marked deviations from this format may delay the review process. While dossiers must provide sufficient detail to give transparency to the analytical methods used, the *Format* provides considerable flexibility. Where specific sections or data are unavailable or incomplete, the manufacturer should indicate and explain why they are missing and when they will be provided, if at all.

OVERVIEW

continued

Manufacturers should provide the following additional information:

1) A comprehensive list of references for all studies cited and for information sources from which estimates were drawn for use in the economic evaluation for section 2.4.
2) Identify the author(s) of the submission document. *(See Disclosure section above.)*
3) Identify the author(s) of primary economic evaluations conducted for section 2.3 of this document. *(See Disclosure section above.)*
4) Identify a contact person who can answer questions and provide additional information regarding the submission materials for [– –] reviewers.

SAMPLE UNSOLICITED REQUEST LETTER

Date

Name of Acct Manager/Medical Science Liaison
Name of Company
Address
Address

Dear...:

The [Organization name] has adopted the Academy of Managed Care Pharmacy's (AMCP) *Format for Formulary Submissions* detailing the process and evidentiary requirements for the provision of clinical and economic information to support drug formulary consideration. [Organization name] considers this document an unsolicited request for medical, economic and other scientific information (including any unpublished and/or off-label study data that are to be considered by our organization) and pharmacoeconomic modeling on all pharmaceutical products that we consider for formulary inclusion or as part of therapeutic class reviews. The specific details of the [Organization name] request have been sent to you previously and are available on the [Organization name] web site (www.xxx.com).

We consider this unsolicited request to represent the desired information to accompany a formulary submission. Manufacturers should submit a complete dossier well before they expect the product to be considered for formulary review. Our goal is to enable all of the [Organization name] Pharmacy & Therapeutics (P&T) Committees to make evidence-based decisions representing good value for money when selecting preferred treatment options. The AMCP *Format* describes a standardized template for pharmaceutical manufacturers to construct and submit a formulary dossier. The dossier is designed to make the product evaluation process in formulary development more complete, evidence-based and rational.

By submitting this request [– –] recognizes that confidential information may be provided. [– –] recognizes the need to respect and honor commercial-in-confidence information and may be willing to sign necessary confidentiality agreements under agreed circumstances.

Please consider this letter as an unsolicited request for information required by [Organization name] for your product Name of Product or Products here. If you require additional information, please call .....

Sincerely,

HEALTH SYSTEM GUIDELINES FOR MANUFACTURERS

(Evidentiary Requirements for Formulary Submission Dossiers)

1. PRODUCT INFORMATION

1.1 PRODUCT DESCRIPTION [20 PAGES MAXIMUM]

Manufacturers are required to provide detailed information about their product. They should compare the new product with other agents commonly used to treat the condition, whether or not these products are currently on [– –] formulary. The product description consists of information that traditionally has been incorporated in a product monograph or formulary kit and includes the following:

a) Generic, brand name and therapeutic class of the product,

b) All dosage forms, including strengths and package sizes,

c) The National Drug Code (NDC) for all formulations,

d) A copy of the official product labeling/literature, and

e) The AWP and WAC cost per unit size. (The [– –] contract price, if available, should be included as well.)

f) AHFS or other Drug Classification

g) FDA Approved and other Studied Indication(s): A detailed discussion of the approved Food and Drug Administration (FDA) indications and the date approval was granted (or is expected to be granted) must be included. Information on pending off-label indications and other non-labeled uses, if available, should be included.

h) Pharmacology

i) Pharmacokinetics/Pharmacodynamics

j) Contraindications

k) Warnings/Precautions

l) Adverse Effects

m) Interactions, with suggestions on how to avoid them

- Drug/Drug
- Drug/Food
- Drug/Disease

n) Dosing and Administration

o) Access, e.g., restrictions on distribution, supply limitations, anticipated shortages

p) Co-Prescribed / Concomitant Therapies, including dosages

q) Comparison with the pharmacokinetic / pharmacologic profile of other agents in the therapeutic area. The material may include a discussion of comparator product(s) or services that the proposed product is expected to substitute for, or replace (including drug and non-drug interventions). This information should be presented in tabular form.

HEALTH SYSTEM GUIDELINES FOR MANUFACTURERS

(Evidentiary Requirements for Formulary Submission Dossiers)

1.2 PLACE OF THE PRODUCT IN THERAPY [LIMIT 1–3 PAGES]

The disease description should include the disease and characteristics of the patients who are treated for the condition. Present a brief summary of information from the literature for each topic. When information from studies is presented, the manufacturer should compile the results in detailed evidence tables.

Next, an attempt should be made to generalize these findings to the populations of [– –]. Discuss the implications of any differences that exist between the literature and typical practice patterns and patient populations. When more than one disease is addressed, complete the description for each separate condition.

Specific disease descriptive information requested: [Not more than 2–3 pages per disease]

a) Epidemiology and relevant risk factors

b) Pathophysiology

c) Clinical presentation

d) Approaches to treatment — principal options / practice patterns

e) A description of alternative treatment options (both drug and non-drug)

f) The place and anticipated uses of the proposed therapy in treatment (e.g., first line)

g) The expected outcomes of therapy and

h) Other key assumptions and their rationale.

[– –] and the manufacturer should determine the relevant treatment options for comparison during the initial pre-submission meeting.

2. SUPPORTING CLINICAL AND ECONOMIC INFORMATION

2.1 SUMMARIZING KEY CLINICAL AND ECONOMIC STUDIES

Submit the key clinical and economic studies that have been conducted, whether published or not, for clinical safety, efficacy, economic and health outcomes evaluations. Studies reported in this section should be summarized in a clear, concise format; presenting data from multiple studies in tabular form within a category is strongly encouraged. All of the following that apply should be included:

a) Name of the clinical trial or study, location and study date;

b) Trial design, randomization and blinding procedures;

- Research question(s);
- Study perspective;

c) Washout, inclusion and exclusion criteria;

d) Sample characteristics (demographics, number studied, disease severity, co-morbidities);
   - Treated population (actual or assumed)

e) Patient follow-up procedures (e.g., If an intention-to-treat design is used, were drop-outs followed and for what time period?);
   - Treatment period

f) Treatment and dosage regimens;
   - Treatment framework
   - Resource utilization classification
   - Unit costs;

g) Clinical outcome(s) measures;
   - Outcomes evaluated;

h) Other outcome measures (e.g., quality of life);
   - Principal findings

i) Statistical significance of outcomes and power calculations;

j) Validation of outcomes instrument (if applicable);

k) Compliance behavior;

l) Generalizability of the population treated;
   - Relevance to enrolled populations of [– –].

m) Publication citation(s)/references used.

2.2 PUBLISHED AND UNPUBLISHED CLINICAL STUDY RESULTS [2 PAGE MAXIMUM PER STUDY; PLEASE COMPLETE EVIDENCE TABLES IN THE [– –] FORMAT

Provide summaries addressing items a–m *(see 2.1 above)* for studies in each of the categories listed below (items a–d). The manufacturer should complete evidence tables that summarize the data. [– –] is particularly interested in head-to-head comparison clinical studies between the proposed product and the principal comparators. Summaries of trial results of key comparator products are desirable but not required. Discuss important study findings and comment on their implications for the patient populations represented by [– –]. Systematic reviews or meta-analyses may be referenced in item (e). In the appendix, include a reprint or unpublished manuscript of each study discussed or referenced:

a) Pivotal safety and efficacy trials [Usually no more than one (1) page per study + evidence table]

b) Prospective effectiveness (e.g., large simple) trials [usually no more than one (1) page per study + evidence table]

c) Additional prospective studies examining other non-economic endpoints such as health status measures and quality of life. If the instruments utilized in these studies are supported by previous validation and reliability studies, also refer-

HEALTH SYSTEM GUIDELINES FOR MANUFACTURERS

(Evidentiary Requirements for Formulary Submission Dossiers)

ence these studies. [No more than one (1) page per study]

d) Retrospective studies [No more than one (1) page per study + evidence table]

e) Review articles and meta-analyses. Place particular emphasis on the inclusion and exclusion criteria and main outcome measure(s) for studies analyzed.

In addition, information from all known studies on the product should be summarized in a spreadsheet format (item f), noting which studies were presented previously (items a–d).

f) Evidence table spreadsheets (noted above) of all published and unpublished trials. A standard evidence table format, such as that contained in Appendix C, Template for P&T Monograph, should include the following data elements:

- Citation, if published
- Design
- Sample size
- Inclusion/exclusion criteria
- Endpoints
- Statistical significance
- Study dates
- Results
- Treatments

2.3 CLINICAL AND DISEASE MANAGEMENT INTERVENTION STRATEGIES [3 PAGES MAXIMUM]

Identify and summarize any proposed ancillary disease or care management intervention strategies that are intended to accompany the product at launch.

2.4 OUTCOMES STUDIES AND ECONOMIC EVALUATION SUPPORTING DATA [2 PAGES MAXIMUM PER STUDY]

Concern has been expressed over the quality of some published economic evaluations.[3, 4, 11] Since the focus of this portion of the dossier is a comprehensive assessment of available evidence, the number of studies considered will not be restricted by imposing methodological standards. However, [– –] and its consultants will judge the merit of individual studies based on published standards for conducting and reporting these analyses.[4–12]

Provide summaries addressing items a–m *(see 2.1 starting on page 11)* for all studies in each of the categories listed below (items a–d). [– –] is particularly interested in head-to-head comparison studies between the proposed product and the principal comparators. Analyses that focus on actual outcomes rather than intermediate endpoints are preferred. Summaries of principal trial results of key comparator products when these data are referenced or used in economic models are extremely helpful, but not required. Discuss important study findings and comment on their implications for the patient populations of [– –]. In the appendix, include a reprint of each study discussed or referenced:

a) Prospective cost-efficacy studies [No more than two (2) pages per study + evidence table]

b) Prospective cost-effectiveness studies trials [No more than two (2) pages per study + evidence table]

c) Cross-sectional or retrospective costing studies, treatment pattern studies or

economic evaluations [No more than two (2) pages per study + evidence table]

d) Review articles

e) Spreadsheet of all published and unpublished economic evaluations utilizing the format specified in Section 2.2, Item (f), noting which studies were presented previously (items a–d).

3. MODELING REPORT [MAXIMUM 20 PAGES]

3.1 MODEL OVERVIEW

Properly constructed economic and budget impact models can combine treatment effectiveness, the resources consumed (and costs) by each treatment process, and a measure of uncertainty in any estimates. The goal is to project the health and economic consequences of [– –] formulary changes. Models developed in this manner can:

- Aid decisions regarding the addition of a new product to the formulary,
- Help define a product's specific role, and
- Assist in creating benchmarks against which the product's future performance can be measured.

Specifically, these analyses should depict the following:

a) Disease or condition, patient population, natural history, clinical course and outcomes.

b) Primary treatment options and the treatment process for each option. Each process of treatment utilizing a specific product or other intervention follows a clinical pathway. If the [– –] employs a treatment guideline for this condition, this framework should be followed. Alternative clinical pathways presented by the manufacturer may also be considered.

c) Patient population eligible for treatment.

d) Product and other medical resources used when following clinical pathway (include treatments for complications related to treatment).

e) Costs of product and other medical resources consumed within each clinical pathway.

f) Outcomes of therapy for each clinical pathway, including expected proportion of treatment failures and mean or median time to failure, if known. These outcomes can be broadly and uniquely defined by the manufacturer and can be modeled from other data sources. The manufacturer should address the relevance of the selected outcomes measure and generate both baseline and projected outcome impact assessments.

g) Incremental cost and outcomes analysis presented in either cost/consequences tables or as cost-effectiveness ratios.

h) Time horizon for expected costs and outcomes. Suggested time horizons include 1-year, 5-year and over the course of the disease. The exact time horizon used

will depend on the natural course of the disease. In some cases, multiple time horizons might be appropriate.

In addition, the manufacturer is requested to:

i) Separate the volume of resources utilized and the unit costs for each resource.

j) Perform sensitivity analyses on pivotal estimates and assumptions and display a one-way sensitivity analysis of all variables in a tornado diagram.

k) Consult with [– –] staff in the early stages of model development to ensure the incorporation of appropriate comparator products and endpoints.

l) Present the following information in tabular form: data and sources, assumptions, total resource utilization, total costs, total effectiveness, incremental costs, and incremental effectiveness. Measures of total and incremental effectiveness should incorporate natural units (e.g., clinically important events avoided) as well as quality-adjusted survival when possible.

The analysis should be based on scientifically appropriate clinical trial, epidemiological and economic data and should be capable of being modified by [– –] to better reflect practice patterns in their enrolled population. For the analysis and model to be realistic, it may be necessary to include data from [– –], e.g., demographic data. Data derived from expert panels are not generally acceptable, especially for key clinical and treatment pattern variables. But this approach may be understandable for other variables where estimates are not available through literature, databases, trials or other normal sources.

The model framework should consider recommendations published by the *Panel on Cost-Effectiveness in Health and Medicine* convened by the U.S. Public Health Service.[8] Although no standard model approach is proposed, good modeling practices should always be followed. We have found that models have certain desirable qualities. These are listed below and are in no way meant to proscribe model development or impede good scientific design. Rather, this list is to provide some guidance to the manufacturer as to those elements of an economic model that are desirable to [– –] evaluators.

Desirable Qualities of Economic Models for Inclusion in [– –] Submissions

Model Structure

- A transparent disease progression model with an appropriate time horizon for a health system.
- Treatment pathways that are relevant to the formulary decision and correspond to nationally recognized or [– –] treatment guidelines. To help illuminate the proposed treatment pathways, the manufacturer is encouraged to provide decision trees.
- Usual clinical practice, including relevant comparators to [– –], is included in the model.
- Mathematics and calculations included in the model are accurate and available for inspection.
- Allowance for analysis of relevant sub-populations (age, gender, co-morbidities) where applicable.
- An interactive model that allows the health system to incorporate its own data

(membership size, prevalence rates, cost estimates, etc.) or, if requested, use default data, such as national norms.

Data

- Sources of data are clearly defined and from the most recent studies.
- Data have been interpreted and accurately incorporated into the model.
- Uncertainty is defined, especially for key variables.
- Linkages between intermediate and longer-term endpoints are valid and based on reasonable scientific evidence.
- Assumptions that drive the model are clearly identified.

Results/Output

- Outcomes need to be relevant to the [– –] formulary decision.
- Incremental analyses of both health effects and costs.
- Results are verifiable and traceable back to the inputs.
- Uncertainty in model and data tested in a reasonable fashion and reported.
- A tornado diagram depicting the results of a comprehensive (on all variables) one-way sensitivity analysis.
- Results presented in such a fashion that facilitates incorporation into drug reviews and monographs.

The model's time frame is a critical element. For chronic illnesses, a one to three-year period should be adopted as well as a longer period, as appropriate for the clinical problem and its resolution. For this longer period, a final and disease appropriate health outcome determination is recommended, possibly including more patient-centered outcomes, such as Quality of Life Year Saved. For acute illness, shorter periods may be appropriate.

3.2 PARAMETER ESTIMATES FOR MODELS

Randomized, controlled efficacy studies are required for licensing and registration. These data comprise the foundation for FDA approval, labeled indications and marketing. [– –] recognizes that manufacturers must conduct these studies for the FDA. In addition, [– –] recognizes that the results observed in randomized trials are likely to represent optimal effects and are difficult to generalize to populations because of patient selection and the close oversight given subjects in clinical trials.

In general, the best quantitative estimates of clinical effectiveness are required, with uncertainty in the estimate(s) handled analytically via sensitivity analysis. Thus, where possible, feasible and scientifically plausible, scientists preparing the economic model are encouraged to attempt transformation of efficacy results into effectiveness parameters. This may involve inclusion of an adherence parameter into the model or may involve the creative use of retrospective data. Documentation and clear description of the methodology will be necessary in order for [– –] staff to evaluate the validity of this approach.

Translation of claims from an efficacy to an effectiveness context should be considered when:

a) The model's treatment period extends beyond that represented by the clinical trial;

b) Outcomes supported by the trial are intermediate or surrogate in nature;

c) Compliance, dosing, co-morbid conditions and the population of interest (e.g., children, elderly) are expected to differ from the efficacy trial data.

Poor adherence to therapy, especially for chronic conditions, can impact manufacturer claims that are based exclusively on carefully monitored clinical efficacy trials. All claims (promotional or otherwise) made for new products should state clearly the assumptions concerning patient adherence. It is suggested that manufacturers provide documentation of anticipated adherence patterns from populations similar to the treatment populations of [– –], if available. This may be more plausible for manufacturers who have launched products in other countries before the US introduction.

3.3 PERSPECTIVE, TIME HORIZON AND DISCOUNTING

The payer perspective is recommended for the primary analysis. We welcome a societal perspective analysis as a secondary evaluation. The analytic model should consider a time horizon that is appropriate to the disease being studied and reflect the decision-making and financial and budget constraints of [– –]. When appropriate, adjustment for the time preference should be incorporated and should follow US PHS Panel recommendations.[8]

3.4 ANALYSES

Analyses should follow accepted approaches for economic models. Transparency and clarity of presentation make for understandable modeling exercises. [– –] staff needs to be able to understand all steps in the modeling process, so researchers are encouraged to spend time thinking about clarity and transparency of results.

<u>All assumptions must be presented and justification should be attempted.</u>

A tornado diagram with a comprehensive (all variables) one-way sensitivity analysis is highly recommended. Base case and other appropriate sensitivity analyses also are recommended. Confidence interval determination, best/worse case scenario analyses, net-benefit and acceptability curve estimation are allowable as necessary and appropriate.

When a product is to be used in the treatment of more than one disease, its impact should be modeled for each approved indication, unless a reasonable case can be made for a single model. Because of the complexity involved in constructing a model that simultaneously addresses several indications, we recommend using a separate model for each condition.

3.5 PRESENTATION OF MODEL RESULTS

Results should be presented as follows:

a) Disaggregated results (cost-consequence presentation style) should be presented before viewing incremental cost-effectiveness ratios. These data are more easily understood and interpretable by the [– –] formulary committees.

b) Costs should be presented as total medical and pharmacy costs of introduction

of the new product and then disaggregated into various resource components including drug costs. Estimates must include the cost of any additional resources associated with implementing the therapy (e.g., disease management).

c) Health effects should be presented in disaggregated form before inclusion in a ratio.

d) Sensitivity analyses are to be shown in tabular or graphical form (tornado diagram), with the base case results displayed alongside.

e) Factors that drive the cost and cost-effectiveness results must be presented clearly (for example, tornado diagrams).

3.6 EXCEPTIONS

A pre-existing model developed for another health system or for another country may eliminate the need to develop a new model for this submission. A model based on national norms may also be acceptable provided it is submitted in such a manner (spreadsheet) that [...] can either use the default values or insert its own. To be acceptable, the existing model should follow the general framework described in this document and must be able to demonstrate the system-wide impact of introducing the product to [– –] formularies. It is the manufacturer's responsibility to justify the adequacy of pre-existing models. Developing a model that can be adaptable and allow [...] to make changes in multiple elements will greatly enhance this process.

4. PRODUCT VALUE AND OVERALL COST [2 PAGE MAXIMUM]

This section of the submission requirements represents the principal opportunity for a manufacturer to communicate the value of its product to [– –]. The manufacturer should briefly summarize the information presented previously, state the expected per unit product cost, and estimate the total pharmacy expenditures of [– –] for the product. Based on this information, the manufacturer should articulate a value argument to justify these expected expenditures for this product in the context of its anticipated effects on the clinical and other outcomes and the economic consequences for [– –] and its clients and members. Through this process, product value is redefined as both parties move beyond cost containment to focus on optimizing drug utilization in an environment of limited resources.

5. SUPPORTING INFORMATION

5.1 REFERENCES CONTAINED IN DOSSIERS

Submissions should list and provide copies of all clinical and pharmacoeconomic references made in Sections 2 and 3 above.

5.2 ECONOMIC MODELS

Media: In addition to the written report, the manufacturer must provide a transparent, unlocked copy of the model without the graphical interface. It should be presented on a

3.5" disk or CD-ROM as an Excel workbook, ASCII tab-delimited file or an alternative format that is agreed upon by [– –] or its consultants and the manufacturer. The model should be transparent, i.e., designed to allow staff or consultants to investigate the assumptions and calculations, and to perform independent sensitivity analyses by varying individual parameters. **[...] will retain this model for internal analyses and *will not release it to any other party*.** Manuscripts that support the development and reporting of the model are to be attached as appendices.

5.3 FORMULARY SUBMISSION CHECKLIST

A. SUBMISSION PROCESS		
A.1 Have you met with [– –] staff to review the submission process?	Yes	No
A.2 Have you agreed to the submission date with [– –]?	Yes	No
A.3 Have you requested estimates to identify baseline characteristics of the populations of the health systems represented by [– –]?	Yes	No
A.4 Have you included an explanation for any missing data? (Check yes if N/A)	Yes	No
A.5 Have you submitted a copy of the dossier in both paper and electronic form?	Yes	No

A completed formulary submission checklist should accompany each submission.

B. PRODUCT INFORMATION		
B.1 Has a product description been provided for the product?	Yes	No
B.2 Has a list of approved indications been given for the product?	Yes	No
B.3 Has the place of this product in therapy been given for each indication?	Yes	No
B.4 Have copies been provided of treatment guidelines for this product?	Yes	No
B.5 Have intermediate and final outcomes of therapy for this product been listed?	Yes	No
B.6 Have you listed any co-prescribed drugs for this product by indication?	Yes	No
B.7 Have you identified the comparator drugs for this product by indication?	Yes	No

HEALTH SYSTEM GUIDELINES FOR MANUFACTURERS

(Evidentiary Requirements for Formulary Submission Dossiers)

C. SUPPORTING CLINICAL INFORMATION		
C.1 Have you identified all relevant clinical and other studies for the product and its comparators?	Yes	No
C.2 Are copies of all summarized studies included in the submission package?	Yes	No
C.3 Have you provided an electronic spreadsheet summary of all studies identified using the [– –] format?	Yes	No
C.4 Have you included all relevant non-experimental studies for the product?	Yes	No
C.5 Have you provided an electronic spreadsheet summary of all non-experimental studies using the [– –] format?	Yes	No

A brief explanation for all missing data should also be included.

D. SUPPORTING ECONOMIC INFORMATION		
D.1 Have you identified all relevant pharmacoeconomic (PE) studies for the product?	Yes	No
D.2 Are copies of all summarized studies included in the submission package?	Yes	No
D.3 Have you justified the relevance of these PE studies for this population?	Yes	No
D.4 Have you provided an electronic spreadsheet summary of the PE studies?	Yes	No
D.5 Will a disease or care management strategy be employed with the introduction of this product?	Yes	No
D.6 Is documentation on this intervention program included in the submission?	Yes	No

E. ECONOMIC MODEL		
E.1 Are the model structure, data and assumptions transparent and clearly presented for a non-economist reader?	Yes	No
E.2 Is an unlocked spreadsheet version of the model included with the submission?	Yes	No
E.3 Are the results presented in a style suitable for [– –] formulary committee evaluation?	Yes	No

TERMS AND DEFINITIONS

Care pathways: A general method of using predetermined, time-staged, evidence-based actions for managing the care of patients who have clearly defined diagnoses or require certain procedures. Ideally, care pathways should be applicable to the management of patients moving among a managed health care system's multiple levels of care and practice settings. Other terms for care pathways include clinical care plans, clinical pathways, critical pathways, care guides, and care maps.

Dossier: A detailed report (in paper and electronic form) for each product submitted by the manufacturer for consideration that contains (1) clinical and economic data from published and unpublished studies and (2) a disease-based economic model to project the potential impact that introducing the product would have on health and economic consequences occurring across the entire system.

Effectiveness: The actual effects of treatment by the drug under "real life" conditions [patients not always remembering to take their doses, physicians often not prescribing the lowest FDA-recommended doses, side effects not all controlled, etc]. 'Head to head' effectiveness studies with similar medications are preferable.

Efficacy: The potential effects of treatment by the drug under optimal circumstances [e.g., patients all taking their doses at the right times, physicians prescribing FDA-recommended doses, side effects appropriately monitored, etc]. Efficacy studies are typically the foundation of new drug submissions to the FDA. Studies that compare the efficacy of similar drugs, rather than just efficacy compared to placebo are preferable.

Formulary: A periodically updated list of medications, related products and information, representing the clinical judgment of physicians, pharmacists, and other experts in the diagnosis and/or treatment of disease and promotion of health.

Formulary system: An ongoing process whereby a health care system, through its physicians, pharmacists and other health care professionals, establishes policies on the use of drugs, related products and therapies, and identifies drugs, related products and therapies that are the most medically appropriate and cost-effective to best serve the health interests of the patient populations of the health systems it represents.

Modeling: A quantitative modeling method used to estimate the impact of formulary changes on: 1) potential health outcomes; 2) total costs of drug and medical care in a population. One possible use of cost and outcomes modeling, for example, is to extrapolate trial-based efficacy data into effectiveness and cost-effectiveness endpoints of relevance to health care systems. Cost and outcomes impact data from models can then be used to assess the health and overall fiscal consequences of formulary changes.

REFERENCES

[1] Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the *BMJ*. The *BMJ* Economic Evaluation Working Party. *BMJ* 1996; 313:275–83.

[2] Task Force on Principles for Economic Analysis of Health Care Technology, Economic Analysis of Health Care Technology, *Annals of Internal Medicine*, 1995; 123:61–70

[3] Hillman AL, Eisenberg JM, Pauly MV, Bloom BS, Glick H, Kinosian B, Schwartz JS. Avoiding bias in the conduct and reporting of cost-effectiveness research sponsored by pharmaceutical companies. *N Engl J Med* 1991; 324:1362–5.

[4] Agro KE, Bradley CA, Mittmann N, et. al. Sensitivity analysis in health economic and pharmacoeconomic studies: an appraisal of the literature. *PharmacoEconomics* 1997; 11(1):75–88.

[5] Detsky AS. Guidelines for economic analysis of pharmaceutical products: a draft document for Ontario and Canada. *PharmacoEconomics* 1993; 3(5):354–61.

[6] Drummond MF, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programs. Oxford, Oxford University Press, 1987.

[7] Glick H, Kinosian B, Schulman K. Decision analytic modeling: some uses in the evaluation of new pharmaceuticals. *Drug Information Journal* 1994, 28:691–707.

[8] Gold MR, Siegel JE, Russell LB, Weinstein MC. Cost-Effectiveness in Health and Medicine. New York, NY, Oxford University Press, 1996.

[9] Henry D. Economic analysis as an aid to subsidisation decisions: the development of Australian guidelines for pharmaceuticals. *PharmacoEconomics* 1992; 1:54–67.

[10] Johannesson M, Jönsson B, Göran K. Outcome measurement in economic evaluation. *Health Econ* 1996;5:279–96.

[11] Kassirer JP, Angell M. The journal's policy on cost-effectiveness analyses. *N Engl J Med* 1994; 331:669–70.

[12] Sheldon TA. Problems of using modeling in the economic evaluation of health care. *Health Econ* 1996;5:1–11.

[13] Langley PC, Sullivan SD. Pharmacoeconomic evaluations: guidelines for drug purchasers. *J Managed Care Pharm* 1996;2:671–77.

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

[15] *Principles of a Sound Drug Formulary System*. consensus document. October 2000. http://www.amcp.org/publications/drugformulary.pdf

[16] Drummond M. Should commercial-in-confidence data be used by decision makers

APPENDIX A — Guidelines for Authors and Peer Reviewers of Economic Submissions to the *British Medical Journal*

***BMJ* 1996;313:275–283 (3 August)**

M F Drummond, *chair of working party*
chedir@york.ac.uk,[a] **T O Jefferson**, *secretary of working party*
ak15@dial.pipex.com,[b] on behalf of the BMJ Economic Evaluation Working Party

[a] Centre for Health Economics, University of York, York YOI 5DD, [b] Ministry of Defence, Army Medical Directorate 5, Keogh Barracks, Ash Vale, Hampshire GUI2 5RR

Members of the working party are listed at the end of the paper. Correspondence to: Dr Jefferson.

Over the past decade interest in the economic evaluation of health care interventions has risen.[1] Reviews of published studies have, however, shown gaps in the quality of work.[2 3 4 5] As far back as 1974 Williams listed the essential elements of economic evaluations,[6] and more recently Drummond and colleagues set out the methodological areas generally agreed among economists.[7] Guidelines for economic evaluations have been promulgated and reviewed by many bodies,[8 9 10 11 12 13 14] but few medical journals have explicit guidelines for peer review of economic evaluations or consistently use economist reviewers for economic papers even though they are a major publication outlet for economic evaluations.[15 16 17] In January 1995 the *BMJ* set up a working party on economic evaluation to improve the quality of submitted and published economic articles.

It was not our intention to be unduly prescriptive or stifle innovative methods; our emphasis is on improving the clarity of economic evaluations. We also did not address those issues of conduct that have been emphasised in other guidelines.[13 14 15 16 17 18]

The working party's methods

The working party's objectives were to improve the quality of submitted and published economic evaluations by agreeing acceptable methods and their systematic application before, during, and after peer review. Its task was to produce: (a) guidelines for economic evaluation, together with a comprehensive supporting statement which could be easily understood by both specialist and non-specialist readers; (b) a checklist for use by referees and authors; and (c) a checklist for use by editors.

In producing the guidelines the working party has concentrated on full economic evaluations comparing two or more health care interventions and considering both costs and consequences.[19] Articles sent to the *BMJ* and other medical journals are often more broadly based "economic submissions,"[20] which comprise essentially clinical articles that report approximate cost estimates or make statements that a given treatment was "cost effective."

We took the view that submissions reporting partial evaluations, such as a costing study or an estimate of the value to individuals of improved health, should adhere to the relevant sections of the guidelines given below, as should anecdotal reports or commentaries drawing economic conclusions about alternative forms of care. In addition to a referees' (and authors') checklist, therefore, the working party has produced shorter checklists to help *BMJ* editors distinguish between full economic evalu-

APPENDIX A — Guidelines for Authors and Peer Reviewers of Economic Submissions to the *British Medical Journal*

ations and other types of economic submission and to help them decide which articles should be sent to referees. The main checklist and the editors' checklists are given in the boxes and a flow chart explaining their use is given in figure 1. The checklists do not replace the need for an overall judgment on the suitability of a paper.

Drafts of the guidelines and their supporting statement and the checklists have been circulated to health economists and journal editors and were debated at the biannual meeting of the UK Health Economists' Study Group in January 1996. A survey of members attending the meeting was used to identify those items of the full referees' checklist that should be used by editors.

The final document reflects a broad consensus among the working party. Any differences reflect different perspectives on the role of economic evaluation and the extent of members' interests in particular aspects of methodology rather than basic differences over the need to improve standards of reporting.

Finally, in drafting the guidelines, the working party recognised that authors may not be able to address all the points in the published version of their paper. This being so, they may care to submit supplementary documents (containing, for example, the details of any economic model used) or refer the reader to other published sources.

Guidelines for submission of economic evaluations

The guidelines are given below, grouped in 10 sections under three headings: study design, data collection, and analysis and interpretation of results. Under each section is a commentary outlining the reasons for the requirements and the main unresolved methodological issues and explaining why firm guidelines cannot be given in some cases. The guidelines are designed to be read in conjunction with other more general guidance to authors from the BMJ and the existing BMJ guidelines on statistical methods.[21]

Study design (1) STUDY QUESTION

- The economic importance of the research question should be outlined.
- The hypothesis being tested, or question being addressed, in the economic evaluation should be clearly stated.
- The viewpoint(s) — for example, health care system, society — for the analysis should be clearly stated and justified.

The research question, or hypothesis, needs to satisfy three criteria.

Firstly, the question should be economically important (in terms of its resource implications) and be relevant to the choices facing the decision maker. The question "Is health promotion worthwhile?" does not meet this criterion because it fails to specify alternatives — worthwhile compared with what? Furthermore, any alternatives need to be realistic. An option of "doing nothing," or maintaining the status quo, should be included when appropriate.

Secondly, the question should be phrased in a way that considers both costs and outcomes. The research question "Is drug X more costly than the existing therapy?" will

APPENDIX A — Guidelines for Authors and Peer Reviewers of Economic Submissions to the *British Medical Journal*

provide incomplete information because the decision maker also needs to consider comparative effectiveness.

Different forms of economic evaluation

Study type	Measurement of benefits	Question posed
Cost minimisation analysis	Benefits found to be equivalent	Which is the most efficient way of achieving a given goal (or objective)?
Cost effectiveness analysis Cost-utility analysis	Natural units (eg life years gained) or Healthy years (eg quality adjusted life years, healthy years equivalents)	What is the most efficient way of spending a given budget?
Cost-benefit analysis	Monetary terms	Should a given goal (or objective) be pursued to a greater or lesser extent?

Thirdly, the research question should clearly state the viewpoint of the economic evaluation, and this should be justified. Possible viewpoints include those of the provider institution, the individual clinician or professional organisation, the patient or patient group, the purchaser of health care (or third party payer), and society itself. For example, hospital and other providers may need information to help in making procurement and related technology management decisions; individual clinicians to inform patient care decisions; health insurers or purchasers to support decisions on whether to pay for a procedure or which services to develop; and patients to know the level of costs they may incur in travelling to hospital or providing informal nursing care at home. The viewpoint chosen will in turn influence both the costs included in the evaluation — for example, whether to limit these to a given department, hospital, or locality and whether patient costs are included — and the types of outcome measured — for example, disease specific outcomes or generic measures of patients' quality of life.

Health economists generally advocate adopting the broader societal viewpoint when possible. This is because data can usually be disaggregated and the analysis carried out from a number of viewpoints. Also, the additional cost of adopting a broader perspective at the outset of a study is probably less than the cost of attempting to gather additional information later. Researchers should therefore identify key potential decision makers (government, purchaser, or provider) at the outset and be able to show that the research question posed will meet the needs of all key groups.

(2) SELECTION OF ALTERNATIVES

- The rationale for choice of the alternative programmes or interventions for comparison should be given.
- The alternative interventions should be described in sufficient detail to enable the reader to assess the relevance to his or her setting — that is, who did what, to whom, where, and how often.

APPENDIX A — Guidelines for Authors and Peer Reviewers of Economic Submissions to the *British Medical Journal*

The choice of the alternative must be designed to help get as close a measure as possible of the opportunity cost of using the new treatment. In principle the comparator should be the most cost effective alternative intervention currently available. In practice the comparator is usually the most widely used alternative treatment. Unless current practice is "doing nothing," it is usually best not to use placebo as the comparator. Such a study could, however, if well conducted and reported, provide information for use in conjunction with studies of other treatments also compared with placebo.

The alternatives being compared should be described in enough detail to enable the reader to relate the information on costs and outcomes to the alternative courses of action. The use of decision trees and other decision analytic techniques (discussed in section 7) can help to clarify the alternative treatment paths being followed and provide a framework for incorporating cost and outcome data. Clear exposition of alternative treatment paths and the probabilities, cost, and outcomes linked to them should enable decision makers to use those parts of the analysis that are relevant to their viewpoint.

(3) FORM OF EVALUATION

- The form(s) of evaluation used — for example, cost minimisation analysis, cost effectiveness analysis — should be stated.
- A clear justification should be given for the form(s) of evaluation chosen in relation to the question(s) being addressed.

There are two types of question which require the use of different forms of evaluation (see box).

The first is: "Is it worth achieving this goal?" or "How much more or how much less of society's resources should be allocated to pursuing this goal?" Such questions can be answered formally only by the use of cost-benefit analysis. Looking at one intervention alone, cost-benefit analysis addresses the question of whether its benefits are greater than its costs — that is, the best alternative use of the resources. When several competing interventions are being considered the costs and benefits of each should be examined and that combination which maximises benefits chosen.

The main practical problem with cost-benefit analysis is that of valuing benefits, such as the saving of life or relief of pain, in money units. However, if we are to examine whether more or less should be spent on health care, we need to find a way of comparing the costs (benefits forgone elsewhere) with the benefits of improved health and any other resulting benefits. Even when all benefits cannot be measured in terms of money, cost-benefit analysis provides a useful framework for structuring decision making problems.

The second type of question is: "Given that a goal is to be achieved, what is the most efficient way of doing so?" or "What is the most efficient way of spending a given budget?" Such questions are addressed by cost effectiveness analysis, which can take one of two forms. In the first the health effects of the alternatives are known to be equal, so only the costs need to be analysed, and the least costly alternative is the most efficient. This type of analysis is often referred to as cost minimisation analysis. Secondly, alternatives may differ in both cost and effect, and a cost effectiveness ratio (cost per unit of health effect) is calculated for each. For example, given a fixed budget

APPENDIX A — Guidelines for Authors and Peer Reviewers of Economic Submissions to the *British Medical Journal*

for dialysis, the modality (home dialysis, hospital dialysis, or continuous ambulatory peritoneal dialysis) with the lowest cost per life year saved would, if implemented, maximise the amount of life years produced by the dialysis programme. In practice, however, the selection of the most efficient mix of programmes, given a budget constraint, is more complicated: it depends on whether alternative programmes are mutually exclusive and whether the scale of programmes can be changed without changing their incremental cost effectiveness ratios.

The concept "within a given budget" is also crucial. Often authors produce a ratio of extra costs per extra unit of health effect for one intervention over another and argue that a low cost effectiveness ratio, relative to other existing health care programmes, implies that a given intervention should be provided. However, judgment is still required as the resources to meet such extra costs would inevitably come from another programme, from within or outside health care. (This point is returned to in section 10.)

The third category of evaluation, cost-utility analysis, lies somewhere between cost effectiveness and cost benefit analysis. It can be used to decide the best way of spending a given treatment budget or the health care budget. The basic outcome of cost-utility analysis is "healthy years." Years of life in states less than full health are converted to healthy years by the use of health state preference values, resulting in generic units of health gain, such as quality adjusted life years (QALYs) or healthy years equivalents.[22] (These approaches are discussed in section 5.)

Data Collection (4) EFFECTIVENESS DATA

- If the economic evaluation is based on a single effectiveness study — for example, a clinical trial — details of the design and results of that study should be given — for example, selection of study population, method of allocation of subjects, whether analysed by intention to treat or evaluable cohort, effect size with confidence intervals.
- If the economic evaluation is based on an overview of a number of effectiveness studies details should be given of the method of synthesis or meta-analysis of evidence — for example, search strategy, criteria for inclusion of studies in the overview.

Economic evaluation of interventions relies on the assessment of their clinical effectiveness. The data can come from a single clinical study, a systematic overview of several studies, or an ad hoc synthesis of several sources. Any limitations which weaken the assessment of effectiveness weaken any economic evaluation based on it. The gold standard for assessing the efficacy of interventions is the randomised, double blind controlled trial. This design has the highest internal validity — that is, freedom from bias.

In most clinical trials the primary assessment is based on an intention to treat analysis, which assesses the clinical outcomes of all randomised patients, whether or not they completed their allocated treatment. Other analyses serve as secondary or exploratory analyses in clinical studies and should be justified if used as the primary analysis for the economic evaluation.

APPENDIX A — Guidelines for Authors and Peer Reviewers of Economic Submissions to the *British Medical Journal*

Clinical trials may include active or placebo controls. In active controlled studies the appropriate comparator for economic analysis is the most cost effective available therapy, or the most widely used therapy. In placebo controlled studies the economic analysis should indicate whether there are active comparators that could be considered as alternative therapies.

The generalisability of the study population is important in assessing the results of clinical trials and hence their suitability for economic evaluations. Factors that can limit generalisability include: differences across countries or health systems; costs and benefits resulting only from the trial protocol but which would not arise in practice; unrealistically high compliance rates; or the appropriateness of usual practice in clinical studies that compare a therapy with best usual care. Clinical data from studies employing a "pragmatic" protocol are often more generalisable and hence preferable for economic evaluation.

In a pragmatic trial subjects are still randomised to treatment groups, but the patient and doctor may not necessarily be blind to the treatments. The treatment protocol is also kept as close to normal care as possible and monitoring kept to a minimum. Such trials are attractive for economic analysis since they reflect what may happen in practice, but the results apply only to similar settings. Unfortunately many clinical studies are still performed under fairly restrictive conditions, so some adjustments may be required for economic evaluation (discussed below).

Clinical data can also be generated from overviews or syntheses of clinical literature. Before the data from any such overview are used in economic assessments the methods used for the overview, including the search strategy and the criteria for inclusion and exclusion of studies, need reporting.

Effectiveness data from overviews have the advantage that the confidence interval around the point estimate of clinical effect is usually narrower than that from an individual trial and the result may be more generalisable.[23] Typically the economic analyst would take the point estimate of effect from the overview as the base case value and use the confidence interval as the relevant range for sensitivity analysis (see section 9).

Sometimes clinical trial data may be insufficient for economic evaluation because some of the relevant endpoints have not been measured, patients have not been followed for long enough, or the design was not pragmatic. In such cases it may be possible to adjust or supplement the data by modelling.

Ad hoc synthesis of effectiveness data from several sources, including expert opinion, is justifiable when no relevant well controlled clinical studies have been performed.[24] In many cases the economic evaluation may be based on a previously published clinical trial or systematic overview. In such a case it would be sufficient to provide a brief summary, addressing the points in the guidelines, and to refer the reader to the published source.

(5) BENEFIT MEASUREMENT AND VALUATION

- The primary outcome measure(s) for the economic evaluation should be clearly stated — for example, cases detected, life years, quality adjusted life years (QALYs), willingness to pay.

APPENDIX A — Guidelines for Authors and Peer Reviewers of Economic Submissions to the *British Medical Journal*

- If health benefits have been valued details should be given of the methods used — for example, time trade off, standard gamble, contingent valuation — and the subjects from whom valuations were obtained — for example, patients, members of the general public, health care professionals.
- If changes in productivity (indirect benefits) are included they should be reported separately and their relevance to the study question discussed.

In cost effectiveness analysis benefits are usually measured in natural units. For programmes whose main effect is to extend life the usual measure is life years gained. When the main effect is on quality of life a disease specific or generic quality of life index might be used.

Sometimes the benefit measure may be an intermediate marker rather than a final outcome. For example, in comparing programmes for preventing coronary heart disease reductions in blood pressure might be used. Similarly, if two antenatal screening programmes are being compared cases detected might be chosen. Such intermediate endpoints need to be justified, however, as they may be poor surrogates for final outcomes.

Only a single measure can be used in the calculation of a given cost effectiveness ratio. It cannot reflect the effects of a particular intervention on both quantity and quality of life; nor can more than one aspect of quality of life be expressed. This restriction is the main limitation of cost effectiveness analysis, as other important benefits may be overlooked. Nevertheless, several cost effectiveness ratios could be calculated relating to different outcomes — but this may lead to problems of interpretation. Authors using cost effectiveness analysis should explain why they have chosen a particular outcome measure for calculation of the ratio and reassure the reader that important outcomes are not being overlooked.

In cost-utility analysis the outcome is healthy years. Quality adjusted life years measure healthy years by combining data on the life years gained by programmes with a value (usually obtained from samples of patients or the population in general) reflecting the quality of those years. Two years of life in a health state judged to be halfway between death and full health would be equivalent to one year in full health. Incremental health gain is given by the difference in quality adjusted life years produced by one intervention as compared to another.

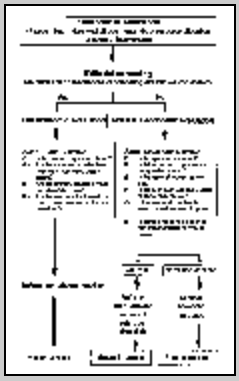
Rather than obtaining valuations for each health state and then multiplying by the time spent in each, the use of healthy years equivalents requires a scenario of a specified sequence of health states and their duration. Respondents are asked how many healthy years of life this scenario is equivalent to — hence the term “healthy years equivalents.”

Most methods of measuring quality adjusted life years and healthy years equivalents are based on the notion of sacrifice. In economics something is not of value unless one is prepared to give up something else in order to get it. For example, using a time trade off a respondent is asked how many years of life in a health state he or she would be prepared to give up to be in full health. Using a “standard gamble” the respondent is asked to choose between a certain health state and a gamble with two possible outcomes (one worse and the other better than the health state being valued).

APPENDIX A —

Guidelines for Authors and Peer Reviewers of Economic Submissions to the *British Medical Journal*

Estimates obtained by time trade off methods reflect respondents' attitudes to time as well as their attitudes to the health state being valued. Likewise, estimates obtained by standard gamble methods reflect respondents' attitudes to risk as well as their attitudes to the health state being valued. Economists are still debating which approach is most desirable.



Manuscript management flow diagram and checklists for editors

See page 43

Another cheaper approach is to include in the clinical trial a generic health state preference instrument, such as the EuroQoL (EQ5D)[25] or McMaster health utilities index.[26] The responses from patients to a simple questionnaire can then be expressed as a health state preference value by reference to pre-scaled responses (obtained by standard gamble or time trade oft) from a relevant reference group.

Values can be provided by the population at large or by a sample of patients with the condition for which the treatment is being evaluated. The choice depends on the perspective of the study. If the issue is allocating resources between competing programmes the former might be used; if it is deciding the best way to treat a given condition the latter might be used. In reporting their results authors should explain why a particular source of values has been used.

In cost-benefit analysis the benefits of health care are traditionally valued in money terms by using either the human capital approach or the willingness to pay approach. The former values a health improvement on the basis of future productive worth to society from being able to return to work. Values have to be imputed for activities such as homemaking, so the human capital approach suffers from problems of how to value health improvements for retired and unemployed people.[27] This fairly narrow view of the value of improved health is rarely used nowadays.

Debate continues about whether productivity gains from improved health ("indirect benefits") should be included alongside other measures of the value of improved health. Some analysts argue it introduces inequalities between those interventions that are aimed at individuals who could potentially return to productive activity return to productive activity and those that are not. Other researchers are concerned about the potential for double counting if indirect benefits are calculated alongside another method of valuing improved health. Finally, some researchers are concerned about the standard method of measuring productivity gains, which values work days lost by gross earnings. Koopmanschap et al have proposed an approach for measuring productivity changes,

APPENDIX A — Guidelines for Authors and Peer Reviewers of Economic Submissions to the *British Medical Journal*

called the friction cost method, which recognises that the amount of production lost due to disease depends on the time an organisation needs to restore the initial production level.[28] Whatever estimation method is used, indirect benefits should be reported separately so that readers can decide whether or not they should be included in the overall result of the study.

The other approach values health improvement (or types of health care) on the basis of people's willingness to pay for them — usually associated with individuals' ability to pay. If diseases affect rich and poor in different proportions, and if richer people tend to have different preferences from poor people, then treatment of diseases of the rich may appear to be "valued" more highly. A willingness to pay value will, to an extent, reflect ability to pay as well as strength of preference. It is the latter (strength of preference) which reflects "values," so when using willingness to pay a check is needed for its association with income and social class.

Willingness to pay has advantages over techniques like quality adjusted life years since the latter focuses on valuation of health gains only, while willingness to pay permits respondents to take into account other factors (such as the value they attach to the process of care). In some cases health gain is not even an issue. For example, two different ways of screening may simply provide information in different ways from those screened,[29] and respondents will still have preferences which can be assessed by use of willingness to pay. Also, in some situations individuals other than the patient may be willing to pay for improved health — for example, in the case of communicable diseases.

(6) COSTING

- Quantities of resources should be reported separately from the prices (unit costs) of those resources.
- Methods for the estimation of both quantities and prices (unit costs) should be given.
- The currency and price date should be recorded and details of any adjustment for inflation, or currency conversion, given.

Costing involves estimating the resources used — for example, days in hospital — and their prices (unit costs). These estimates must be reported separately to help the reader judge their relevance to his or her setting. When there are many cost items reporting should concentrate on the main costs.

When economic evaluations are undertaken alongside clinical trials data on physical quantities may be gathered as part of the trial. The interpretation of resource use resulting from the trial protocol may, however, prove difficult. One view is that everything done to a patient during a clinical trial could potentially influence outcome, so the costs of all procedures should be included. On the other hand, procedures such as clinic visits solely for data collection would not take place in regular clinical care and may seem unlikely to affect outcome. Authors should consider whether the procedures followed in the trial are typical of normal clinical practice and should justify any adjustments they make to the actual observed resource use.

APPENDIX A — Guidelines for Authors and Peer Reviewers of Economic Submissions to the *British Medical Journal*

Outside the context of a trial, estimates of resource quantities should be based on data on real patients, collected either prospectively or retrospectively from medical records. The use of physician "expert panels" to estimate resource quantities, while common, runs the risk that respondents may give inaccurate estimates or specify the resources required for ideal care, rather than that provided in practice.

Prices of resources can be obtained from the finance departments of particular institutions or from national statistics, but charges (or fees) can differ from real costs. The authors of studies should comment on the extent to which the use of charges may bias their estimates.

Guidelines on economic appraisal rarely discuss in detail whether the interventions being compared should be costed at marginal or average cost. Marginal costs are the additional costs of changes in the production of a service. Some authors claim the superiority of marginal costing over average costing, but this choice can be related to context and timeframe. In the short run few costs may be variable if a change in treatment is introduced, whereas over longer periods all resources, including buildings, can be switched to other uses.

Thus if the study relates to a decision of a hospital manager the short run marginal costs of the various options in his or her hospital may be the relevant costs in the current budget period. If the decision relates to a matter of national policy, however, average costs may be more appropriate as these reflect the true variable costs when many services are provided in a large number of facilities across the country.

Finally, the dates of both the estimates of resource quantities and prices should be recorded, along with details of any adjustments to a more recent price level. Also, attention should be paid to the generalisation of cost estimates, since relative prices and the opportunities to redeploy resources may differ from place to place.[30] Currency conversions should, when possible, be based on real purchasing power, rather than financial exchange rates, which fluctuate according to money market changes.[31 32]

(7) MODELLING

- Details should be given of any modelling used in the economic study — for example, decision tree model, epidemiology model, regression model.
- Justification should be given of the choice of the model and the key parameters.

Modelling techniques enable an evaluation to be extended beyond what has been observed in a single set of direct observations. The model will necessarily be simplified, and the extent to which the simplification is appropriate will be a matter of judgment. Modelling may involve explicit and recognised statistical or mathematical techniques. It may, however, simply bring together data from a variety of sources into a formal prespecified conceptual framework, such as a decision analysis model incorporating best available evidence from a wide variety of sources. It may be "what if" modelling, exploring what values for particular uncertain parameters would be needed for a treatment to be cost effective.

Modelling may be required (a) to extrapolate the progression of clinical outcomes (such as survival) beyond that observed in a trial — for example, the progression of disease in

APPENDIX A — Guidelines for Authors and Peer Reviewers of Economic Submissions to the *British Medical Journal*

patients with asymptomatic AIDS[33]; (b) to transform final outcomes from intermediate measures — for example, survival and coronary heart disease events from cholesterol concentrations[34]; (c) to examine the relation between inputs and outputs in production function models to estimate or apportion resource use — for example, in a cost analysis of neonatal intensive care[35]; (d) to use data from a variety of sources to undertake a decision analysis — for example, of screening options for prostate cancer[36]; (e) to use evidence from trials, or systematic reviews of trials, to reflect what might happen in a different clinical setting or population — for example, treatments for respiratory distress syndrome in preterm infants.[37]

The key requirements are that the modelling should be explicit and clear. The authors should explain which of the reported variables/parameters have been modelled rather than directly observed in a particular sample; what additional variables have been included or excluded; what statistical relations have been assumed or derived; and what evidence supports these assumptions or derivations.

All this information may not be included in the published paper, but it should be available to the reviewer. The overall aim of published reports should be to ensure transparency so that the importance and applicability of the methods can be clearly judged (see section 9).

Analysis and interpretation of results (8) ADJUSTMENTS FOR TIMING OF COSTS AND BENEFITS

- The time horizon over which costs and benefits are considered should be given.
- The discount rate(s) should be given and the choice of rate(s) justified.
- If costs or benefits are not discounted an explanation should be given.

The time horizon should be long enough to capture all the differential effects of the options. It should often extend to the whole life of the treated individuals and even to future generations. If the time horizon is shortened for practical reasons this decision should be justified and an estimate made of any possible bias introduced. Justifying a short time horizon on the grounds of the duration of the available empirical evidence may be fallacious.[38] If the relevant horizon for the decision is long term additional assumptions may need to be made.

In health care there is a still debate on discounting.[39,40] Most analysts agree that costs should be discounted in any study having a time horizon longer than one year. At present most recommendations seem to vary between 3 and 6%, and a common rate in the literature is 5% per year. Certainly the analyst should use the government recommended rate, probably as the baseline value, and provide a sensitivity analysis with other discount rates. It is also helpful to provide the undiscounted data to allow the reader to recalculate the results using any discount rate.

Most analysts argue that health benefits should be discounted at the same rate as costs in the baseline analysis, even if they are expressed in non-monetary units, such as life years or quality adjusted life years. A zero discount rate — or one lower than that used for costs — can be introduced in the sensitivity analysis. A lower rate is advocated so as not to penalise preventive programmes and also because the results of some studies seem to suggest it.[39]

APPENDIX A — Guidelines for Authors and Peer Reviewers of Economic Submissions to the *British Medical Journal*

However, there is no a priori economic reason to favour preventive programmes and the comparisons may be between them. Imagine two programmes having the same discounted costs and the same total (undiscounted) amount of benefits, say 100 life years, but programme A obtains these benefits between years 2 and 3 and programme B between years 52 and 53. Not discounting health benefits would result in both programmes having the same cost effectiveness ratio, which seems absurd. Moreover, if the absolute benefits of programme B were 100 years and 1 day, it would be preferred — again absurdly.

It is doubtful if there is enough empirical evidence on which to base a decision on the appropriate discount rate. Moreover, if the empirical argument is accepted it should also be applied to the discounting of costs. In favour of a single discount rate for costs and benefits are, firstly, consistency between cost effectiveness and cost-benefit analysis and, secondly, the idea that it is always possible to transform wealth (resources) into health at any point in time. Then, if resources are discounted, why should health not be discounted?

Given the current debates about discounting, the main emphasis should be on transparency in reporting the methods used.

(9) ALLOWANCE FOR UNCERTAINTY

- When stochastic data are reported details should be given of the statistical tests performed and the confidence intervals around the main variables.
- When a sensitivity analysis is performed details should be given of the approach used — for example, multivariate, univariate, threshold analysis — and justification given for the choice of variables for sensitivity analysis and the ranges over which they are varied.

A recent review suggested that one in four published economic evaluations failed to consider uncertainty at all, and only one in eight handled it well. Without proper consideration of uncertainty the reader may be unable to judge whether conclusions are meaningful and robust.[41]

At least three broad types of uncertainty are recognised.[42]

Uncertainty relating to observed data inputs — When observed data have been sampled from an appropriate population standard statistical methods should be used. Typically, confidence intervals might be presented. When both costs and effects have been derived from a single set of individual patient data a stochastic approach may be used to the presentation of the confidence intervals surrounding the cost effectiveness ratio.[43 44 45] When data come from a sample attention should also be given to sample size and power. In many studies alongside clinical trials sample size may have been determined entirely by clinical endpoints. In some cases a subsample is assumed to be adequate for collecting data on resource use, but in many cases the variability in resource use data is greater than for clinical parameters, and the distribution of values is often non-normal. Attention must be paid to whether sample sizes are adequate for the economic analyses. Ideally power calculations should be presented.

APPENDIX A — Guidelines for Authors and Peer Reviewers of Economic Submissions to the *British Medical Journal*

Uncertainty relating to extrapolation — When data have been extrapolated or modelled (see section 7) the uncertainty inherent in that process is best handled by appropriate sensitivity analysis.

Uncertainty relating to analytical methods — Uncertainties may stem from the existence of alternative analytical methods. Some issues will be avoided by an explicit statement of the approach to be adopted, but others may be usefully handled by using sensitivity analysis — for example, to present results for different discount rates, or with and without indirect costs.

Except for sampled data, uncertainty is usually handled using some form of sensitivity analysis. Simple sensitivity analysis (one way or multi-way), threshold analysis, analysis of extremes, and probabilistic sensitivity analysis may each be appropriate in particular circumstances.[42] The ranges of values tested need to be justified and ideally should be based on evidence or logic.

Authors and reviewers should pay particular attention to whether the important question is the precision of the quantitative results or the robustness of the conclusions drawn from them. Firm conclusions may be shown to hold despite considerable uncertainty; on the other hand, relatively tight estimates of parameters may still leave substantial uncertainty about the policy implications of the study.

(10) PRESENTATION OF RESULTS

- An incremental analysis — for example, incremental cost per life year gained — should be reported, comparing the relevant alternatives.
- Major outcomes — for example, impact on quality of life — should be presented in a disaggregated as well as aggregated form.
- Any comparisons with other health care interventions — for example, in terms of relative cost effectiveness — should be made only when close similarity in study methods and settings can be demonstrated.
- The answer to the original study question should be given; any conclusions should follow clearly from the data reported and should be accompanied by appropriate qualifications or reservations.

The main emphasis in the reporting of study results should be on transparency. The main components of cost and benefit — for example, direct costs, indirect costs, life years gained, improvements in quality of life — should be reported in a disaggregated form before being combined in a single index or ratio.

The results of economic evaluations are usually presented as a summary index such as a cost effectiveness or cost-utility ratio. When two or more interventions are being compared in a given study, the relevant ratio is the one that relates the additional (or incremental) benefits to the additional costs. Reporting disaggregated data allows the reader to calculate other ratios that he or she sees fit.

Beyond the individual study the reporting and interpretation of cost effectiveness ratios need to be handled with care. For example, authors often compare the cost effectiveness ratios generated in their own study with those for other interventions evaluated in previous studies in “league tables,” where rankings are produced, rang-

APPENDIX A — Guidelines for Authors and Peer Reviewers of Economic Submissions to the *British Medical Journal*

ing from the intervention with the lowest cost per life year (or cost per quality adjusted life year) gained to the one with the highest.

Referees' checklist (also to be used, implicitly, by authors)

Item	Yes	No	Not Clear	Not Appropriate

Study design: (1) The research question is stated (2) The economic importance of the research question is stated (3) The viewpoint(s) of the analysis are clearly stated and justified (4) The rationale for choosing the alternative programmes or interventions compared is stated (5) The alternatives being compared are clearly described (6) The form of economic evaluation used is stated (7) The choice of form of economic evaluation is justified in relation to the questions addressed

Data collection: (8) The source(s) of effectiveness estimates used are stated (9) Details of the design and results of effectiveness study are given (if based on a single study) (10) Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies) (11) The primary outcome measure(s) for the economic evaluation are clearly stated (12) Methods to value health states and other benefits are stated (13) Details of the subjects from whom valuations were obtained are given (14) Productivity changes (if included) are reported separately (15) The relevance of productivity changes to the study question is discussed (6) Quantities of resources are reported separately from their unit costs (17) Methods for the estimation of quantities and unit costs are described (18) Currency and price data are recorded (19) Details of currency of price adjustments for inflation or currency conversion are given (20) Details of any model used are given (21) The choice of model used and the key parameters on which it is based are justified

Analysis and interpretation of results

(22) Time horizon of costs and benefits is stated
(23) The discount rate(s) is stated
(24) The choice of rate(s) is justified
(25) An explanation is given if costs or benefits are not discounted
(26) Details of statistical tests and confidence intervals are given for stochastic data
(27) The approach to sensitivity analysis is given
(28) The choice of variables for sensitivity analysis is justified
(29) The ranges over which the variables are varied are stated
(30) Relevant alternatives are compared
(31) Incremental analysis is reported
(32) Major outcomes are presented in a dissaggregated as well as aggregated form
(33) The answer to the study question is given
(34) Conclusions follow from the data reported
(35) Conclusions are accompanied by the appropriate caveats

APPENDIX A — Guidelines for Authors and Peer Reviewers of Economic Submissions to the *British Medical Journal*

Two sets of objections may be raised to such rankings. Firstly, different studies may have used different methods. Differences in cost per quality adjusted life year could arise from differences in methodological approach, rather than real differences in the interventions themselves.[46] Secondly, a simplistic interpretation of league tables may be misleading. For example, each cost effectiveness or cost-utility ratio in the league would have been generated by reference to a comparison programme. In some cases this would have been doing nothing; in others it would have been current care. The incremental ratio will therefore vary in relation to the comparison chosen, which may not itself be an efficient intervention.

Birch and Gafni argue that, in deciding whether or not to adopt a particular intervention, the decision maker needs to assess the opportunity cost for the health care budget.[47] Whether or not the total health care budget should grow is a question for cost-benefit analysis, not cost effectiveness or cost-utility analysis. On the other hand, Johannesson argues that cost effectiveness analysis is best viewed as a subset of cost benefit analysis and that, to interpret and use cost effectiveness analysis as a tool to maximise the health effects for one specified real world budget, would be inconsistent with a societal perspective and likely to lead to major problems of suboptimisation.[48]

Editors' short checklist and partial evaluation checklist

Item	Yes	No	Not Clear	Not Appropriate
Short checklist				
(1) Is the research question stated?	☐	☐	☐	☐
(2) Are the source(s) of effectiveness estimates used clearly stated?	☐	☐	☐	☐
(3) Are the primary outcome measure(s) clearly stated?	☐	☐	☐	☐
(4) Are the methods for the estimation of quantities and unit costs described?	☐	☐	☐	☐
Partial evaluation checklist				
(1) Is the question important?	☐	☐	☐	☐
(2) Is the economic importance of the question stated?	☐	☐	☐	☐
(3) Is the topic of interest to the BMJ?	☐	☐	☐	☐
(4) Is there enough economic detail to allow peer review?	☐	☐	☐	☐
(5) If the economic content is sound would we want to publish it?	☐	☐	☐	☐
(6) Is there a reasonable chance that the economic content is sound?	☐	☐	☐	☐

APPENDIX A — Guidelines for Authors and Peer Reviewers of Economic Submissions to the *British Medical Journal*

In practice, the answer may lie in the way the results of economic evaluations are interpreted. Published data are inevitably specific to a context and will need some reinterpretation by decision makers in other settings. Transparency in reporting can help decision makers generalise results from one setting to another.

Finally, apart from being modest about the generalisability of their results, authors should ensure that their analysis is relatively conservative. Sensitivity analysis plays an important part here, and enough results should be presented to enable the reader to assess the robustness of the study conclusions.

Evaluating the guidelines

We intend to evaluate the guidelines. The options are still under discussion, but the evaluation will probably focus on four questions:

(1) Do the guidelines help *BMJ* editors filter out unpublishable economic studies at an early stage? This has two components: (a) distinguishing full economic evaluations from other types of economic submissions and (b) avoiding wasting time refereeing papers that are fundamentally flawed. This question could be answered by undertaking a study of economic submissions before and after the publication of the guidelines.

(2) How satisfied are editors, reviewers, and authors with their respective checklists? This question could be answered by assessing the checklists with a questionnaire.

(3) Do the guidelines improve the quality of referees' reports on economic evaluations? This question could be answered by a prospective study to compare reports from reviewers who had and had not been asked to apply the referees' checklist.

(4) Do the guidelines improve the quality of the economic evaluations that are eventually published? This is probably the most difficult question to answer, since it requires a view to be taken about the methodological principles of economic evaluation. However, the evaluation might focus on the transparency of reporting of results, since the main objective of the guidelines is to improve this. Again, a prospective evaluation would be required, comparing the version of economic evaluations submitted to the *BMJ* with the version eventually published. We forsee two practical problems with this component of the evaluation. Firstly, the *BMJ* currently receives only a limited number of full economic evaluations, so a prospective study might take some time. Secondly, it will be difficult to separate out the distinctive contribution of the guidelines from the benefits of the peer review process more generally.

Members of the working party were: M Buxton, London; V Demicheli, Pavia, Italy; C Donaldson, Aberdeen; M Drummond (chair), York; S Evans, London; TO Jefferson (secretary), Aldershot, UK; B Jonsson, Stockholm; M Mugford, Oxford; D Rennie, Chicago; J Rovira, Barcelona; F Rutten, Rotterdam; K Schulman, Washington, DC; R Smith (editor, BMJ), London; A Szczepura, Warwick, UK; A Tonks (assistant editor, *BMJ*), London; G Torrance, Hamilton, Canada; A Towse, London.

APPENDIX A — Guidelines for Authors and Peer Reviewers of Economic Submissions to the *British Medical Journal*

We thank Vanessa Windass and Gaby Shockley for secretarial help and an anonymous referee for helpful comments.

Funding: Since no funding was sought for this project we thank our own institutions for bearing the cost.

Conflict of interest: None.

[1] Elixhauser A, ed. Health care cost benefit and cost-effectiveness analysis (cost benefit analysis/cost effectiveness analysis). From 1979 to 1990: a bibliography. Medical Care 1993;31 (suppl):JS1–149.

[2] Gerard K. Cost-utility in practice: a policy maker's guide to the state of the art. *Health Policy* 1992;21 :249–79. [Medline]

[3] Udvarhelyi S, Colditz GA, Rai A, Epstein AM. Cost-effectiveness and cost benefit analyses in the medical literature. Are methods being used correctly? *Ann Intern Med* 1992: 116:238–44.

[4] Adams ME, McCall NT, Gray DT, Orza MJ, Chalmers TC. Economic analysis in randomised controlled trials. Medical Care 1992;30:231–8. [Medline]

[5] Jefferson TO, Demicheli V. Is vaccination against hepatitis B efficient? A review of world literature. Health Economics 1994; 3:25–37.

[6] Williams AH. The cost-benefit approach. *Br Med Bull* 1974;30:252–6. [Medline]

[7] Drummond MF, Brandt A, Luce B, Rovira J. Standardising methodologies for economic evaluation in health care. *International Journal of Technology Assessment in Health Care* 1993;9:26–36. [Medline]

[8] Commonwealth Department of Health, Housing and Community Services. Guidelines for the pharmaceutical industry on preparation of submissions to the pharmaceutical benefits advisory committee. Canberra: Australian Government Publishing Service, 1992.

[9] Ministry ofHealth (Ontario). Ontario guidelines for economic analysis of pharmaceutical products. Toronto: Ministry of Health, 1994.

[10] Clemens K, Townsend R, Luscombe F, Mauskopf J, Osterhaus J, Bobula J. Methodological and conduct principles for pharmacoeconomic research. *Pharmacoeconomics* 1995;8: 169–74. [Medline]

[11] Department of Health and Association of British Pharmaceutical Industry. Guidelines for the economic evaluation of pharmaceuticals [press release]. London: Department of Health, 1994.

[12] Canadian Coordinating Office for Health Technology Assessment. Guidelines for economic evaluation of pharmaceuticals: Canada. Ottawa: CCOHT A, 1994.

APPENDIX A — Guidelines for Authors and Peer Reviewers of Economic Submissions to the *British Medical Journal*

[13] Task Force on Principles for Economic Analysis of Health Care Technology. Economic analysis of health care technology. A report on principles. *Ann Intern Med* 1995;123:61–70. [Medline]

[14] NHS Centre for Reviews and Dissemination. The NHS economic evaluation database. York: CRD, 1996.

[15] Kassirer JP, Angel M. The journal's policy on cost effectiveness analyses. *N Engl J Med* 1994;331:669–70. [Medline]

[16] Schulman K, Sulmasy DP, Roney D. Ethics, economics and the publication policies of major medical journals. *JAMA* 1994;272: 154–6. [Medline]

[17] Jefferson TO, Demicheli V. Are guidelines for peer reviewing economic evaluations necessary? A survey of current editorial practice. *Health Economics* 1995;4:383–8. [Medline]

[18] Smith R. Conflict of interest and the BMJ. *BMJ* 1994;308:4–5. [Full Text]

[19] Drummond, MF, Stoddart GL, Torrance oW. Methods for the economic evaluation of health care programmes. Oxford: Oxford University Press, 1987.

[20] Jefferson TO, Demicheli V, Entwistle V. Assessing quality of economic submissions to the BMJ. *BMJ* 1995;311:393–4. [Full Text]

[21] Guidelines for referees. *BMJ* 1996;312:41–4. [Full Text]

[22] Mehrez A, Gafni A. Quality-adjusted life years, utility theory and healthy years equivalents. *Medical Decision Making* 1989;9:142–9. [Medline]

[23] Mugford M, Kingston J, Chalmers I. Reducing the incidence of infection after caesarean section: implications of prophylaxis with antibiotics for hospital resources. *BMJ* 1989;299:1003–6. [Medline]

[24] Sackett DL, Haynes RB, Guyatt GH, Tugwell P. Clinical epidemiology: a basic science for clinical medicine. 2nd ed. Boston: Little Brown, 1991.

[25] Kind P. The EuroQoL Instrument: an index of health-related quality of life. In Spilker B, ed. Quality of life and pharmacoeconomics in clinical trials. 2nd ed. Philadelphia: Lippincott-Raven, 1996:191–202.

[26] Feeny D, Furlong W, Boyle M, Torrance aw. Multi-attribute health status classification systems: health utilities index. *PharmacoEconomics* 1995;7:490–502. [Medline]

[27] A vorn J. Benefit and cost analysis in geriatric care: turning age discrimination into health policy. *N EnglJ Med* 1994;310:1294–1300.

[28] Koopmanschap MA, Rut ten FFH, van Ineveld BM, van Roijen L. The friction cost method for measuring indirect costs of disease. *Journal of Health Economics* 1995;14: 171–89. [Medline]

[29] Wald N. Couple screening for cystic fibrosis. Lancet 1991;338:1318. [Medline]

APPENDIX A — Guidelines for Authors and Peer Reviewers of Economic Submissions to the *British Medical Journal*

[30] Drurnrnond MF, Bloom BS, Carrin a, Hillman AL, Hutchings HC, Knill-Jones RP, et al. Issues in the cross-national assessment of health technology. *International Journal of Technology Assessment in Health Care* 1992;8:671–82. [Medline]

[31] Organisation for Economic Cooperation and Development. Purchasing power parities. Paris: OECD, 1993.

[32] World Bank. World development report 1993. New York: Oxford University Press, 1993.

[33] Schulman KA, Lynne LA, alick HN, Eisenberg JM. Cost-effectiveness oflow-dose zidovudine therapy for asymptomatic patients with human immunodeficiency virus (HIV) infection. *Ann Intern Med* 1991;114:798–801. [Medline]

[34] Oster a, Epstein AM. Cost-effectiveness of antihyperlipidemic therapy in the prevention of coronary heart disease: the case of cholestyramine. *JAMA* 1987;258: 2381–7 .[Medline]

[35] Fordham R, Field Dl, Hodges S, Normand C, Mason E, Burton P, et al. Cost of neonatal care across a health authority. *J Pub Health Med* 1992;61:127–30.

[36] Krahn MD, Mahoney JE, Eckman MH, Trachtenberg l, Pauker sa, Detsky AS. Screening for prostate cancer: a decision analytic view. *JAMA* 1994;272:773–80. [Medline]

[37] Egberts J. Estimated costs of different treatments of the respiratory distress syndrome in a large cohort of preterm infants of less than 30 weeks gestation. *Biology of the Neonate* 1992;61:59–85. [Medline]

[38] Schulman KA, Yabroff R, Glick H. A health services approach for the evaluation of innovative pharmaceutical and biotechnology products. *Drug Information Journal* 1995;29:1405–14.

[39] Parsonage M, Neuburger H. Discounting and health benefits. *Health Economics* 1992;1:71–6. [Medline]

[40] Cairns J. Discounting and health benefits: another perspective. *Health Economics* 1992;1:76–9. [Medline]

[41] Briggs A, Sculpher M. Sensitivity analysis in economic evaluation: a review of published studies. *Health Economics* 1995;4(5):355–72.

[42] Briggs AH, Sculpher Ml, Buxton MJ. Uncertainty in the economic evaluation of health care technologies: the role of sensitivity analysis. *Health Economics* 1994;3:95–104. [Medline]

[43] O'Brien B, Drummond MF, Labelle R, Willan A. In search ofpower and significance: issues in the design and analysis of stochastic economic appraisals. *Medical Care* 1994;32:150–63. [Medline]

[44] van Hout BA, Al MJ, Gordon GS, Rutten FFH. Costs, effects and cost effectiveness ratios alongside a clinical trial. *Health Economics* 1995;3(5):309–19.

APPENDIX A — Guidelines for Authors and Peer Reviewers of Economic Submissions to the *British Medical Journal*

[45] Wakker P, Klaassen MF. Confidence intervals for cost effectiveness ratios. *Health Economics* 1995;4(5):373–81.

[46] Drummond, MF, Mason J, Torrance G. Cost-effectiveness league tables: more harm than good? *Soc Sci Med* 1993;37:33–40.

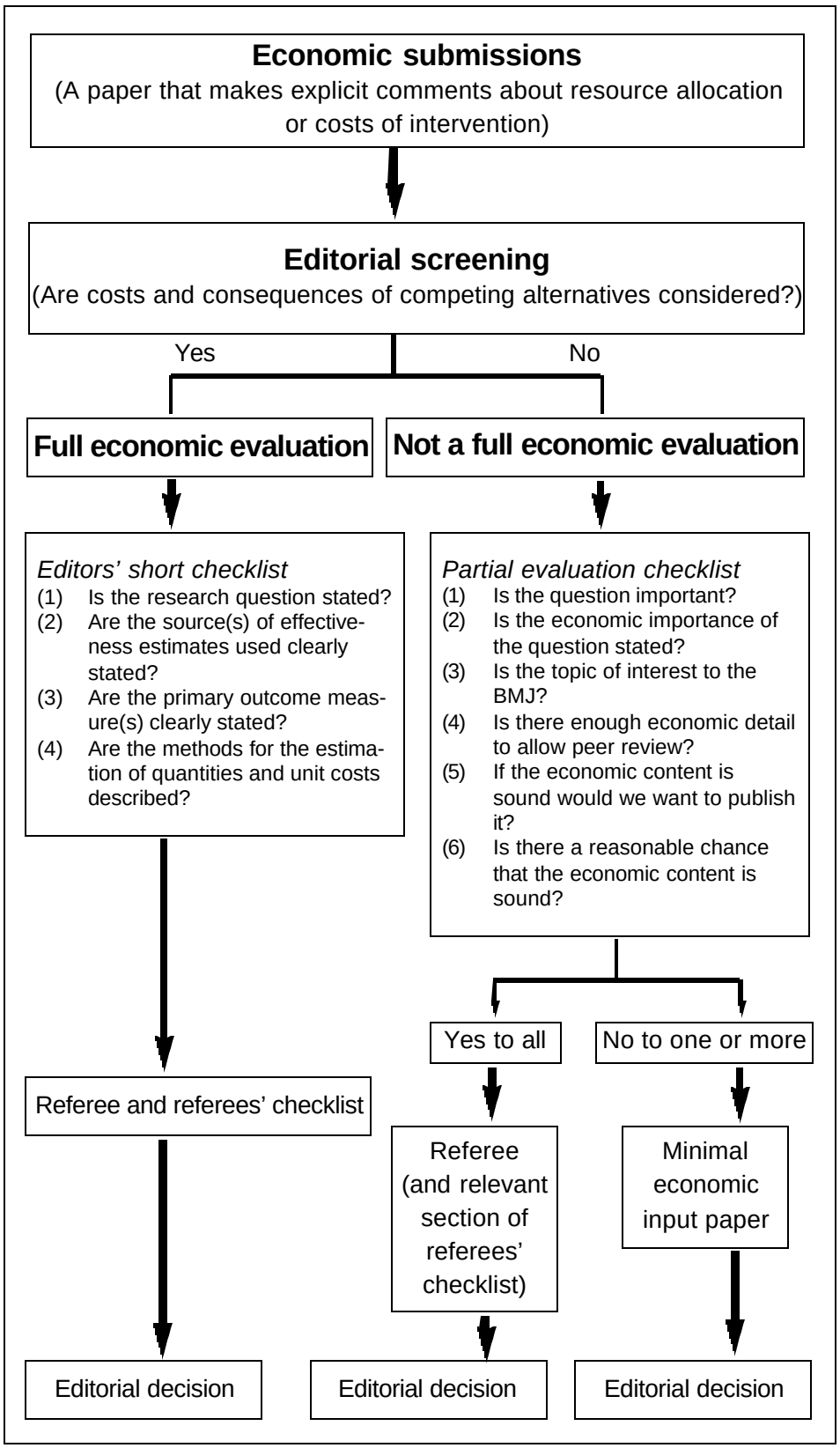
[47] Birch S, Gafni A. Cost-effectiveness ratios: in a league of their own. *Health Policy* 1994;28:133–41. [Medline]

[48] Johannesson M. The relationship between cost effectiveness analysis and cost benefit analysis. *Soc Sci Med* 1995;41:483–9. [Medline]

(Accepted 11 July 1996)

APPENDIX A —

Guidelines for Authors and Peer Reviewers of Economic Submissions to the *British Medical Journal*



Principles of a Sound Drug Formulary System

These principles have been endorsed by the following organizations:

- Academy of Managed Care Pharmacy
- Alliance of Community Health Plans
- American Medical Association
- American Society of Health-System Pharmacists
- Department of Veterans Affairs,
  Pharmacy Benefits Management
  Strategic Healthcare Group
- National Business Coalition on Health
- U. S. Pharmacopeia

October 2000

Principles of a Sound Drug Formulary System

PREAMBLE

A coalition of national organizations representing health care professionals, government, and business leaders formed a working group (See Appendix III) to develop a set of principles specifying the essential components that contribute to a sound drug formulary system. The Coalition was formed in September 1999 in response to the widespread use of drug formularies in both inpatient and outpatient settings and the lack of understanding about formularies among the public. Also, proposed federal legislation that would provide a prescription drug benefit for Medicare beneficiaries has brought increased attention to the appropriate role and management of drug formulary systems within drug benefit programs.

The formulary system, when properly designed and implemented, can promote rational, clinically appropriate, safe, and cost-effective drug therapy. The Coalition has enumerated these principles, however, because it recognizes that patient care may be compromised if a formulary system is not optimally developed, organized and administered. This document contains "Guiding Principles" that the Coalition believes must be present for a drug formulary system to appropriately serve the patients it covers. The absence of one or more of these "Guiding Principles" should be cause for careful scrutiny of a formulary system. A glossary (See Appendix I) and bibliography (See Appendix II) are included with the "Guiding Principles" to clarify terminology and to provide additional resources, respectively.

The Coalition believes that the presence of consensus-based Formulary System Principles can assist decision-makers who must balance the health care quality and cost equation. Further, the Guiding Principles will be a valuable educational tool for national, state and local public policy makers, health care system administrators, purchasers and third party payers, practitioners, and consumers and patient advocates. These parties all have an interest in designing formulary systems that ensure patients have access to rational, clinically appropriate, safe, and cost-effective therapy and which supports an affordable and sustainable drug benefit program.

DEFINITIONS

Drug Formulary System - an ongoing process whereby a health care organization, through its physicians, pharmacists, and other health care professionals, establishes policies on the use of drug products and therapies, and identifies drug products and therapies that are the most medically appropriate and cost-effective to best serve the health interests of a given patient population.

Drug Formulary - a continually updated list of medications and related information, representing the clinical judgement of physicians, pharmacists and other experts in the diagnosis and/or treatment of disease and promotion of health.

GUIDING PRINCIPLES

Formulary system decisions are based on scientific and economic considerations that achieve appropriate, safe and cost effective drug therapy.

- Clinical decisions are based on the strength of scientific evidence and standards of practice that include, but are not limited, to the following:
  - Assessing peer-reviewed medical literature, including: randomized clinical trials (especially drug comparison studies), pharmacoeconomic studies, and outcomes research data.
  - Employing published practice guidelines, developed by an acceptable evidence-based process.
  - Comparing the efficacy as well as the type and frequency of side effects and potential drug interactions among alternative drug products.
  - Assessing the likely impact of a drug product on patient compliance when compared to alternative products.
  - Basing formulary system decisions on a thorough evaluation of the benefits, risks and potential outcomes for patients; risks encompass adverse drug events (adverse drug reactions and medication errors, such as those caused by confusing product names or labels).

- Economic considerations include, but are not limited, to the following:
  - Basing formulary system decisions on cost factors only after the safety, efficacy and therapeutic need have been established.
  - Evaluating drug products and therapies in terms of their impact on total health care costs.
  - Permitting financial incentives only when they promote cost management as part of the delivery of quality medical care. Financial incentives or pressures on practitioners that may interfere with the delivery of medically necessary care are unacceptable.

The formulary system encompasses drug selection, drug utilization review, and other tools to foster best practices in prescribing, dispensing, administration, and monitoring of outcomes.

- The formulary system:
  - Provides drug product selection and formulary maintenance (see above).
  - Provides drug use evaluation (also called drug utilization review) to enhance quality of care for patients by assuring appropriate drug therapy.
  - Provides for the periodic evaluation and analysis of treatment protocols and procedures to ensure that they are up-to-date and are consistent with optimum therapeutics.
  - Provides for the monitoring, reporting, and analysis of adverse results of drug therapy (e.g., adverse drug reactions, medication errors) to continuously improve the quality of care.

GUIDING PRINCIPLES

The Pharmacy and Therapeutics (P&T) Committee, or equivalent body, comprised of actively practicing physicians, pharmacists and other health care professionals, is the mechanism for administering the formulary system, which includes developing and maintaining the formulary and establishing and implementing policies on the use of drug products.

❖ The Pharmacy and Therapeutics Committee:

- Objectively appraises, evaluates, and selects drugs for the formulary.
- Meets as frequently as is necessary to review and update the appropriateness of the formulary system in light of new drugs and new indications, uses, or warnings affecting existing drugs.
- Establishes policies and procedures to educate and inform health care providers about drug products, usage, and committee decisions.
- Oversees quality improvement programs that employ drug use evaluation.
- Implements generic substitution and therapeutic interchange programs that authorize exchange of therapeutic alternatives based upon written guidelines or protocols within a formulary system. (Note: Therapeutic substitution, the dispensing of therapeutic alternates without the prescriber's approval, is illegal and should not be allowed-See Glossary.)
- Develops protocols and procedures for the use of and access to non-formulary drug products.

Physicians, pharmacists, and other health care professionals provide oversight of the formulary system.

- Health care organization policies should ensure appropriate oversight of the P&T Committee and its decisions by the medical staff or equivalent body.

The formulary system must have its own policies, or adhere to other organizational policies, that address conflicts of interest and disclosure by P&T committee members.

❖ Formulary system policies should:

- Require P&T committee members to reveal, by signing a conflict of interest statement, economic and other relationships with pharmaceutical entities that could influence Committee decisions.
- Exclude product sponsor representatives from P&T committee membership and from attending P & T committee meetings.
- Require P&T committee members to adhere to the formulary system's policy on disclosure and participation in discussion as it relates to conflict of interest.

GUIDING PRINCIPLES

The formulary system should include educational programs for payers, practitioners, and patients concerning their roles and responsibilities.

❖ The formulary system should:

- Inform physicians, pharmacists, other health care professionals, patients, and payers about the factors that affect formulary system decisions, including: cost containment measures; the procedures for obtaining non-formulary drugs; and the importance of formulary compliance to improving quality of care and restraining health care costs.
- Proactively inform practitioners about changes to the formulary or to other pharmaceutical management procedures.
- Provide patient education programs that explain how formulary decisions are made and the roles and responsibilities of the patient, especially the importance of patient compliance with drug therapy to assure the success of that therapy.
- Disclose the existence of formularies and have copies of the formulary readily available and accessible.
- Provide rationale for specific formulary decisions when requested.

The formulary system should include a well-defined process for the physician or other prescriber to use a non-formulary drug when medically indicated.

❖ The formulary system should:

- Enable individual patient needs to be met with non-formulary drug products when demonstrated to be clinically justified by the physician or other prescriber.
- Institute an efficient process for the timely procurement of non-formulary drug products and impose minimal administrative burdens.
- Provide access to a formal appeal process if a request for a non-formulary drug is denied.
- Include policies that state that practitioners should not be penalized for prescribing non-formulary drug products that are medically necessary.

APPENDIX I

GLOSSARY

Drug Formulary System - an ongoing process whereby a health care organization, through its physicians, pharmacists and other health care professionals, establishes policies on the use of drug products and therapies, and identifies drug products and therapies that are the most medically appropriate and cost effective to best serve the health interests of a given patient population.

Drug Formulary - a continually updated list of medications and related information, representing the clinical judgement of physicians, pharmacists, and other experts in the diagnosis and/or treatment of disease and promotion of health.

Pharmacy & Therapeutics (P&T) Committee - an advisory committee that is responsible for developing, managing, updating, and administering the drug formulary system.

Generic Substitution - the substitution of drug products that contain the same active ingredient(s) and are chemically identical in strength, concentration, dosage form, and route of administration to the drug product prescribed.

Therapeutic Alternates - drug products with different chemical structures but which are of the same pharmacological and/or therapeutic class, and usually can be expected to have similar therapeutic effects and adverse reaction profiles when administered to patients in therapeutically equivalent doses.

Therapeutic Interchange - authorized exchange of therapeutic alternates in accordance with previously established and approved written guidelines or protocols within a formulary system.

Therapeutic Substitution - the act of dispensing a therapeutic alternate for the drug product prescribed without prior authorization of the prescriber. This is an illegal act because only the prescriber may authorize an exchange of therapeutic alternates.

Drug Utilization Review (Drug Use Review, DUR, and Drug Use Evaluation) - process used to assess the appropriateness of drug therapy by engaging in the evaluation of data on drug use in a given health care environment against predetermined criteria and standards.

APPENDIX II

BIBLIOGRAPHY

1. Academy of Managed Care Pharmacy, Concepts in Managed Care Pharmacy Series - Formulary Management (Alexandria, VA: 1998).
2. American Medical Association. Board of Trustees Report PPP, Principles of Drug Utilization Review. In, American Medical Association House of Delegates Proceedings, 140th Annual Meeting. Chicago: American Medical Association; June 1991; 225-227.
3. American Medical Association. Board of Trustees Report 45, Drug Formularies and Therapeutic Interchange. In, American Medical Association House of Delegates Proceedings, 47th Interim Meeting. New Orleans: American Medical Association; December 1993; 155-158.
4. American Medical Association. Council on Ethical and Judicial Affairs Report 2, Managed Care Cost Containment Involving Prescription Drugs. In, American Medical Association House of Delegates Proceedings, 144th Annual Meeting. Chicago: American Medical Association; June 1995; 207-213.
5. American Medical Association. Board of Trustees Report 9, Pharmaceutical Benefits Management Companies. In, American Medical Association House of Delegates Proceedings, 51st Interim Meeting. Dallas: American Medical Association; December 1997; 33-44.
6. American Society of Consultant Pharmacists. Guidelines for the Development of Formulary Systems in Nursing Facilities; July 1996.
7. American Society of Hospital Pharmacists. ASHP Statement on the Formulary System. Am J Hosp Pharm. 1983; 40:1384-5.
8. American Society of Hospital Pharmacists. ASHP Guidelines on Formulary System Management. Am J Hosp Pharm. 1992; 49:648-52.
9. American Society of Hospital Pharmacists. ASHP Statement on the Pharmacy and Therapeutics Committee. Am J Hosp Pharm. 1992; 49:2008-9.
10. American Society of Health-System Pharmacists. ASHP Guidelines on Medication-Use Evaluation. Am J Health-Syst Pharm. 1996; 53:1953-5.
11. American Society of Hospital Pharmacists. ASHP Technical Assistance Bulletin on Drug Formularies. Am J Hosp Pharm. 1991; 48:791-3.
12. American Society of Hospital Pharmacists. ASHP Technical Assistance Bulletin on the Evaluation of Drugs for Formularies. Am J Hosp Pharm. 1988; 45:386-7.
13. Covington TR and Thornton JL. The formulary system: A cornerstone of drug benefit management, in A Pharmacist's Guide to Principles and Practices of Managed Care Pharmacy. Ito S and Blackburn S. eds. Foundation for Managed Care Pharmacy, Alexandria VA. 1995: 35-49.
14. Dillon MJ. Drug Formulary Management, in Managed Care Pharmacy Practice. Navarro RP ed. Aspen Publishers, Inc., Gaithersburg, MD. 1999: 145-165.
15. Hejna CS and Shepherd MD. Pharmacy and therapeutics committee and formulary development, in A Pharmacist's Guide to Principles and Practices of Managed Care Pharmacy. Ito S and Blackburn S. eds. Foundation for Managed Care Pharmacy, Alexandria VA. 1995: 27-34.
16. National Committee for Quality Assurance. UM 10 procedures for pharmaceutical management. 2000 Standards for Accreditation of MCOs. 1999: 58-60.
17. National Committee for Quality Assurance. UM 10 procedures for pharmaceutical management. 2000 Surveyor Guidelines for the Accreditation of MCOs. 1999: 173-182.
18. PCMA Response to American Medical Association Report, I-97, "Pharmaceutical Benefits Management Companies." September 1998.
19. Rucker TD and Schiff GD, Drug formularies: myths-in-formation. Medical Care 1990; 28:928-942. Reprinted in Hospital Pharmacy 1991; 26:507-514.

APPENDIX III
COALITION WORKING GROUP

Academy of Managed Care Pharmacy
Judith A. Cahill, C.E.B.S.
Executive Director

Richard Fry
Senior Director, Pharmacy Affairs

American Medical Association
Joseph W. Cranston, Ph.D.
Director-Science, Research and Technology

American Society of Health-System Pharmacists
William A. Zellmer, M.P.H.
Deputy Executive Vice President

Department of Veterans Affairs
John E. Ogden
Director, Pharmacy Services

Michael A. Valentino
Associate Chief Consultant
for Pharmacy Benefits Management

National Business Coalition on Health
Catherine Kunkle
Vice President

U.S. Pharmacopeia
Jacqueline L. Eng
Senior Vice President, Program Development

Keith W. Johnson
Vice President and Director
New and Off-Label Uses

Thomas R. Fulda
Program Director, Drug Utilization Review Programs

Nancy B. Mabie
Assistant Director, Pharmacy Affairs

Observer
AARP
David Gross
Senior Policy Advisor
Public Policy Institute

Public Comment Requested
To ensure that knowledgeable and interested parties beyond the Coalition Working Group had an opportunity to contribute to the Principles development process, a preliminary set of principles was distributed for public comment to 50-plus organizations in February 2000. Comments received were thoroughly reviewed and considered by the Coalition Working Group.

Appendix C – Sample P & T Committee Monograph

[Instructions: This is a generic template for P&T Monographs. Delete this and other bracketed instruction paragraphs when you are finished. Replace text in square brackets [ ] with your text. The brackets [ ] should be replaced too. Parentheses ( ) should be left in the text. Just replace the text inside them.]

[HEALTH SYSTEM NAME]
FORMULARY MONOGRAPH

Generic Name (Brand) [Manufacturer]

Therapeutic Use: [Disease State(s) or Clinical Use(s)]

Similar Drugs: [List all applicable]

ISSUES FOR CONSIDERATION BY THE FORMULARY COMMITTEE [These ***Issues*** are automatically numbered paragraphs. If you delete one, the others will renumber. If you add a hard return ↵ after the last issue, another issue number will appear.]

Should [generic name] be added to the formulary?

Is there a specific therapeutic niche and/or subpopulation of patients to which its use should be restricted? If so, how are they to be defined/identified?

Should [generic name] be declared to be therapeutically equivalent to [similar drug(s)]?

[text]

INDICATIONS

[Per FDA approved manufacturer's labeling. If appropriate, may include off-label indications, identifying them as such.]

CLINICAL PHARMACOLOGY

[Keep very brief. Focus on pharmacology which is *clinically relevant* to the drug's Formulary status.]

PHARMACOKINETICS [Keep brief, bulleted. List only clinically relevant parameters.]

Rt of Admin: [text]
Peak Levels: [text]
Time to Peak:[text]
Elimination: [text]
Half Life: [text]

ADVERSE EFFECTS

Summary: [text]

Monitoring: [text]

Table I. Reported Adverse Effects

Adverse Effect	Reported Incidence in Trials(%)	
	Drug Therapy	Placebo

ALLERGIES AND INTERACTIONS

[text]

AVAILABILITY AND DOSING [Use indication headings below to break down the dosing information for different indications (if dosing varies with indication) or for different age groups and special populations, e.g. infants, children ages 6-12, renal failure, etc.)]

Available Products: [text]

[Indication 1]: [text]

[Indication 2]: [text]

THERAPEUTIC EFFICACY ***See Evidence table, next page***

[This section should contain the following:

1. Text summary of the evidence from the clinical trials listed in the following evidence table.

2. Any background info needed to interpret the results, e.g., explanation of clinical scores used as trial endpoints, should be provided.

NOTE: Although this section appears before the table, you should prepare the table first, then write this summary afterwards, as this follows the logical flow from massive amounts of detailed input to more condensed, summarized output.]

Table II. Summary of Published Evidence

[Note: This is a generic table format. You can change column headings, subdivisions, etc. as necessary to fit the data you are reporting. A general overview of these data including the key "take home" points for P&T members should be given in the section just above this table. Detailed comments about a particular study, such as weaknesses in data or study design, can be put in the right hand column of this table.]

Ref.	Drug Regimens	n	Duration	Demographics	Design*	End Points	Results/Comments	NNT
1.	1. [TEXT] 2. [TEXT] 3. [TEXT] 4. [TEXT]			[TEXT] • [text] • [text]		• [text] • [text]	[Arm 1] [Arm 2] [Arm3] [Arm 4] x x x x x x x x	
2.	1. [TEXT] 2. [TEXT] 3. [TEXT] 4. [TEXT]			[TEXT] • [text] • [text]		• [text] • [text]	[Arm 1] [Arm 2] [Arm 3] [Arm 4] x x x x x x x x	
3.	1. [TEXT] 2. [TEXT] 3. [TEXT] 4. [TEXT]			[TEXT] • [text] • [text]		• [text] • [text]	[Arm 1] [Arm 2] [Arm 3] [Arm 4] x x x x x x x x	
4.	1. [TEXT] 2. [TEXT] 3. [TEXT] 4. [TEXT]			[TEXT] • [text] • [text]		• [text] • [text]	[Arm 1] [Arm 2] [Arm 3] [Arm 4] x x x x x x x x	
5.	1. [TEXT] 2. [TEXT] 3. [TEXT] 4. [TEXT]			[TEXT] • [text] • [text]		• [text] • [text]	[Arm 1] [Arm 2] [Arm 3] [Arm 4] x x x x x x x x	
***Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.								

Table III. ECONOMIC EVALUATIONS:

[Note: This is similar in format to Table 2. Since pharmacoeconomic studies vary considerably more in format than clinical trials, you should feel free to change this around. Delete the columns that don't apply. A general overview of these data including the key "take home" points for P&T members should be given in the section just above this table. Detailed comments about a particular study, such as weaknesses in data or study design, can be put in the right hand column of this table.]

Ref.	Drug/Treatment Arms	n	Time Horizon	Method*	Outcome Measures	Cost Measures	Results/Comments
1.	1. [TEXT] 2. [TEXT] 3. [TEXT] 4. [TEXT]			[TEXT] • [text] • [text]		• [text] • [text]	[Arm 1] [Arm 2] [Arm 3] [Arm 4] x x x x x x x x
2.	1. [TEXT] 2. [TEXT] 3. [TEXT] 4. [TEXT]			[TEXT] • [text] • [text]		• [text] •	[Arm 1] [Arm 2] [Arm 3] [Arm 4] x x x x x x x x
3.	1. [TEXT] 2. [TEXT] 3. [TEXT] 4. [TEXT]			[TEXT] • [text] • [text]		• [text] •	[Arm 1] [Arm 2] [Arm 3] [Arm 4] x x x x x x x x
4.	1. [TEXT] 2. [TEXT] 3. [TEXT] 4. [TEXT]			[TEXT] • [text] • [text]		• [text] •	[Arm 1] [Arm 2] [Arm 3] [Arm 4] x x x x x x x x
5.	1. [TEXT] 2. [TEXT] 3. [TEXT] 4. [TEXT]			[TEXT] • [text] • [text]		• [text] •	[Arm 1] [Arm 2] [Arm 3] [Arm 4] x x x x x x x x

***Method abbreviations:** CEA=cost- effective analysis, CUA=cost-utility analysis, CBA=cost- benefit analysis, CCA=cost-consequence analysis.
Evidence grades: Grade 1 = randomized controlled trials, Grade 2 = nonrandomized concurrent studies, Grade 3 = historical cohort & case-control studies, Grade 4 = case series, Grade 5 = expert opinion. (move evidence grades to the clinical table)

SUMMARY OF PHARMACOECONOMIC STUDIES

[Summarize the key "take home" points from Table III.]

BUDGET IMPACT/COST-EFFECTIVENESS MODELLING:

- **Describe type of model (Budget Impact, Markov, Decision Analysis, Simulation, etc…) [Show illustration of model, if applicable]**
- **List key assumptions and elements of the model [What drives the model and its results?]**
- **Describe sensitivity analyses and scenarios**
- **List model results and conclusions**
- **Discuss the projected impact of Formulary addition on the plan's drug budget.**

SUMMARY AND RECOMMENDATION:

[Final summary of findings: a further condensation of the Therapeutic Efficacy and Pharmacoeconomic summaries into one or more sentences.]

MONOGRAPH PREPARED BY:

[Author's name and title.]

REFERENCES: [List of references. (Package inserts can be referenced as: Nudrug Prescribing Information, Blank Pharmaceuticals, 2001. Unpublished studies supplied by the manufacturer should be referenced as: Unpublished. Data on file with …)]

RESPONSE TO COMMENTS

Regarding AMCP's *Format for Formulary Submissions*

RESPONSE TO COMMENTS

Since publication of The Academy of Managed Care Pharmacy's (AMCP) *Format for Formulary Submissions* in October 2000, AMCP and the Foundation for Managed Care Pharmacy (FMCP) have received hundreds of questions and comments regarding its use. To fully comprehend the significance of the *Format* it is important to understand AMCP's mission and place within the community of managed care pharmacy practitioners and organizations. The Academy is a professional membership association that represents pharmacists who have chosen to practice pharmacy in a variety of managed care settings. Therefore, AMCP does not act in the role of a trade association, representing businesses. The Academy strives to improve the practice of managed care pharmacy through outstanding educational programs, initiatives and tools, such as the *Format*, that assist its members in promoting wellness, providing rational drug therapy for individuals and enrolled patient populations and raising the bar of professional conduct for pharmacists.

Regarding the AMCP *Format*, the Academy has created a set of guidelines designed to improve the evaluation of medications for formulary consideration. The *Format* is intended to help pharmacists and their health systems achieve two principal goals; (1) decisions regarding a medication's inclusion on a formulary will be based on the overall value that medication brings to a specific population, and (2) the value argument will be based on good scientific evidence.

It is not the Academy's role, responsibility or desire to dictate to health care systems how they should implement the AMCP *Format.* However, this does not preclude AMCP from strongly recommending that its members follow certain procedures to improve the process. As AMCP and FMCP staff and a committee of select experts sifted through the hundreds of comments received by health system and pharmaceutical industry personnel, they identified several common themes. This document is devoted to addressing many of those common themes. By addressing these comments and concerns, the Academy and the Foundation hope to foster greater understanding and widespread adoption of the *Format* process. The Revision Committee did not intend to address every comment or concern, but rather those that have been repeatedly and consistently communicated to them since the *Format's* publication.

COMMENT ONE

The AMCP *Format* requires a significant effort to evaluate medications. P&T Committees could simply put new or expensive drugs on the third tier of their benefit structure and avoid the cost and effort of the AMCP *Format* process.

One of the key purposes of a formulary is to make medications that produce the best positive outcomes at reasonable costs (those drugs that show value) available to a plan's membership. The AMCP *Format* guidelines are specifically designed for that purpose. They allow a P&T Committee to determine the clinical benefits of a drug, verify any cost savings the drug may generate, and determine the overall cost consequences to their health system.

If a health system simply puts a new or expensive medication on the third tier, two negative consequences could arise. First, despite its high cost, the medication may have significant clinical value. Providing appropriate incentives for its use could ultimately improve health and possibly lower overall health care costs. By simply choosing to place it on the third tier, a plan would in effect be disincentivizing their members from using it, resulting in missed opportunities to improve the health outcomes for individuals and groups of patients. Second, automatically putting the medication on the third tier denies the Pharmacy & Therapeutics (P&T) Committee or other decision making body the opportunity to fully assess the clinical and economic impact of the product on the health system's patient population. Paying for a drug that has little or no value could result in unforeseen dire consequences for patients and health systems.

COMMENT TWO

The AMCP *Format* is actually just a pharmacoeconomic tool and many P&T Committees have little expertise in evaluating outcome models.

A careful examination of the *Format* document will clearly show that these guidelines, first and foremost, require the health system staff to perform a thorough clinical evaluation of the medication based on all possible available information obtained from the manufacturer and other sources. If the desired outcome of the medication is not significant or the side effects too onerous, an economic review would be unnecessary. It is imperative to determine the potential clinical impact of a drug on its target patient population before considering the economic consequences.

The field of pharmacoeconomics is relatively new. Therefore, the current number of individuals in this country with a great deal of knowledge and experience in analyzing the type of information required by the *Format* is limited. While pharmacoeconomic models and outcomes research have become increasingly accepted as tools for helping health care systems make formulary decisions, many health systems do not have a pharmacist on staff with sufficient experience to analyze this information. There are at least two solutions to this problem. One would be to acquire the training on pharmacoeconomics for one or two staff pharmacists. Numerous organizations around the country provide this type of training, including the Foundation for Managed Care Pharmacy. Another solution is to hire an outside consultant to perform the reviews on the pharmacoeconomic models. Private consultants and faculty at colleges of pharmacy can help meet the needs of our health systems.

COMMENT THREE

The FDA closely regulates the information a pharmaceutical company can provide regarding their medications. There is concern that complying with the *Format* information requirements may raise concerns at the FDA.

Beginning long before the *Format's* publication, the Academy has maintained an ongoing dialogue with the FDA to keep them apprised of the project's progress and to seek their guidance. FDA officials have stated on several occasions that they are comfortable with the Academy's position that the *Format* represents an unsolicited request from a health system to a pharmaceutical company for all possible published and unpublished studies and information regarding both FDA-approved indications and anticipated off-label uses of the product. However, the FDA has three areas of concern relative to this process. First, the information provided cannot be false or misleading. Second, the request must truly be unsolicited. Third, the response must be specific to the requestor.

Regarding the first concern, FDA regulations require pharmaceutical companies to provide accurate information that will benefit the requestor. The pharmaceutical industry takes this responsibility seriously and the AMCP *Format* recognizes the importance of these requirements. Health systems and manufacturers can virtually eliminate the second and third concerns if they follow some simple procedures. Health systems must initiate the request and make clear what information they desire. The AMCP *Format* is a template designed specifically for this purpose. AMCP recommends that health systems also submit a signed request letter to accompany the *Format.* Pharmaceutical companies must refrain from taking any proactive steps that could be construed as marketing or promotion such as preparing identical formulary submission documents (dossiers) for a product with the intent of soliciting health system pharmacists by asking them to request a dossier. In this scenario, the request would not be truly unsolicited nor would the contents of the response (the dossier) be specific to the requestor.

COMMENT FOUR

Pharmaceutical companies have repeatedly expressed concern about the confidentiality of dossier contents.

AMCP has always supported the desire by the pharmaceutical industry to maintain the confidentiality of certain information contained in product dossiers. The most recent version of the *Format* contains the following statement, "By submitting this request (the health system) recognizes that confidential information may be provided. (The health system) recognizes the need to respect and honor commercial-in-confidence information and may be willing to sign necessary confidentiality agreements under agreed circumstances." As public agencies such as state Medicaid agencies and the Department of Defense have begun to adopt the *Format*, some pharmaceutical companies have expressed an increasing level of concern about the need for confidentiality. The Academy has counseled public agencies that are considering the use of the AMCP *Format,* to develop procedures that will allow them to keep the dossiers confidential. The Academy strongly recommends that any organization that is using AMCP's *Format* should work diligently to find ways to keep the dossiers confidential and examine all opportunities to work within state statutes in meeting this goal. If issues of confidentiality cannot be overcome due to state public disclosure statutes, the information provided by a pharmaceutical manufacturer may not contain sufficient evidence for a public agency to make a rational evidence-based decision regarding the value of the product under consideration. In addition, AMCP encourages any organization that begins using AMCP's *Format* hold the presubmission meeting with pharmaceutical companies called for in the *Format* to disclose the level of confidentiality that will be possible and to ascertain what level of data can be expected to be furnished.

COMMENT FOUR
continued

In supporting this concern, it is important to point out that this stipulation is unique to the United States, since dossiers submitted in Canada, the United Kingdom and Australia are available to the public. The concerns in this country seem to revolve around the pharmacoeconomic model, the submission of unpublished studies and off-label use information and the creation of the dossier itself. While some pharmaceutical companies have spent a great deal of time and money on outcomes research, pharmacoeconomic modeling, and creation of dossiers, others are not as scientifically sophisticated. Because of this broad variation, some pharmaceutical companies would like to keep their work confidential to prevent their competitors from capitalizing on their efforts.

COMMENT FIVE

There should be substantial on-going communication between the health system and the pharmaceutical company throughout this process to manage expectations and maximize the quality of the deliverables.

Those organizations that have been early adopters of the AMCP *Format* have expressed the importance of and concern for good communication. The basic element in most project failures whether it is from employee performance, the business plan, or vendor relationships, is communication. When a dossier is requested from a health system, it is important for that organization to explain to the pharmaceutical company some basic information, such as their time-line, the evaluation process, potential data sources, any special needs that might exist, etc. This also gives the pharmaceutical company an opportunity to discuss deliverables. If they cannot submit specific studies or provide a certain piece of the economic analysis, it is better to understand the limitations up front. Again, AMCP will not presume to dictate to its members that they should significantly alter or disrupt their normal lines of communication with pharmaceutical manufacturers. However, both parties should recognize that when there is a high level of collaboration, there is a relative increase in the chances that the process will be smoother and the quality of the dossiers submitted will be higher.

COMMENT SIX

While many acknowledge the benefits of the AMCP *Format,* there is the tendency on the part of many organizations to want to recreate their own similar process.

There is an important element in the AMCP *Format* that many people overlook. The element is consistency and standardization. As indicated previously, the AMCP *Format* is a template that any health system can readily adapt to their specific needs. This not only makes it easy for the health system, but also makes it dramatically easier for the pharmaceutical company. Although manufacturers must tailor their responses to the requesting health system, utilizing the AMCP *Format* allows a pharmaceutical company to have 80 to 90 percent of the information, especially the clinical information, completed and formatted. Individual health systems will severely diminish the element of standardization if they choose to create their own processes. While the Academy understands the need for some health systems to make small modifications in the AMCP *Format* template, the hope is that those health systems will refrain from making wholesale modifications.

COMMENT SEVEN

Some health care systems are under the impression that only pharmacoeconomic models that strictly mirror a health system's targeted patient population are acceptable.

The AMCP *Format* describes in some detail the most important elements of the requested pharmacoeconomic model. The *Format* further stipulates that the economic data called for must be broadly applicable to a health system's population addressing the system-wide impact of formulary changes on both clinical outcomes and resource utilization and costs. The *Format*, however, does not specify methods for economic evaluation. It is the submitter's responsibility to utilize appropriate techniques and data sources. Ideally, a manufacturer would use a health system's own data to customize the model. Realistically, a highly individualized model may not be necessary, feasible, or scientifically plausible. Often, the information necessary to create a highly individualized model will not be available because health systems will be either unwilling or unable to supply it. A reasonable compromise would be for the health system to request a model based on national norms or a pre-existing model with the manufacturer justifying the relevance of the data to the health system's patient population. In addition, the model should be adaptable, allowing the health system to change multiple elements by inserting its own data. Once a manufacturer has received an unsolicited request letter, it could facilitate this process and avoid misunderstandings by asking the health system to answer a standard set of questions that would detail the information they would be willing to accept, such as national norm data or a pre-existing model. A manufacturer's dossier that met the health system's criteria would conform to the FDA's requirements for responses to Unsolicited Requests.

COMMENT EIGHT

There is an attitude among many health care professionals that all information coming from pharmaceutical companies is biased. Therefore, they assume that all pharmacoeconomic models created or sponsored by the pharmaceutical industry are of little value.

Certainly health care systems should expect that pharmaceutical manufacturers would exert considerable effort to put their products in the best light. Pharmacy & Therapeutics Committee members understand this principle and therefore examine all information with a degree of skepticism. It is healthy to be skeptical of information if it motivates an individual to carefully review studies to determine the accuracy of data and the conclusions drawn from them. If health care professionals assume that all pharmacoeconomic work or any other data is completely biased and of limited value simply because it is completed by industry, they ignore the fact that some of the best scientists and thought leaders trained in pharmacoeconomics have been hired by the pharmaceutical industry. Their work can be excellent. Successful implementation of the *Format* process requires a commitment on the part of the health system to devote resources to critically appraise the data supplied by manufacturers before its submission to the P&T Committee. In addition to a critical evaluation of the clinical information, the review should include an evaluation of the economic data by one trained in pharmacoeconomics.