



The AMCP *Format for Formulary Submissions*
Version 3.1

*A Format for Submission of Clinical and Economic
Evidence of Pharmaceuticals in Support of
Formulary Consideration*

Developed by the AMCP *Format* Executive Committee

December 2012



Academy of
Managed Care
Pharmacy®

100 North Pitt Street | Suite 400 | Alexandria, VA 22314

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of Pharmaceuticals in Support of Formulary Consideration**

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(Addenda added December 2012)

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100 N. Pitt Street, Suite 400
Alexandria, VA 22314
(703) 683-8416
www.amcp.org

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Version 3.0 Work Group Members: Jon Montague Clouse, BS Pharm, MS, Director, Pharmacoeconomic Evaluations, UnitedHealth Pharmaceutical Solutions; Lida R. Etemad, PharmD, MS, Senior Director, PDL Development, UnitedHealth Pharmaceutical Solutions; Helen Lee Phan, PharmD, MBA, Clinical Pharmacist, CareFirst BlueCross BlueShield; David L. Veenstra, PharmD, PhD, Professor of Pharmacy & Public Health Genetics, Pharmaceutical Outcomes Research and Policy Program, University of Washington (Also Chair of CDT Addendum Work Group); and Richard J. Willke, PhD, Head, Global Health Economics and Outcomes Research, Primary Care, Pfizer Inc.

Addenda Writing and Review Work Group Members: Eleni Samaras Allen, PharmD, Senior Medical Writer, Payer & Value-Based Communications, Amgen, Inc; Rebecca B. Arbuckle, RPh, MS, Director, Drug Use Policy & Pharmacoeconomics (Retired), M.D. Anderson Cancer Center; Trisha Brown, MS, CGC, Vice President, Clinical Affairs, DNA Direct; Josh J. Carlson, MPH, PhD, Assistant Professor, PORPP, University of Washington Department of Pharmacy; Talia Foster, MS, Senior Research Scientist, United BioSource; Kevin Host, PharmD, Sr. Vice President, Specialty Pharmacy, OptumRx; Anne M. Libby, PhD, Associate Professor, Center for Pharmaceutical Outcomes Research, University of Colorado School of Pharmacy; Dell Mather, PharmD, VP Clinical Services & Operations, NovoLogix, Inc.; Michael A. Nameth, RPh, MBA, Executive Vice President, Walgreens Specialty Pharmacy; John Ridge, Director, Global Reimbursement & Healthcare Economics, Ventana Medical Systems, Inc.; Evelyn Sarnes; PharmD, MPH, Senior Director, Medical Communications, Xcenda; Brian K. Solow, MD,

FAACP, Chief Medical Officer, OptumRx; and Daryl Spinner, MBA, PhD, Senior Life Sciences Consultant, Quintiles Consulting.

PREFACE

VERSION 3.1: CHANGES TO THIS VERSION OF THE AMCP *FORMAT* ARE LIMITED TO THE INCLUSION OF THREE ADDENDA INTENDED TO CLARIFY THE USE OF COMPARATIVE EFFECTIVENESS RESEARCH WITHIN THE CONTEXT OF THE *FORMAT* AND CLARIFY THE EVIDENCE REQUIREMENTS FOR AND THE USE OF THE *FORMAT* WHEN CONSIDERING FORMULARY PLACEMENT, COVERAGE AND REIMBURSEMENT FOR SPECIALTY PHARMACEUTICALS AND COMPANION DIAGNOSTIC TESTS. SEE PAGE VIII FOR MORE INFORMATION AND PAGE 21 FOR THE ADDENDA.

NOTE: The term healthcare system is used throughout this document to refer to ANY healthcare organization that uses an evidence based process for making pharmaceutical coverage and reimbursement decisions including, but not limited to integrated delivery systems, managed health care plans, pharmacy benefit management companies, health insurance companies, medical groups, hospitals and other institutions, and other organized healthcare systems.

THE ROLE OF THE AMCP *FORMAT*

The evidence requirements contained herein are intended for use by manufacturers of pharmaceuticals, biologics and vaccines who are responding to an unsolicited request from a healthcare system to support reimbursement and/or formulary placement consideration of a new product, new indication, or new formulation of an existing product.

The *Format* and other formulary submission templates and guidelines support the informed selection of pharmaceuticals, biologics and vaccines by:

- a) Standardizing and communicating product and supporting program information requirements;
- b) Requiring projections of product impact on both the organization and its enrolled patient population;
- c) Requesting information on the value of products; and
- d) Making evidence and rationale supporting all choice(s) more clear, transparent and evaluable by decision makers.

The AMCP *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 healthcare system's evaluators and ultimately to its Pharmacy and Therapeutics (P&T) or other technology assessment committees. Further, by assessing the healthcare system impact of using a product, the evidence requested can improve the healthcare system's ability to compare the effects of formulary alternatives on clinical outcomes, value, and economic consequences for the entire healthcare system. According to Neumann, the type of rigorous clinical and economic analysis called for in the *Format* "forces and focuses discussions about the value of health and medical services within a clear theoretical framework. It generates a more careful consideration of available evidence and sheds light on how to target resources to particular clinical practices or subgroups of patients."¹ However, it is important that this information is weighed in the context of other values such as equity, social justice, and the health of individuals as opposed to populations, the "rule of rescue" and other elements of rational resource allocation.^{2,3,4}

¹ Neumann PJ. Why don't Americans use cost-effectiveness analysis? *Am J Manag Care*. 2004;10:308-312.

² 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.

Second, the AMCP *Format* streamlines the evidence acquisition and review process for healthcare system staff. By clearly specifying the standards of evidence implicit in the existing formulary process, the *Format* furnishes pharmaceutical manufacturers with consistent direction concerning the nature and format of information that is expected. In addition, the standardized format allows healthcare system staff to formally evaluate the completeness of submissions received and to easily add the results of the healthcare system's own systematic literature reviews and analysis. Manufacturers should understand that submission of information in the recommended format does not guarantee approval of their product for formulary listing. Manufacturers and healthcare systems should view discussion about, and subsequent submission of a dossier, as a process to improve the quality and layout of information provided, but not as a formula for approval. The *Format* offers a clear, shared vision of the requirements to facilitate the collaboration necessary between healthcare systems and manufacturers to support appropriate and evidence-based drug product evaluation. Recognizing that manufacturers may not have all the requested evidence, especially for new products, the *Format* describes the information requirements necessary to support a comprehensive assessment of the proposed product.

The Academy of Managed Care Pharmacy continues to view the AMCP *Format* as a template or guide, and not a mandate. As such, it does not claim to establish a standard of practice for managed care pharmacy that is directly applicable to the evidence needs of each healthcare system. It is up to individual healthcare systems to decide if and how they will use the AMCP *Format* and how they will operate their formulary review processes.

While the AMCP *Format* does not specify methods for assessing clinical benefit, harms or economic impact, the evidence presented should meet accepted standards of evidence-based medicine and health technology assessment. It is the manufacturer's responsibility to utilize appropriate study designs, analytic techniques and data sources, and the requester's responsibility to critically evaluate the evidence supplied.

CONFIDENTIALITY

The confidentiality of evidence dossiers. The confidentiality of evidence dossiers has been an area of concern since AMCP published the first version of the *Format* in October, 2000. Manufacturers have expressed concern that confidential information submitted as part of an evidence dossier -- e.g., unpublished studies, off-label information, economic modeling data -- will become publicly available, thus exposing sensitive data to competitors, and potentially alarming regulatory authorities worried about misleading promotion. To a large extent, the concerns should be addressed through compliance with FDA guidance on unsolicited requests and with appropriate confidentiality agreements between the healthcare system and the manufacturer. Healthcare systems should be aware that the ability of manufacturers to provide complete information is dependant on the recipient to preserve the confidentiality of that information. We note that evidence dossiers submitted to government authorities in the US, the UK and certain other countries are made available to the public but commercial-in-confidence information, when properly identified by the manufacturer, is redacted for the online version of the report. Special arrangements with public payers, which require public disclosure of information received, may be necessary.

³ Daniels N. Four unsolved rationing problems. *Hastings Center Report*. 1994, 24:27-9.

⁴ 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://www.buseco.monash.edu.au/centres/che/pubs/wp112.pdf>

WARNING: Product dossiers prepared in accordance with the evidence requirements contained in the *AMCP Format for Formulary Submissions* may contain off-label information and information deemed proprietary by the product manufacturer. Therefore, such dossiers may only be distributed in response to an unsolicited request.

Manufacturers may require requesting organizations to sign a confidentiality agreement before providing a dossier. Such agreements may also be required where prepublication data are shared with a healthcare system. Healthcare systems should be willing to sign such agreements and adhere to their terms.

AMCP recommends that manufacturers place a statement on the dossier that it is being provided in response to an unsolicited request.

UNSOLICITED REQUESTS

To qualify as an unsolicited request, the request for information must be truly *unsolicited*. Specifically, the inquiry must be initiated by the requester (formulated in his/her own mind) without prompting, suggestion or solicitation by the drug manufacturer or its employees. The general principles and well-accepted standards that have been established in this field, include: 1) the manufacturer does not prompt or encourage requests, 2) responses focus on data rather than company-generated discussions of those data, 3) individuals with the appropriate scientific and medical training prepare responses, 4) responses do not deliberately go beyond the scope of the request, 5) responses do not include promotional materials, and 6) responses are objective, balanced and scientifically rigorous.

Therefore, at no time, shall an evidence dossier in the *AMCP Format* be sent to a healthcare system without an authentic, validated unsolicited request from the healthcare system directly to the manufacturer. Any violation of this rule, intentional or not, jeopardizes the regulatory safe harbor for unsolicited requests that allows industry to prepare and respond to requests for product dossiers in the *AMCP Format*, as well as the Academy's original intent and mission for the *AMCP Format*.⁵

NOTE UPDATE FROM FDA: In December 2011, the FDA issued a draft guidance called "Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices". Please refer to FDA document for full details at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf>. Also See Appendix C for a more detailed treatment of this issue.

REQUESTS FOR AND SUBMISSION OF UPDATES TO EXISTING DOSSIERS

During recent discussions, FDA regulatory staff has stated that individual unsolicited requests are required to obtain updates to product dossiers that include information on unlabeled uses. **To avoid health systems having to submit potentially numerous unsolicited requests FDA staff agreed that health systems may include in their original unsolicited request for an evidence dossier, a statement**

⁵ Salter FJ, Kramer PF, Palmer-Shevlin NL. Pharmaceutical industry medical communications departments: regulatory and legal perils and pitfalls. *Drug Information Journal* 2000;34;1009-1015.

requesting any new published and unpublished information on labeled and unlabeled uses, including updated dossiers for the specific product. NOTE: The request for updated information must pertain only to the specific information or dossier included in the original unsolicited request. Also, the request for updates must specify a length of time, e.g., 6 months.

MULTIPLE DOSSIERS GENERALLY ARE NOT NEEDED

AMCP recognizes that the evidence requirements contained herein may not meet the evidence needs of all healthcare systems. For example, WellPoint^{6,7} and The Regence Group^{8,9} have recently issued their own detailed evidence requirements. AMCP has learned from WellPoint and The Regence Group that **unless otherwise specified by the healthcare system, manufacturers should submit a single evidence dossier prepared according to the AMCP *Format* with an addendum that contains the additional evidence requirements requested by the healthcare system.**

IMPLEMENTATION DATE FOR VERSION 3.1

Dossiers under development may be converted to Version 3.1 with relative ease. New dossiers developed after February 1, 2013, particularly those incorporating comparative effectiveness research studies and those for specialty pharmaceuticals and companion diagnostic tests should be completed using Version 3.1 evidence guidelines.

NEW EVIDENCE GUIDELINES – Addenda added on Companion Diagnostic Tests, Comparative Effectiveness Research, and Specialty Pharmaceuticals: Since the release of Version 1.0 of the AMCP *Format*, FMCP and AMCP have continued to collect constructive comments on the use of the *Format* from numerous colleagues in the clinical pharmacy and health economics fields. Since the release of Version 3.0 in 2009, we have fielded numerous inquiries regarding the development and use of AMCP *Format*-based dossiers for specialty pharmaceuticals and companion diagnostic tests and the place of comparative effectiveness research within the context of the *Format*.

In order to maintain the *Format* as a “living document” that continues to track with the current trends in technology assessment for coverage and reimbursement, the AMCP *Format* Executive Committee issued a call for comments from creators, users and potential users of AMCP *Format*-based dossiers in health care systems, hospitals and other health care entities, and the pharmaceutical industry. The Committee assembled a panel of experts, vetted all comments and consequently developed addenda specifically related to clarifying the use of Comparative Effectiveness Research within the context of the *Format* and clarifying evidence requirements for and the use of the *Format* when considering formulary placement, coverage and reimbursement for Specialty Pharmaceuticals and Companion Diagnostic Tests... **SEE PAGE 21 and references within each section of the Evidence Requirements**

⁶ WellPointNextRx. The WellPoint Outcomes Based FormularySM. WellPoint Health Technology Assessment Guidelines: drug submission guidelines for new products, new indications, and new formulations, September 2008.

http://www.anthem.com/shared/noapplication/f0/s0/t0/pw_b155849.pdf?refer=ahpprovider&state=in Accessed 11/3/12.

⁷ WellPointNextRx. The WellPoint Outcomes Based FormularySM. WellPoint Health Technology Assessment Guidelines: drug submission guidelines for re-evaluation of products, indications, and formulations, September 2008.

http://www.anthem.com/shared/noapplication/f0/s0/t0/pw_b155850.pdf?refer=ahpprovider&state=in . Accessed 11/3/12.

⁸ RegenceRx. AMCP dossier request form. <http://www.regencerox.com/docs/amcp-dossier-request-form.pdf>. Accessed September 3, 2009.

⁹ The Regence Group. Medication policy development and review process, September 2007.

<http://blue.regence.com/policy/medication/introduction.html>. Accessed September 3, 2009.

COMMUNICATION – THE KEY TO SUCCESS

AMCP believes that to conduct an appropriate technology assessment function for the purpose of making coverage and formulary decisions, there should be substantial on-going communication between the healthcare system and the pharmaceutical company throughout the assessment process in order to manage expectations and maximize the quality of available evidence. Those organizations that have been early adopters of the AMCP *Format* have expressed the importance of and concern for good communication. When a dossier is requested from a healthcare system, it is important for that organization to communicate to the pharmaceutical company basic information such as time-lines, the evaluation process, potential data sources, any special needs that might exist, etc. This also gives the pharmaceutical company an opportunity to discuss its available evidence. If they cannot submit specific studies or provide a certain component of the economic analysis, it is better to understand the limitations up front. AMCP does not suggest that healthcare systems 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.¹⁰

MEDIA FOR DOSSIER AND MODEL SUBMISSIONS

AMCP and FMCP encourage manufacturers to submit dossiers in an electronic format rather than in print. This will help reduce resource expenditures and improve healthcare system staff's ability to transfer evidence directly into P&T committee submission monographs. As with printed dossiers, manufacturers and healthcare systems must ensure that all tenets of the FDA's unsolicited request process are followed (see Appendix C). **In addition manufacturers must provide a transparent, unlocked copy of the model without a graphical interface.** It should be presented electronically as an Excel workbook, ASCII tab-delimited file or an alternative electronic format that is agreed upon by the requesting organization or its consultants and the manufacturer.

CONCLUSION

The persistent rise in health care expenditures, particularly with medical technology, is attributable in part to the unwillingness of the American public to accept limits on the use of health care services. This is also a major factor contributing to resistance to the use of cost-effectiveness analysis in the United States as a policy making tool.¹ Other contributing factors such as a lack of understanding about the conceptual approach, a mistrust of methods and motives, and regulatory and legal barriers may be more easily overcome. However, Daniels and Sabin, writing in *Health Affairs* in 1998 stated, "To change that culture requires a concerted effort at education, and education requires openness about the rationales for managed care plan's decisions."¹¹ 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."¹¹ AMCP and FMCP believe that the AMCP *Format* is a valuable tool that will continue to help healthcare systems establish a record of commitment to rational evidence-based decision-making, thus gaining the confidence of patients, clinicians, payers and members.

¹⁰ Foundation for Managed Care Pharmacy. Response to comments for AMCP's format for formulary submissions Version 2.0. Alexandria, VA. October 2002. Available at <http://www.amcp.org/AMCPFormatforFormularySubmissions>.

¹¹ Daniels N, Sabin JE. The ethics of accountability in managed care reform. *Health Affairs*. 1998; 17(5):50-64.

EVIDENCE REQUIREMENTS FOR FORMULARY SUBMISSION

EVIDENCE REQUIREMENTS FOR FORMULARY SUBMISSION

1.0 EXECUTIVE SUMMARY – CLINICAL AND ECONOMIC VALUE OF THE PRODUCT

Based on the clinical and economic evidence presented in Sections 2 through 5 of the dossier, justify the value of the product. This section of the submission requirements replaces Section 4 of the Version 2.1 of the *AMCP Format for Formulary Submissions* and represents the principal opportunity for a manufacturer to briefly summarize the value of its product. The manufacturer should briefly describe the clinical and economic information presented in the dossier using the layout prescribed in Sections 1.1 and 1.2 and state the expected per unit product cost. 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 evidence, health outcomes, and the economic consequences for the healthcare system.

NOTE NEW EVIDENCE GUIDELINES: If the technology under consideration is a Companion Diagnostic Test or Specialty Pharmaceutical and/or evidence from Comparative Effectiveness Research is included in the dossier, *Format* users should follow the evidence inclusion guidelines in the appropriate addendum beginning on Page 21.

1.1 CLINICAL BENEFITS: Begin with the FDA-approved indication for the drug and a short (1 to 2 paragraph) synopsis of the efficacy and safety information (from the prescribing information and clinical trials). Summarize (**No more than 1 page**) the clinical benefits of the PROPOSED THERAPY, in terms of:

- Efficacy and Effectiveness
- Safety/tolerability
- Shortcomings of current treatment and the unmet medical need that the PROPOSED THERAPY addresses

1.2 ECONOMIC BENEFITS: Summarize (**No more than 1 page**) the economic benefits of the PROPOSED THERAPY, in terms of:

- Cost per unit
- Context of the proposed cost: potential clinical benefits provided (including quality of life benefits) and potential economic benefits (including savings or cost offsets)
- Shortcomings of other therapies

Briefly present results of any observational research or economic data, with inclusion of the PMPM or ICER result at minimum. Briefly summarize other published information on the cost or economic impact of the product (such as impact of resource utilization or other cost offsets).

1.3 CONCLUSIONS - (No more than 1/2 page) - Summarize the value of the PROPOSED THERAPY in 1 to 2 paragraphs. Highlight key points regarding the clinical and economic advantages and uniqueness of the product are highlighted. Finally, based on the information presented in Sections 2 to 5 that follow, the conclusions should include a statement regarding the expected impact of the product, relative to other available treatment options both pharmaceutical and non-pharmaceutical.

2.0 PRODUCT INFORMATION and DISEASE DESCRIPTION

2.1 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 the healthcare system's formulary.

NOTE NEW EVIDENCE GUIDELINES: If the technology under consideration is a Companion Diagnostic Test or Specialty Pharmaceutical and/or evidence from Comparative Effectiveness Research is included in the dossier, *Format* users should follow the evidence inclusion guidelines in the appropriate addendum beginning on Page 21.

The product description consists of information that traditionally has been incorporated in a product monograph, Package Insert (PI) or formulary kit as described below. It also contains information that goes beyond the scope of the package insert, monograph and formulary kit that can only be provided pursuant to an unsolicited request.

NOTE: Basic product information should be provided, including a brief discussion of what the product is, and any significant attributes that define the product's place in therapy (e.g. kinetics, adverse event profile, etc.). Verbatim language from the Package Insert (PI) should not be supplied here. If there is not substantive data and information that can be provided beyond what is in the PI, these sections should be left blank and the reader referred to the copy of the PI which is in the Appendix. In those cases where one or more of these attributes (pharmacology, pharmacokinetics, pharmacodynamics, contraindications, warnings, precautions, adverse events, interactions, and/or dosing) is of major significance in defining the value of a drug, additional information beyond that found in the PI should be provided.

The following are the components that should be supplied:

- 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. The ASP and WAC cost per unit size. (The payers contract price, if available, should be included as well).
- e. AHFS or other Drug Classification
- f. FDA approved indication(s) and the date approval was granted (or is expected to be granted). Also other significant off-label uses and potential new indications being studied.
- g. Pharmacology*
- h. Pharmacokinetics/Pharmacodynamics*
- i. Contraindications*Warnings/Precautions/Adverse Effects*
- j. Interactions,* with suggestions on how to avoid them
 - Drug/Drug
 - Drug/Food
 - Drug/Disease
- k. Dosing and Administration*
- l. Access, e.g. restrictions on distribution, supply limitations, anticipated shortages, and/or prescribing restrictions.
- m. Co-Prescribed / Concomitant Therapies, including dosages, and recommended use of other agents or treatments with the product.

***Verbatim language from the Approved Package Insert should not be supplied here. If there is not substantive data or information that can be provided beyond the label, these sections should be left blank and the reader referred to the copy of the PI which is in the Appendix.**

n. Concise comparison of PI information with the primary comparator products in the same therapeutic area to include: dosing, indications, pharmacokinetic / pharmacologic profile, adverse effects, warnings, contraindications, interactions and other relevant characteristics. (Expand as appropriate for the therapeutic class.) The material may include a discussion of comparator product(s) or services that the proposed product is expected to substitute for, or replace. **This information should be presented in tabular form.** If direct head-to-head trials have been conducted on the drug and its comparators, this should be noted here, and the reader referred to the review of those trials in Section 3 of the dossier.

2.2 PLACE OF THE PRODUCT IN THERAPY (NOTE: FOR PRODUCTS WITH MULTIPLE INDICATIONS, THE FOLLOWING INFORMATION SHOULD BE PROVIDED FOR EACH INDICATION.) IDEALLY, INFORMATION SHOULD BE PROVIDED IN A TABLE OR BULLETED LIST

NOTE NEW EVIDENCE GUIDELINES: If the technology under consideration is a Companion Diagnostic Test or Specialty Pharmaceutical and/or evidence from Comparative Effectiveness Research is included in the dossier, *Format* users should follow the evidence inclusion guidelines in the appropriate addendum beginning on Page 21.

NOTE: INFORMATION PRESENTED IN THIS SECTION SHOULD BE BRIEF. DO NOT DUPLICATE INFORMATION PRESENTED IN SECTIONS 3.0, 4.0, AND 5.0

THIS SECTION INCLUDES THREE PARTS:

2.2.1 DISEASE DESCRIPTION (Limit to 1-2 pages per disease.) The intent is to give the reader a good overall sense of the disease. The disease description should be brief, and should include the disease and characteristics of the patients who are treated for the condition. **Manufacturers should provide a description of specific patient subpopulations in which the drug is expected to be most effective, if known. Include clinical markers, diagnostic or genetic criteria, or other markers, if known, that can be used to identify these subpopulations.** Present a brief summary of information from the literature for each topic. Ideally, information should be provided in a table or bulleted list.

Disease specific descriptive information should include, but not be limited to:

- a. Epidemiology and relevant risk factors, with a focus on identifiable subpopulations that would be appropriate for the use of the product
- b. Pathophysiology
- c. Clinical presentation
- d. Societal, humanistic and/or economic burden

2.2.2 APPROACHES TO TREATMENT (Limit to 1-2 pages per major indication)
The key questions to address are: How is the disease/condition currently treated? How does the new product fit into standard or existing therapy?

Provide a VERY brief summary of information from the literature for each topic; do not duplicate information included in other sections:

- a. Approaches to treatment - principal options / practice patterns
- b. A description of alternative treatment options (both drug and non-drug)
- c. The place and anticipated uses of the proposed therapy in treatment (e.g. first line), especially for any subpopulations that can be targeted for the use of the product.

- d. Proposed ancillary disease or care management intervention strategies to be provided by the manufacturer that are intended to accompany the product at launch.
- e. The expected outcomes of therapy, e.g. a cure, palliation, relief of symptoms, etc. Describe any clinical markers that are linked to disease outcome, e.g. LDL lowering
- f. Description of other drug development or post-marketing obligations as required by the FDA such as a Risk Evaluation and Mitigation Strategy (REMS), Phase IV trial, patient registry, restricted distribution channel, and other elements designed to assure the safe use of the product.
- g. Other key assumptions and their rationale.

2.2.3 RELEVANT TREATMENT GUIDELINES AND CONSENSUS STATEMENTS FROM NATIONAL AND/OR INTERNATIONAL BODIES.

This section should describe the treatment guideline’s position on the therapy. Include position statements and validated tools from national organizations and international HTA bodies, e.g., NICE. Next, an attempt should be made to generalize these findings to the populations of the requesting organization. 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. The requesting organization and the manufacturer should determine the relevant treatment options for comparison during the initial pre-submission meeting.

2.3 EVIDENCE FOR PHARMACOGENOMIC TESTS AND DRUGS

In considering the appropriate use of genetic testing to guide drug therapy (variously referred to as ‘pharmacogenomics’, ‘pharmacogenetics’, ‘personalized medicine’, or ‘targeted therapy’), clinicians and healthcare system decision makers must consider the accuracy with which a test identifies a patient’s genetic status (analytic validity), clinical status (clinical validity), and the risks and benefits resulting from test use (clinical utility).¹² The following evidence should be presented as appropriate in support of submissions involving pharmacogenomic testing, or drugs for which pharmacogenomic testing is available:

See the Companion Diagnostic Tests Addendum on Page 21 for detailed evidence guidelines.

Analytic Validity

- Accuracy with which a particular genetic characteristic can be identified using a genetic test in relation to professional standards and federal regulation requirements.

Clinical Validity

- Strength of the association between the genetic variant(s) and clinical outcome(s) (e.g., efficacy, adverse drug reaction)
- Expected prevalence of genetic variant(s) in target population; positive predictive value (PPV) and negative predictive value (NPV) of test

Clinical Utility

- Effectiveness and safety of the clinical intervention implemented as a result of the genetic test, as per Sections 3.1-3.3 of the *Format*; consider inclusion of quantitative risk-benefit decision analytic modeling (Section 4.1.1 of the *Format*).

¹² U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research and Center for Devices and Radiologic Health. Guidance for industry: pharmacogenomic data submissions. March 2005. (<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126957.pdf>). Accessed November, 2012.

Cost Effectiveness

- Expected difference in costs and outcomes with pharmacogenomic testing compared to usual care, as per Section 4.2.3 of the *Format*, including cost offsets from changes in drug utilization and health outcomes.

3.0 SUPPORTING CLINICAL EVIDENCE

3.1 SUMMARIZING KEY CLINICAL STUDIES: [2 page maximum per study; please complete evidence tables in the design requested by the healthcare system or as suggested in appendix F]

Submit summaries of all relevant clinical studies that have been conducted, whether published or not, in each of the categories listed in Sections 3.1.1 and 3.1.2. Refer also to the Relevance Criteria below.

NOTE NEW EVIDENCE GUIDELINES: If the technology under consideration is a Companion Diagnostic Test or Specialty Pharmaceutical and/or evidence from Comparative Effectiveness Research is included in the dossier, *Format* users should follow the evidence inclusion guidelines in the appropriate addendum beginning on Page 21.

NOTE: To avoid duplication, include ALL relevant clinical studies (summaries and evidence tables) only in Section 3.0 and all relevant economic studies (summaries and evidence tables) only in Section 5.0. However, if a study reported both clinical and economic outcomes, include the study summary in this section. Tabulate the clinical results in Section 3.1.1. To avoid duplication, Section 5.0 should refer to the summary description in Section 3.1. Economic outcomes should be tabulated in Section 5.0.

Include detailed summaries for all relevant clinical studies.

All of the following items that apply should be included in the study summaries:

- a. Name of the clinical trial or study and publication citation(s)
- b. Objective, location and study date;
- c. Trial design, randomization and blinding procedures;
- d. Setting, inclusion and exclusion criteria;
- e. Sample characteristics (demographics, number studied, disease severity, co-morbidities)
- f. Drop-out rates and procedures for handling drop-outs (ITT, per protocol, etc.);
- g. Treatment: dosage regimens, washout period, etc.
- h. Clinical outcome(s) measures;
 - Outcomes evaluated
 - **Delineate primary vs. secondary study endpoints and their corresponding results**
- i. Other outcome measures (e.g., patient-reported outcomes);
 - Principal findings
- j. Statistical significance of outcomes and power calculations;
- k. Validation of outcomes instruments (if applicable);
- l. Generalizability of the population treated;
- m. Study limitations, as stated by the authors;
- n. Publication citation(s)/references used including funding source of the study.

RELEVANCE CRITERIA - Use the following criteria to determine relevance:

1. Relevant studies that provide clinical information that may impact formulary decisions, including but not limited to:
 - Safety, including total number of patients exposed to the drug
 - Efficacy, effectiveness and comparative effectiveness
 - **See the Comparative Effectiveness Research (CER) Addendum on page 27 for details on inclusion of CER.**
 - Identification of patient subgroups, practice settings, etc. in which use of the drug may be more appropriate.
2. Include all Phase 3 clinical trials.
3. In general, include all large, randomized controlled trials.
4. Include smaller studies, e.g., Phase 2 trials, only if they contain relevant information that is not provided by larger studies.
5. Include studies conducted in settings outside the U.S. if they add new information not contained in the U.S. trials.
6. Do not include basic pharmacologic studies, e.g., Phase 1 studies.
7. Do not include purely pharmacokinetic studies, unless the value proposition is based on the pharmacokinetic properties of the product, or the studies identify an appropriate patient subgroup.

3.1.1 INCLUDE ALL RELEVANT PUBLISHED AND UNPUBLISHED CLINICAL STUDIES SUPPORTING LABELED INDICATIONS:

1. Placebo-controlled safety and efficacy trials
2. Prospective effectiveness and comparative effectiveness trials, including pragmatic trials
 - a. **See the Comparative Effectiveness Research (CER) Addendum on page 27 for details on inclusion of CER in dossiers.**
3. Open-label safety extension studies
4. Prospective studies examining other non-economic endpoints such as health status measures and patient-reported outcomes. If the instruments utilized in these studies are supported by previous validation and reliability studies, also reference these studies
5. Unpublished data: Provide as much detail as can be disclosed.

3.1.2 INCLUDE ALL PUBLISHED AND UNPUBLISHED DATA AND CLINICAL STUDIES SUPPORTING OFF-LABEL INDICATIONS:

1. Include all relevant studies of the types listed in 3.1.1 above.
2. Include off-label indications that are reasonably likely to be considered by practitioners, based on the available supporting evidence. Provide contact information for questions about other uses.
3. Unpublished data: Provide as much detail as can be disclosed.
4. This constitutes an unsolicited request for ALL relevant studies supporting off-label uses of the product.

Studies reported in this section should be summarized in a clear, concise format **and include all relevant positive and negative findings**. (See above relevance criteria.) If the results of a trial have been published as more than one paper, all may be combined into one summary and one evidence table row, citing all the articles from which data have been drawn and clearly stating the total number of subjects. The payer 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 different patient populations. Systematic reviews or meta-analyses are to be included in Section 5.0

Include citations for all known published clinical studies in the bibliography section. **Reprints of relevant published studies should be available upon request. Where possible, provide a link to original sources if they are free.**

Additional items:

- Include relevant data and findings from the Center for Drug Evaluation and Research’s Office of Drug Safety.
- Include confirmation that trials for the product are registered in a public trials registry and provide access information (e.g. www.clinicaltrials.gov).
- Include list of ongoing clinical trials and links to their registry information.

3.1.3 CLINICAL EVIDENCE SPREADSHEETS OF ALL PUBLISHED AND UNPUBLISHED TRIALS

Information from all relevant studies on the product should be summarized in evidence tables in the design requested by the healthcare system or as suggested in Appendix F, Template for P&T Committee Monograph. **Include negative or null findings as well as positive findings.**

When including pragmatic trials or observational studies that contain both clinical and economic endpoints include the clinical endpoints in the clinical evidence table and include the economic endpoints in the table that summarizes published CEAs (Section 5.1.2).

Evidence tables should include the following data elements:

- Citation, (if unpublished, give abstract information or indicate “data on file”)
- Treatments
- Sample size and length of follow-up
- Inclusion/exclusion criteria
- Design
- Primary Endpoints
- Secondary Endpoints
- Results: Provide an explicit statement of effect size, not just relative risk reduction and/or statistical significance. Within the Results column, include a table of key results
- Statistical significance

3.1.4 SUMMARY OF EVIDENCE FROM SECONDARY SOURCES

Relevant evidence may be available from a variety of secondary sources. The following may be submitted. Summaries should be concise, focusing only on the major conclusions:

- Cochrane Collaboration systematic reviews
- Formal, published systematic reviews from peer-reviewed journals
- Agency for Healthcare Research and Quality (AHRQ) evidence summaries
- Health technology assessments from other recognized agencies, public or private, including reviews from other countries.
- Evidence-based clinical practice guidelines, medical society position statements, etc. These documents should include explicit evidence grading criteria

- Compendia officially recognized by the Secretary of Health and Human Services that list the drug. If these references are available only by subscription, provide PDF documents or reprints of the relevant content.

Summaries of information from one of these sources should be limited to a maximum of one page.

4.0 ECONOMIC VALUE and MODELING REPORT [maximum 20 pages]

“Far better an approximate answer to the right question, which is often vague, than an exact answer to the wrong question, which can always be made precise.” *John W. Tukey, 1962*

4.1 MODELING OVERVIEW

This section presents an overview of the rationale, approach, and suggested methods for developing a decision-analytic based cost-effectiveness model. The intent of the model is to quantify for the healthcare system the risk-benefit tradeoff of the product, and its economic value.

NOTE NEW EVIDENCE GUIDELINES: If the technology under consideration is a Companion Diagnostic Test or Specialty Pharmaceutical and/or evidence from Comparative Effectiveness Research is included in the dossier, *Format* users should follow the evidence inclusion guidelines in the appropriate addendum beginning on Page 21.

4.1.1 UTILITY OF MODELING FOR DECISION-MAKING

Available data on the clinical benefits and harms and economic impact of the drug under consideration are provided in Sections 3 and 5 of the AMCP *Format*, and are the core of evidence-based decision-making. These data, however, may have important limitations for decision-making. For example,

- Randomized controlled trials (RCTs) may not include all relevant comparator interventions
- The duration of follow-up in RCTs may be limited
- Patient populations in RCTs may not be reflective of plan populations
- Safety data may be limited, or from disparate sources
- Healthcare cost impacts may not be generalizable across payers

These limitations have led to recent efforts in comparative effectiveness research to improve the quantity and quality of information available to healthcare decision makers. Comparative effectiveness data – derived from studies including relevant populations, comparators, and outcomes - will prove highly valuable to healthcare system formulary decision makers, and should be reported in Section 3 of the *Format*. These data are more likely (and should be expected) to be available for more mature products. In addition, evidence may be generated through pay for performance or coverage with evidence development schemes. Synthesis and evaluation of these data will remain challenging, however, and are unlikely to be available for new products.

See the Comparative Effectiveness Research (CER) Addendum on page 27 for details on inclusion of CER.

Decision-analytic based, cost-effectiveness models are one of the best available means to assess the overall potential value of healthcare technologies. They are disease-based and take into account the impact of the new technology on the clinical outcomes for the target population. Typically, they include evidence on the incidence of the disease or condition in the target population, the medical care required to diagnose and treat the disease, the relative and absolute risk reductions offered by the

technology, survival and quality of life impacts, and the costs of the interventions. Decision models can provide:

- An explicit framework for decision-making
- Synthesis of evidence on health consequences and costs from many different sources
- Formal assessment of uncertainty
- A quantitative measure of clinical risk-benefit
- Explicit and evaluable assumptions
- Specificity for a product's role or place in therapy
- Benchmarks against which the product's future performance can be measured.

Models are not without challenges. In particular, because of the complexity and inherent required assumptions, models can be perceived a 'black-box' approach or biased. The AMCP *Format* has been developed to help address these limitations by providing a consistent format for conducting and reporting cost-effectiveness models to improve their transparency and acceptability.

4.1.2 TYPES OF MODELS

Cost-effectiveness models.

There are several types of models that can be helpful for managed care decision makers. The focus of the AMCP *Format* is the clinical and economic value of drug therapies for plans and their members. Evaluations that include impacts on patients – e.g., morbidity and mortality – and on healthcare costs are thus most relevant, and termed in general 'cost-effectiveness models.' These models are primarily useful for assessing the overall clinical risk-benefit and economic value of a drug in relation to drugs in its class and other healthcare interventions in general, and are the primary focus of this Section. There are several specific types of cost-effectiveness models, which are discussed in the Methods section below.

Budget impact models.

Budget impact models are not intended to establish the overall value of healthcare technologies because they do not include the full impact of the technology on clinical and patient outcomes. They can be useful for estimating system-wide (e.g., pharmacy and medical) budget impacts, however, and are commonly used by managed care payers. These models, as defined here, estimate drug costs, healthcare cost offsets, and adverse event costs, as well as the expected utilization in the healthcare system, to derive projected per member per month costs. Budget impact models utilize clinical data and can be relatively complex, and thus should follow the recommendations in this section, as well as published best practices¹³ (see also Appendix E).

Financial models.

Financial models provide an estimate of the financial impact of a new technology on the pharmacy budget only because they typically include drug costs, network or other discounts, rebates, co-payment and other benefit design impacts, but no evaluation of clinical effects or other economic consequences. Payers usually have the necessary internal resources to develop such models. Although these models may be useful for negotiations between manufacturers and payers, they are not central to the evidence- and value-based decision making process, and are not addressed further in the *Format*.

4.1.3 OTHER CONSIDERATIONS

- When a product is intended for treatment of more than one disease or indication, its impact should be modeled for each, unless a reasonable case can be made for a single model, such as may be the case for budget impact models.

¹³ Mauskopf JA, Sulluvan SD et al. Principles of good practice for budget impact analysis: Report of the ISPOR task force on good research practices-budget impact analysis. *Value Health* 2007; 10:336-347.

- Models that have been previously developed may be adapted for use according to the AMCP *Format*. An existing model should be modified to follow the general framework described in this document and must be able to demonstrate the system-wide impact of introducing the product to healthcare system formularies. Evidence supporting the validity of existing models should be provided, as well as sufficient documentation on their design, functioning, and data inputs.
- Cost-effectiveness analyses conducted alongside RCTs, particularly when of sufficient size and follow-up, can provide useful and sometimes substantial evidence of economic value. Cost-effectiveness models should be considered complementary to such studies, allowing for the adjustment of healthcare resource use, unit costs, effectiveness, and practice patterns.
- Lastly, users of this document should recognize the *Format* is a set of recommendations on the types of evidence and reporting formats that are likely to be useful for managed care decision makers. We recognize the need for flexibility, however. Specific requirements are determined by individual managed care organizations, and may consist of data requests or methods beyond those outlined in this document.

4.2 MODELING APPROACHES AND METHODS

4.2.1 APPROACH AND FRAMEWORK

Guidelines

Manufacturers should consult with healthcare system staff in the early stages of model development to identify optimal modeling approaches and ensure the incorporation of appropriate comparator products and endpoints. In general, the cost-effectiveness framework should consider recommendations published by the *Panel on Cost-Effectiveness in Health and Medicine* convened by the U.S. Public Health Service,¹⁴ and the model should follow the guidance provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Good Practice Modeling Principles.¹⁵ (Also Appendix E)

The model should be disease-based, and 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 – preferably based on treatment guidelines or actual practice
- c) Costs of product and other medical resources consumed within each clinical pathway.
- d) Outcomes of therapy for each clinical pathway
- e) Incremental cost and outcomes analysis presented in cost/consequences tables and as cost-effectiveness ratios.

Analytic framework

The general category of ‘cost-effectiveness’ models includes analyses that value outcomes by assessing clinical events, life expectancy, and/or quality-adjusted life-years (QALYs). Clinical events are more readily interpretable by clinicians and allow for direct assessment of the impact of clinical data, but cost per event avoided calculations are not comparable across disease areas. In contrast, QALYs allow for assessment of overall healthcare value, but may be more difficult to interpret from a healthcare system perspective. It is thus recommended that clinical events, life expectancy, and QALYs all be assessed – with the latter two outcomes primarily relevant for lifetime timeframe analyses. The results should be reported separately, as outlined subsequently in this section. Exclusion of any of these endpoints should be justified.

¹⁴ Gold MR, Siegel JE, Russell LB, Weinstein MC. *Cost-effectiveness in health and medicine*. New York, NY, Oxford University Press, 1996.

¹⁵ Weinstein MC, O’Brien B et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR task force on good research practices – modeling studies. *Value Health*. 2003; 6: 9-17.

Modeling technique

There are several decision-analytic based approaches to constructing disease-based cost-effectiveness models, primarily: 1) decision trees, 2) Markov (cohort) models, and 3) patient-level simulation (discrete event simulation). There are advantages and disadvantages to each technique, primarily related to the conflicting factors of transparency and data availability vs. the complexity of many diseases and their treatments. It is recommended that the simplest feasible modeling approach be utilized – in other words, the model should be sophisticated enough to capture the key aspects of the disease and treatments, yet be well supported by high-quality data that are available to and interpretable by the user.

Perspective and Timeframe

The payer perspective is recommended for the primary analysis, with optional perspectives (i.e., societal, employer) conducted as secondary evaluations. The 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 the healthcare system. Multiple timeframes are recommended for chronic disease – e.g., 5-year, 10-year, and lifetime. Adjustment for time preference should be incorporated as appropriate and follow US PHS Panel recommendations (i.e., discounting both future costs and health effects at a 3% annual rate).¹⁴

4.2.2 DATA SOURCES

The identification, selection, interpretation, and use of data to inform the model is the most important aspect of the modeling process, and should receive ample attention from model developers and users. The analysis should be based on the highest-quality and most up to date clinical, epidemiologic, patient, and economic data available. The process for identifying, evaluating, and selecting all of the data in the model should be clear and systematic.

It is extremely important that modeled claims for cost-effectiveness derive from data from one or more comparative effectiveness trials. These should:

- Directly compare and quantify treatment effects and other relevant patient-reported outcomes (including quality of life)
- Assess patient and community preferences for alternative therapies;
- Quantify costs and benefits over the natural course of the disease;
- Assess resources used to support alternative therapies; and
- Evaluate the impact of uncertainty on the claims made for alternative therapies

See the Comparative Effectiveness Research (CER) Addendum on page 27 for details on inclusion of CER in dossiers.

Parameter estimates used in the model for the drug under consideration should be closely linked with the evidence provided in all Sections of the *Format*. All necessary assumptions should be clearly stated. In addition to the identification of base-case estimates for the model, ranges for parameters should be determined and well-referenced.

Drug effectiveness

Randomized controlled trial data should form the basis of all efficacy or effectiveness estimates, and justification should be provided for inclusion and exclusion of any RCTs potentially relevant to the analysis.

Drug safety data

Clinically relevant adverse events observed in RCTs should be included in the model, as well as safety signals derived from appropriate observational studies. A wide range of estimates should be explored given the challenge of accurately ascertaining the likelihood of low-probability events.

Economic data

Unit costs data ideally would be based on healthcare system data. If specific healthcare system data are not available, costs from representative U.S. private payers, or Medicare, can be used. Decision-analytic models should be sufficiently flexible to adapt the input assumptions to conform to local practice patterns.

Utilities

Preference estimates should be derived from studies surveying either patients or the general population, using a direct elicitation method or an instrument such as the EQ-5D or HUI.

Demographic and practice pattern data

Demographic and practice pattern data from the healthcare system should be incorporated as appropriate to improve the relevance of the model.

Surrogate markers

When surrogate markers are used to model longer-term outcomes, specific evidence should be provided supporting their validity.

Expert opinion

Data derived from expert panels are not generally acceptable, especially for key effectiveness or safety variables. However, this approach may be reasonable for other variables where estimates are not available through literature, databases, trials or other normal sources. In such cases, the expert assumptions should be clearly stated and thoroughly tested in sensitivity analyses. Inputs obtained from an expert panel should be modifiable in case local opinion leaders disagree with the panel members.

Efficacy vs. effectiveness

When feasible and scientifically plausible, efficacy results from RCTs should be transformed into effectiveness parameters. This may involve inclusion of an adherence parameter into the model based on observational data. Documentation and clear description of the methodology will be necessary in order for healthcare system staff to evaluate the validity of this approach.

4.2.3 ANALYSIS

Base-case estimates

The expected (average) clinical and economic outcomes should be calculated for each strategy evaluated, as well as incremental costs, effectiveness, and cost effectiveness. Differences in the absolute risk of events should be determined, and healthcare cost offsets vs. drug costs independently determined. Clinical risk-benefit tradeoffs should be explicitly presented and discussed.

Sensitivity analysis

Comprehensive one-way sensitivity analysis of all parameters in the model is strongly recommended, including assessment of impacts on both incremental effectiveness (e.g., QALYs) and cost-effectiveness. Scenario analyses testing the assumptions used in the model are also highly recommended. The 3-5 parameters and 2-3 assumptions that have the greatest impact on the results should be identified. Probabilistic sensitivity analysis and the generation of cost-effectiveness scatter plots and acceptability curves are recommended, particularly for more complex models.

4.3 MODELING REPORT AND INTERACTIVE MODEL

4.3.1 TRANSPARENCY

Transparency and clarity of presentation are a necessity. The need for and value of transparency is widely recognized and can provide some protection against the negative effects of bias and error. The users of models need to be able to understand all steps in the modeling process to improve their understanding of the key factors and variables in the model and its limitations.¹⁶ Therefore, researchers are encouraged to focus efforts on the clarity and transparency of results. Detailed descriptions that explain the flow of data through the model are recommended. All calculations should be explained in a simple straightforward manner to allow a non-health economist to comprehend the analysis. This information and references should be accessible both in the report format as well as shown directly in the model to maximize the ease of review.

Listed below are the recommended requirements for modeling reports and interactive models.

4.3.2 MODELING REPORT FORMAT

The modeling report should follow the format: 1) Introduction/Background, 2) Methods, 3) Results, 4) Limitations, 5) Discussion. A 500 word abstract following this same format should be provided on the first page of the modeling report, and include an explicit description of the key drivers of the model results identified in sensitivity and scenario analyses.

Below are the minimum recommended figures and tables. Multiple tables in each category (e.g., Table 1a, 1b, etc.) may be used if needed.

Figure 1. Provide a figure displaying the structure of the model (e.g., a decision tree or Markov model). A simplified schematic diagram may be used for ease of presentation, but a detailed figure should also be included.

Table 1. Provide a table listing all of the model inputs, including probabilities, costs, and utility estimates if appropriate. Provide a range of values upon which sensitivity analyses are based for each input.

- a. Include references in the table for all inputs, including ranges.
- b. Note in the table estimates that lack supporting evidence.

Table 2. Provide an explicit list of model assumptions, including assumptions about comparator interventions, clinical events, patient management, and costs.

Table 3. Present the disaggregated results in a table (e.g., cost-consequence style, with costs presented separately from health outcomes). Data presented in this format are more easily understood and interpreted by healthcare system formulary committees. The following specific data should be presented for each strategy:

- a. The projected clinical events (e.g., heart attacks, cirrhosis, recurrence)
- b. The life expectancy and QALY estimates
- c. Total healthcare costs
- d. The cost of implementing therapy and the resulting cost offsets.
- e. Incremental cost-effectiveness ratios

Figure 2. Present one-way sensitivity analyses on all model inputs in a figure (e.g., tornado diagram) or a table.

- a. Clearly present the model inputs or assumptions that drive the difference in 1) costs, 2) effects, and 3) incremental cost-effectiveness.
- b. When appropriate, present multi-way (e.g., 2-way, best/worst case scenario, probabilistic) sensitivity analyses

¹⁶ Garrison LP. The ISPOR good practice modeling principles – a sensible approach: be transparent, be reasonable. *Value Health* 2003; 6:6-8.

4.3.3 INTERACTIVE MODEL

Model characteristics

To improve transparency and ease of use, it is recommended that models be implemented in spreadsheet software. Other software packages should only be used if the user a) is familiar with them, and b) agrees with the manufacturer to their use. Custom software models are generally discouraged, but may be feasible for use if clearly documented in peer-reviewed publications and a users manual. Interactive models should have the following characteristics:

- All data and calculations relevant to the cost-effectiveness model should be contained in the spreadsheet and visible to the user.
- All inputs should be modifiable by the user.
- To the extent feasible, the model, its logic and its calculations should be clear and self-documenting, using best practices for formatting, comments, and explanatory guides such as text boxes.
- Allow for analysis of relevant sub-populations (age, gender, co-morbidities) where applicable.
- Allow the healthcare system to incorporate its own data (membership size, prevalence rates, cost estimates, etc.) in place of default data, such as national norms.
- Provide automated 1-way sensitivity analysis.

Model accessibility

It is recommended that the healthcare system require that an interactive model be made available electronically, preferably after meeting with the manufacturer to discuss its design, results, and use. If the manufacturer will not provide an interactive model for the payer's use, a clear statement to this effect and standing policy should be provided in the modeling report. Alternative approaches include interactive modification of the model with a representative of the manufacturer, although such arrangements are significantly less desirable.

Model users should recognize that input parameters must be plausible, and many combinations of inputs in complex models will not be self-consistent. Thus, users should modify model inputs based on available data and reasonable assumptions.

5.0 OTHER SUPPORTING EVIDENCE

5.1 SUMMARIZING OTHER RELEVANT EVIDENCE: [2 page maximum per study]

See the Comparative Effectiveness Research (CER) Addendum on page 27 for details on inclusion of CER.

Provide summaries of other relevant supporting evidence including, but not limited to, retrospective studies that provide information not available from clinical trials, meta-analyses and systematic reviews of clinical, quality of life and economic outcomes, comparative observational studies of effectiveness and harms, assessments of adherence or persistence, studies of patient preference, predictive risk models, and indirect comparisons of clinical benefit using Bayesian or other appropriate methods, whether published or not. Conduct and reporting of studies of the type described above should follow accepted practice as evidenced by published methodology and reporting guidelines from reputable professional societies or government agencies.

<p>NOTE NEW EVIDENCE GUIDELINES: If the technology under consideration is a Companion Diagnostic Test or Specialty Pharmaceutical and/or evidence from Comparative Effectiveness Research is included in the dossier, <i>Format</i> users should follow the evidence inclusion guidelines in the appropriate addendum beginning on Page 21.</p>
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5.1.1 INCLUDE PUBLISHED AND UNPUBLISHED STUDIES SUPPORTING LABELED AND OFF-LABEL INDICATIONS

Refer to Section 3.1 and 3.1.1 for items to be included in the study summaries and for relevance and grading criteria.

In addition, summaries of relevant economic studies should include the following:

- Definition of economic endpoints (mean overall cost, cancer-related cost, \$/LYG, \$/QALY, etc.) including references for standard of care costs
- Data sources for economic endpoints
- Statistical methods/math used to calculate endpoints
- Modeling methodology (if applicable)
- Sensitivity analysis (if applicable)
- Unpublished data: Provide as much detail as can be disclosed.

Include complete citations for all studies summarized in this section. Reprints of relevant published studies should be available upon request. Where possible, provide a link to original sources if they are free of charge.

5.1.2 EVIDENCE TABLE SPREADSHEETS

Information from all studies described in this section should be summarized in evidence tables (spreadsheet format). **Include negative or null findings as well as positive findings. Use a standard evidence table format, such as that contained in Appendix F, Template for P&T Monograph. Refer to Section 3.1.3 for suggested data elements.**

6.0 SUPPORTING INFORMATION

6.1 REFERENCES CONTAINED IN DOSSIERS

Include citations for all known published clinical and economic studies in the bibliography section. **Reprints of relevant published studies should be available upon request. Include the PI in the Appendix and where possible, provide a link to original sources if they are free.**

6.2 DOSSIERS AND ECONOMIC MODELS

Media: AMCP and FMCP encourage manufacturers to submit dossiers in an electronic format rather than in print. This will help reduce resource expenditures and improve healthcare system staff's ability to transfer evidence directly into P&T committee submission monographs. As with printed dossiers, manufacturers and healthcare systems must ensure that all tenets of the FDA's unsolicited request process are followed (see Appendix C). **In addition manufacturers must provide a transparent, unlocked copy of the model without a graphical interface.** It should be presented electronically as an Excel workbook, ASCII tab-delimited file or an alternative electronic format that is agreed upon by the requesting organization or its consultants and the manufacturer.

Transparency: 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. **The requesting organization 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 should be either attached as appendices or made readily available upon request.

Terms and Definitions

Budget Impact Models: See definition in Section 4.1.2.

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.¹⁷

Comparative Effectiveness Research (CER): A common definition of CER used by the Institute of Medicine states: “Comparative effectiveness research is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population level.”¹⁸ This definition has been adopted for the purposes of the CER addendum on page 28.¹⁸

Companion Diagnostic Tests: Companion diagnostic tests have been defined in various ways. The U.S. Food and Drug Administration (FDA) definition describes a CDT as one that provides information that is essential for the safe and effective use of a corresponding therapeutic product.¹ More generally, in this addendum, a CDT is defined as a test that provides information that improves the safety or effectiveness of a drug or biologic. CDTs can be used to:

- Identify patients who are most likely to benefit from a particular therapeutic product
- Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product
- Monitor patient response to treatment for the purpose of adjusting the treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness

Companion diagnostic tests (both IVDs and medical imaging) may assess the presence of molecular biomarkers including the following forms:

- Genomic/epigenomic (deoxyribonucleic acid-based) biomarkers
- Transcriptomic (ribonucleic acid-based) biomarkers
- Proteomic (protein-based) biomarkers
- Metabolomic (metabolite-based) biomarkers

Cost-Benefit Analysis: An analytical technique derived from economic theory that enumerates and compares the net costs of a health care intervention with the benefits that arise as a consequence of applying that intervention. For this technique, both the net costs and the benefits of the health intervention are expressed in monetary units.¹⁷

Cost-consequence Analysis: An analytical technique that compares the health intervention of interest to one or more relevant alternatives, listing the cost components and various outcomes of each intervention separately. This type of economic analysis does not indicate the relative importance of the components listed and leaves it to the decision maker to form his or her own view.¹⁷

¹⁷ International Society for Pharmacoeconomics and Outcomes Research. Health care cost, quality, and outcomes: ISPOR book of terms. 2003

¹⁸ Institute of Medicine. Initial national priorities for comparative effectiveness research. Report Brief. June 2009. Available at: <http://www.iom.edu/~media/Files/Report%20Files/2009/ComparativeEffectivenessResearchPriorities/CER%20report%20brief%2008-13-09.pdf>. (Accessed 9/1/2012)

Cost-Effectiveness Analysis: A systematic method of comparing two or more alternative programs by measuring the costs and consequences of each. A distinguishing feature of cost-effectiveness analysis is that the consequences (health outcomes) of all programs to be compared must be measured in the same common units-natural units related to the clinical objective of the programs (e.g., symptom-free days gained, cases prevented, quality of life years gained).¹⁷

Cost-Minimization Analysis: A type of pharmacoeconomic analysis comparing two alternative therapies only in terms of costs because their outcomes (effectiveness and safety) are found to be or expected to be identical.¹⁷

Cost-Utility Analysis: A specific type of cost-effectiveness analysis that compares two or more alternative choices in terms of both their costs and outcomes, where the outcomes are measured of utility or preference, often as a quality-adjusted life years gained. Cost-utility analysis can be considered the “gold standard” methodology for evaluating the cost-effectiveness of health care choices.¹⁷

Cost-Effectiveness Model: These models are used to establish the value of a new technology relative to an appropriate comparator, and often use decision analysis techniques. They can be based directly on clinical trials. They are disease-based and account for the impact of new technology on clinical outcomes (efficacy, adverse events), resource use and costs in the short and long-term. They also reveal the relation between data inputs and assumptions and outcomes. These models can be used to conduct a cost-benefit, cost-minimization, cost-effectiveness, and/or cost-utility analysis¹⁷

Decision Analysis: A quantitative approach to decision making under uncertainty in which all relevant elements of the decision – alternative actions, chance events (along with their probabilities of occurrence), and final consequences – are stated explicitly in a model. Multiple types of data can be incorporated from a variety of sources. This model typically takes the form of a decision tree or an influence diagram and permits the decision maker to determine systematically the relative value of alternative courses of action.¹⁷

Decision Tree: A schematic diagram depicting the logical structure of a choice under conditions of uncertainty, including all relevant alternative decisions available to the decision maker as well as the values and probabilities of all relevant downstream consequences.¹⁷

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.

Evidence-Based Medicine (EBM): An approach to health care decision making in which the decision maker is aware of all the relevant evidence and its strengths and weaknesses and is then able to apply that knowledge to decisions. EBM, therefore, consists of clinical expertise and patient preferences combined with critical appraisal of clinical research, with the goal of providing optimal individual patient care. Optimal care thus takes into account patient outcomes and the relative efficiencies among competing alternatives, as demonstrated in the medical literature. This approach to patient care demands that the decision makers' expertise and the appraisal of the clinical evidence base are current and up to date.¹⁷

Evidence-Based Medicine – Alternate Definition: The conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.¹⁹

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 healthcare systems it represents.

Health Economics: A discipline that analyses the economic aspects of health and health care and that usually focuses on the costs (inputs) and the consequences (outputs) of health care interventions using methods and theories from economics and medicine.¹⁷

Health-Related Quality of Life (HRQOL): A broad theoretical construct developed to explain and organize measures concerned with the evaluation of health status, attitudes, values and perceived levels of satisfaction and general well being with respect to either specific health conditions or life as a whole from the individual's perspective. (see Patient-Reported Outcomes).¹⁷

Markov Model: A complex health economics treatment model that describes the natural history of particular diseases, with or without treatment. To capture all critical events, Markov models can categorize health status with a higher level of detail and divide the model's time perspective into finer intervals than is possible with decision trees.¹⁷

Model: In the context of health care evaluation, a model is an analytic methodology that accounts for events over time and across populations, that is based on data drawn from primary and/or secondary sources and whose purpose is to estimate the effects of an intervention on valued health consequences and costs.²⁰

Modeling: The development of a simplified representation of a system (e.g. population). A particular model may be analytical, visual or both. In pharmacoeconomics specifically or health economics in general, analytical models can be used to pose and answer questions about interventions that cannot be directly answered by clinical trials due to time and financial constraints.¹⁷

¹⁹ Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ* 1996; 312: 71-2)

²⁰ Weinstein MC, O'Brien B et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR task force on good research practices – modeling studies. *Value Health*. 2003; 6:9-17.

Outcomes Research: The scientific discipline that evaluates the effect of health care interventions on patient-related, if not patient-specific, clinical, humanistic and economic outcomes. Outcomes research is generally based on the conceptual framework that evaluation of treatment alternatives involves the simultaneous assessment of multiple types of outcomes that are disease-related.¹⁷

Patient-Reported Outcomes: An umbrella term that includes outcome data reported directly by the patient. It is one source of data that may be used to describe a patient's condition and response to treatment. It includes such outcomes as global impressions, functional status, well-being, symptoms, health-related quality of life, satisfaction with treatment and treatment adherence.¹⁷

Pharmacoeconomics: The scientific discipline that assesses the overall value of pharmaceutical health care products, services and programs. Of necessity, it addresses the clinical, humanistic and economic aspects of health care interventions in the prevention, diagnosis, treatment and management of disease. Pharmacoeconomics thus provides information critical to the optimal allocation of health care resources. The field encompasses experts in health economics, risk analysis, technology assessment, clinical evaluation, epidemiology, decision analysis and health services research.¹⁷

Quality-Adjusted Life Year (QALY): A universal health outcome measure applicable to all individuals and all diseases, thereby enabling comparisons across diseases and across programs. A QALY combines, in a single measure, gains or losses in both quantity of life (mortality) and quality of life (morbidity).¹⁷

Rule of Rescue: A term applied to the ethical imperative to save individual lives regardless of the cost if rescue measures are available. Regarding the distribution of health care services, the "rule of rescue" supplements rather than substitutes for the evidence-based consideration of comparative cost-effectiveness. For example, Australia's Pharmaceutical Benefits Advisory Committee considers the rule of rescue a relevant factor when the cost-effectiveness level is unacceptable and:

1. No alternate pharmacological or non-pharmacological intervention exists to treat patients with the identified condition;
2. The defined condition must be severe, progressive and expected to lead to premature death;
3. The defined condition must apply to only a very small number of patients.²¹

Sensitivity Analysis: A way to analyze the impact of uncertainty in an economic analysis or a decision (see Decision Analysis, Modeling, Cost-Effectiveness Model). The simplest form of sensitivity analysis is a one-way analysis where the value of one variable is changed while keeping the other variables constant, and the impact on results evaluated.¹⁷

Specialty Pharmaceuticals: Within the current version of the *Format*, a product can be classified as a specialty pharmaceutical if:

- It requires a difficult or unusual process of delivery to the patient (preparation, handling, storage, inventory, distribution, Risk Evaluation and Mitigation Strategy (REMS) programs, data collection, or administration) or,
- Patient management prior to or following administration (monitoring, disease or therapeutic support systems).

Tornado Diagram: A set of one-way sensitivity analyses displayed in a single graph, with the most critical variable in terms of impact at the top of the graph and the rest ranked according to their impact thereafter; hence the "tornado" or funnel appearance of the graph.¹⁷

²¹ Richardson J and McKie J. The rule of rescue. Centre for Health Program Evaluation. Working Paper 112 [Internet] West Heidelberg, Australia. Available from <http://www.buseco.monash.edu.au/centres/che/pubs/wp112.pdf>

AMCP *FORMAT* Addendum: Companion Diagnostic Tests (CDTs) December 2012

The objectives of this addendum are to:

- 1) Provide drug and companion diagnostic test (CDT) developers with guidance for the provision of clinical and economic evidence in health technology assessments, and
- 2) Inform drug and CDT manufacturers, P&T committees, Medical Technology Assessment committees, and other coverage and reimbursement decision-makers about appropriate types of evidence for a CDT so that well-informed evaluations can be performed.

The information complements existing information in the *AMCP Format for Formulary Submissions*, Version 3.1. The following sections provide background information on CDTs and recommendations for the development and content of both:

- 1) Evidence dossiers for drugs with CDTs and
- 2) Stand-alone evidence dossiers for CDTs.

Section I: Background

Companion diagnostic tests have emerged as a growing and vital technology in the effective use of many drug therapies. CDTs are mainly comprised of laboratory tests (in vitro diagnostics [IVDs]). *In vitro diagnostic* (IVD) products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its related conditions. IVDs are used to inform treatment decisions by enabling detection of molecular biomarkers linked with initial and ongoing response to drug therapies. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. These products are devices as defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the act), and may also be biological products subject to section 351 of the Public Health Service Act. Medical imaging tests may be used as CDTs in the near future,¹ and although they are not the focus of this addendum, many of the principles and approaches outlined herein will be relevant for medical imaging tests.

‘Companion Diagnostic Test’ Definition for Use within the *Format*

Companion diagnostic tests have been defined in various ways. The U.S. Food and Drug Administration (FDA) definition describes a CDT as one that provides information that is essential for the safe and effective use of a corresponding therapeutic product.¹ More generally, in this addendum, a CDT is defined as a test that provides information that improves the safety or effectiveness of a drug or biologic. CDTs can be used to:

- Identify patients who are most likely to benefit from a particular therapeutic product
- Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with a particular therapeutic product
- Monitor patient response to treatment for the purpose of adjusting the treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness

Companion diagnostic tests (both IVDs and medical imaging) may assess the presence of molecular biomarkers including the following forms:

- Genomic/epigenomic (deoxyribonucleic acid-based) biomarkers
- Transcriptomic (ribonucleic acid-based) biomarkers
- Proteomic (protein-based) biomarkers
- Metabolomic (metabolite-based) biomarkers

Regulatory Processes for Companion Diagnostic Tests

The evidence requirements to gain market approval of CDTs are significantly different than those for drugs and biologics, making evidence- and value-based decision processes for CDTs potentially challenging.

Companion diagnostics tests can be made available on the market via two routes: 1) as an FDA-approved laboratory test kit (device), or 2) as a laboratory developed test (LDT). Laboratory test kit devices and components that are manufactured for commercial distribution by in vitro diagnostics device manufacturers are generally subject to the FDA Center for Devices and Radiological Health ‘premarket notification’ (PMN or 510(k)) process, or ‘premarket approval’ (PMA) process. Although 510(k) clearance and PMA for CDTs involve some assessment of safety and effectiveness, neither process routinely involves randomized controlled trials evaluating the safety and effectiveness of a device as is commonly seen with drugs and biologics.

Laboratory developed tests (tests developed in-house by clinical laboratories that conduct these tests) are overseen by the Centers for Medicare and Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments of 1988 (CLIA). CLIA certification involves regulation of laboratory processes, but does not include assessment of specific tests. The FDA generally has chosen not to exercise its regulatory authority over LDTs, although it is in the process of considering a risk-based approach to their regulation.²²

In summary, FDA approval of a test, particularly if approved separately from a drug/biologic, or the availability of a test in a CLIA approved lab, does not necessarily mean that clear evidence of clinical utility exists. And conversely, lack of FDA approval for a LDT test does not automatically mean it is a poor test. Each circumstance typically requires its own evidence review. Section II below identifies common scenarios and provides recommendations for developing dossiers.

Section II: Application of the *Format* for Companion Diagnostic Tests

Implementation of dossier requests for CDTs using the *Format* may be complicated by the variety of potential relationships between a drug/biologic manufacturer and CDT manufacturer/provider. The following are possible CDT development scenarios (in no order of preference):

- 1) CDT co-developed with drug, and FDA-approved together with drug
- 2) CDT developed independently of drug, typically after drug approval
- 3) CDT developed independently and targeted for class of medications

In each of these scenarios, the drug/biologic manufacturer may or may not be the same as the CDT manufacturer. In the case where the drug/biologic manufacturer is different from the CDT manufacturer, the two companies may or may not have business agreements to work collaboratively in the development and/or marketing of the drug and CDT. This scenario may be important in understanding the ability of one company to adequately provide and communicate data and information related to another manufacturer’s product. Obtaining evidence for CDTs is further complicated if the test is developed in-house by clinical laboratories (a LDT) and not FDA approved. Thus, depending on the development pathway, drug/biologic manufacturers and CDT developers will have different responsibilities with regard to evidence submission to health care decision makers.

²² U.S. Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiologic Health. Public meeting: oversight of laboratory developed tests (LDTs). July 2010. Available at: <http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm212830.htm>. Accessed July 30, 2012.

Considerations and Recommendations for Developing CDT Dossiers

Given the potential complexity of regulatory processes, data sources, and manufacturer relationships, the following approaches for developing dossiers for CDTs should be considered when:

1. The CDT is co-developed with the drug or biologic:

- The evidence for the safety, efficacy, and value of the drug/biologic will be inherently linked to the CDT. The drug/biologic manufacturer should provide these data as part of the drug/biologic dossier in the *AMCP Format*.
- Specifically, the clinical validity and clinical utility (see next section), as well as the economic value will be jointly dependent on the clinical evidence from drug/biologic registration.
- Data on the analytic validity of the CDT (see next section) also should be provided (either by the drug/biologic or CDT manufacturer), although it may be independent of the key drug/biologic clinical trial data.
- Evidence for CDTs that are co-developed with the drug will be relevant for both the drug and the test, e.g., the data from a registration clinical trial. The FDA issued a draft Drug-Diagnostic Co-development Concept Paper in early 2005²³ that may be informative for evidence assessment. The draft, however, has not been issued as formal guidance for industry and does not provide final regulatory language informing the process for drug-diagnostic co-development.
- A recent FDA draft guidance indicates the following specifically for IVD companion tests and the regulatory path required for companion tests appearing in FDA drug labels:²⁴
 - “Because the IVD companion diagnostic device is essential to the safe and effective use of the therapeutic, with some exceptions...FDA does not believe it may approve a novel therapeutic product or new therapeutic product indication for use with an IVD companion diagnostic device if the IVD companion diagnostic device is not approved or cleared for that indication.”
 - “The labeling for ... an IVD companion diagnostic device that is intended for use with a therapeutic product must specify the therapeutic product(s) for which it has been approved or cleared for use.”
 - A list of biomarkers included in FDA drug labeling is available on the FDA website at:
<http://www.fda.gov/drugs/scienceresearch/researchareas/pharmacogenetics/ucm083378.htm>.
 - A list of IVD devices is available on the FDA website at:
<http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm>

²³ U.S. Department of Health and Human Services, Food and Drug Administration. Drug-diagnostic Co-Development Concept Paper. April 2005. Available at <http://www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/UCM116689.pdf>. Accessed July 30, 2012.

²⁴ U.S. Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiologic Health. Draft guidance for industry and food and drug administration staff - in vitro companion diagnostic devices. July 2011. Available at <http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm262292.htm> Accessed July 30, 2012.

2. The CDT is developed independently of the drug or biologic:

- If the CDT is required in the drug/biologic label, the drug/biologic manufacturer should provide data on the clinical validity, clinical utility, and economic value of both the CDT and the drug/biologic in the drug/biologic dossier developed in the *Format*. Information on the analytic validity of the test should be provided in the dossier as feasible.
- If the CDT is not required in the drug/biologic label, then the CDT developer should provide a “**CDT dossier**” that provides information as outlined in Section IV below.

3. The CDT is developed independently and is targeted for a class of medications.

- The CDT developer should provide a “CDT dossier” that provides information as outlined in Section IV below specific to drugs in the targeted drug class.

Section III: CDT Evidence Frameworks for Use in the *Format*

A number of evidence-gathering frameworks have been developed to evaluate diagnostic tests. The issue was a topic of a 2011 Institute of Medicine (IOM) workshop, which highlighted key points of consideration when generating evidence to support diagnostic test evaluation.²⁵ Such frameworks can be applied specifically to the evaluation of CDTs.

ACCE Framework

The most commonly applied framework is the Centers for Disease Control and Prevention Office of Public Health Genomics’ “*ACCE*” *Model Process for Evaluating Genetic Tests*, which stands for Alytic validity (technical accuracy and reliability), Clinical validity (ability to detect or predict an outcome, disorder, or phenotype), Clinical utility (whether use of the test to direct clinical management improves patient outcomes), and Ethical, legal, and social implications.²⁶ Of the evaluation metrics identified, managed care decision makers are likely to focus on analytic validity, clinical validity, clinical utility, and economic value.

The ACCE framework is described in the current *Format* in Section 2.3, Evidence for Pharmacogenomic Tests and Drugs. The framework contains four categories of evidence that manufacturers should provide health care decision makers. In this case, the fourth category, rather than being “ethical, legal, social issues,” is specifically “economic value”:

- **Analytic Validity**
 - Accuracy with which a particular genetic *or* phenotypic characteristic can be identified using a CDT in relation to professional standards and federal regulation requirements.
- **Clinical Validity**
 - Strength of the association between the CDT findings and clinical outcome(s) (e.g., effectiveness, adverse drug reaction)
 - Expected prevalence of genetic variant(s) in target population; positive predictive value (PPV) and negative predictive value (NPV) of CDT

²⁵ Institute of Medicine (US) Roundtable on Translating Genomic-Based Research for Health. Generating evidence for genomic diagnostic test development: workshop summary. Washington, DC. The National Academies Press (US); 2011. Available at: http://www.nap.edu/catalog.php?record_id=13133#toc. Accessed July 30, 2012.

²⁶ Centers for Disease Control and Prevention, Office of Public Health Genomics. “ACCE” model process for evaluating genetic tests. Available at <http://www.cdc.gov/genomics/gtesting/ACCE/index.htm>. Accessed July 30, 2012

- **Clinical Utility**
 - Effectiveness and safety of the *clinical intervention* implemented as a result of the CDT, as per Sections 3.1-3.3 of the *Format*; consider inclusion of quantitative risk-benefit decision analytic modeling (Section 4.1.1 of the *Format*).
- **Economic Value**
 - Expected difference in costs and outcomes with CDT compared to usual care, as per Section 4.2.3 of the *Format*, including cost offsets from changes in drug utilization, side effect treatment, and other healthcare services, and health outcomes. The economic analysis should include, among other aspects, the prevalence of the condition, prevalence of the CDT marker of interest, and burden on the patient or health care system to collect and process the biological sample.

Other Frameworks

Other useful frameworks have been put forth including the Fryback-Thornbury²⁷ and the U.S. Preventative Services Task Force (USPSTF) frameworks on screening and counseling²⁸. These frameworks strive to capture essential diagnostic test performance characteristics, along with their application to clinical decision-making, by describing a test in terms of its ability to: 1) conform to technical specifications, 2) classify patients by disease/phenotype or prognosis category, 3) direct clinical management and improve patient outcomes, and 4) benefit society as a whole.

Key criteria and commonly applied terms for evaluating CDT's, regardless of the framework used, are presented in Table 1 (developed by the Agency for Healthcare Research and Quality [AHRQ]). These evaluation criteria are the focus of the AMCP *Format*.

Table 1: Different objectives of medical test evaluation studies (ref: AHRQ)²⁹

Study Objective	Terms Used	Examples
Ability of a test to conform to technical specifications	Technical efficacy	Technical quality of a radiological image
	Analytic validity	Accuracy of a chemical assay for the target analyte Concordance of a commercial genetic test with the true genotype
Ability of a test to classify a patient into a disease/phenotype or prognosis category	Diagnostic accuracy efficacy Clinical validity Test accuracy Test performance Performance characteristics Operating characteristics	Sensitivity and specificity Positive and negative likelihood ratios Positive and negative predictive value Test yield Receiver operating characteristic (ROC) curve
Ability of a test to direct clinical management and improve patient outcomes	Diagnostic thinking efficacy Therapeutic efficacy Patient outcome efficacy Clinical utility	Impact on mortality or morbidity Impact on clinician judgment about diagnosis/prognosis Impact on choice of management
Ability of a test to benefit society as a whole	Societal efficacy	Incremental cost-effectiveness

²⁷ Fryback D. Thornbury J. The efficacy of diagnostic imaging. *Med Decis Making*. 1991;11: 88 -94.

²⁸ Agency for Healthcare Research and Quality. U.S. preventive services task force procedure manual. AHRQ Publication No. 08-05118-EF, July 2008. Available at <http://www.uspreventiveservicestaskforce.org/uspstf08/methods/procmanual.pdf>. Accessed July 30, 2012.

²⁹ Agency for Healthcare Research and Quality. Methods guide for medical test reviews. AHRQ Publication No. 12-EC017. June 2012. Rockville, MD. Available at: http://effectivehealthcare.ahrq.gov/ehc/products/246/558/Methods-Guide-for-Medical-Test-Reviews_Full-Guide_20120530.pdf. Accessed July 30, 2012.

Source: Agency for Healthcare Research and Quality. Methods guide for medical test reviews. AHRQ Publication No. 12-EC017. Rockville, MD June 2012.. Available at: <http://effectivehealthcare.ahrq.gov/ehc/products/246/558/Methods-Guide-for-Medical-Test-Reviews-Full-Guide-20120530.pdf>. Accessed July 2012.

Section IV: CDT Dossier – Supplemental Requirements

When a CDT has been co-developed with a drug/biologic, or when the CDT is required per FDA labeling, then the latter three elements of the ACCE framework (clinical validity, clinical utility and economic value) will generally be captured in the drug/biologic evidence dossier when using the current *Format*. However, in cases where the CDT is not inherently tied to the drug/biologic evidence, then the CDT developer should respond to an unsolicited request with a CDT evidence dossier. In such a case, the following information should be provided.

Evidence Requirements for Diagnostic Tests (include in *Format* section 2.3)

- Generic, Brand Name and Type of Test
- Packaging Description, Regulatory Codes/Classification(s) and Prices
- Approved Indication(s)/Uses with Companion Drug Association
- Clinical Basis for the Test (i.e., therapy, monitoring, etc.)
- Target Patient Population
- Prevalence of CDT variant in target population
- Contraindications, Warnings/Precautions, Interactions Relative to Test Use
- Co-prescribed/Concomitant Therapies
- Place of Test in Therapy; Place in Relative Treatment/Diagnostic Guidelines, as appropriate
- Approaches to Treatment: Principal Practice Options/Practice Patterns
- Alternative Tests and Options, Relative Advantages and Disadvantages
- Other Key Assumptions and Their Rationale
- Supporting Clinical and Economic Evidence for the Test, using ACCE framework:
 - Analytical validity, including:
 - Test quality assurance and control
 - Standardization of test conduct and accuracy of results
 - Clinical validity, including:
 - Sensitivity/false negative %
 - Specificity/false positive %
 - Predictive value in the target population (positive & negative)
 - Threshold(s) used to separate a positive result from a negative result
 - Clinical utility, including:
 - Changes in patient outcomes (treatments received, clinical events, life expectancy, quality of life) and risk-benefit assessment
 - Economic value, including:
 - Incremental cost per diagnosis, treatment modification, events avoided, life years saved, and quality-adjusted life-years gained.

Conclusion

Companion diagnostic tests offer an exciting opportunity to improve the use, safety, and cost-effectiveness of drugs and biologics. This addendum is intended to provide clarification for drug/biologic manufacturers and CDT manufacturers interested in providing evidence of the value of their products to health care decision makers. AMCP will continue to adapt the *Format* to address the needs of stakeholders in the rapidly evolving field of CDTs.

AMCP *FORMAT* Addendum: Comparative Effectiveness Research December 2012

Purpose

This addendum to the AMCP *Format for Formulary Submissions*, Version 3.1, provides an overview of the various forms of comparative effectiveness research (CER) and illustrates the role that comparative evidence plays in the *Format*. The addendum is not intended to serve as a comprehensive review of the many complex policy and methodological issues related to CER. It is not intended to provide guidance on CER methodologies nor guidance specific to submitting CER evidence for consideration of formulary listing; such guidance is beyond the scope of this addendum. Rather, this document illustrates the scope of CER methodologies that are available for manufacturers to consider when submitting comparative evidence in a *Format* dossier.

While the *Format* does not require manufacturers to use any particular research design to present evidence of benefit, harms, cost-effectiveness or financial impact of their products, it does strongly recommend that manufacturers include evidence from comparative effectiveness studies as they become available.

Furthermore, the *Format* is designed to provide a safe harbor for manufacturers to submit all evidence (including CER evidence) in support of formulary evaluation. Although the *Format* provides direction regarding evidence submission, it does not dictate the process by which evidence is *developed*, nor does it provide methodological guidance.

Section I: Background

Comparative effectiveness research has its origin in the field of health services research since the 1970's, but has attracted recent attention, especially at the federal level. This increased attention reflects concern among policy and health care decision makers that the evidence base for informed decision-making can be significantly improved. In particular, high quality comparative evidence of real world safety, clinical effectiveness and cost-effectiveness of alternative health care strategies are often inadequate or non-existent.

A common definition of CER used by the Institute of Medicine states: "Comparative effectiveness research is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, clinicians, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population level."³⁰ This definition has been adopted for the purposes of this addendum.

Focus and Emphasis of CER

CER emphasizes the comparison of *alternative* health care interventions within *typical care settings* with a special focus on what health-care *decision-makers* such as patients and health plans care about. More specifically, CER addresses *patient's* preferences, their health-related quality of life and other outcomes important to them. It also emphasizes generating evidence regarding subgroup differences, also known as

³⁰ Institute of Medicine. Initial national priorities for comparative effectiveness research. Report Brief. June 2009. Available at: <http://www.iom.edu/~media/Files/Report%20Files/2009/ComparativeEffectivenessResearchPriorities/CER%20report%20brief%2008-13-09.pdf>. (Accessed 9/1/2012)

treatment *heterogeneity*.^{31,32,33} Key concerns are that clinical research on alternative strategies and treatments, especially research conducted for regulatory decision makers, is often placebo-controlled, thus not directly comparative with relevant alternatives, not conducted under usual care conditions, not focused on the outcomes that patients and other decision makers consider important, and/or does not adequately identify which patients or patient subgroups would benefit most/least from an intervention.

Section II: Comparative Effectiveness Research Use within the *Format*

The current version of the *Format* makes numerous references to comparative effectiveness. For example,

- Section 3.0 – Supporting Clinical Evidence – makes two clear references on the need for manufacturers to supply comparative effectiveness information to support an assessment of benefits and harms of their product relative to existing treatments.
- Section 4.0 – Economic Value and Modeling Report, discusses the need to use comparative effectiveness evidence as part of the economic evaluation.
- Appendix F describes a template and 5 key questions that managed care organizations and payers can use to summarize and present the evidence contained in product dossiers. The second key question specifically concerns the availability and quality of comparative effectiveness studies. This *Format* template currently is used by a number of managed care organizations for presenting evidence to decision makers (pharmacy & therapeutics committees).

The following are some of the key CER methodologies that may be considered when gathering evidence for submission within a *Format* dossier.

A Brief Overview of Selected Major Types of CER Study Designs:

Traditional randomized controlled trials (RCTs) are considered the gold standard for clinical research by seeking to maximize internal validity. They address the efficacy question “Can it work?” commonly in a controlled research setting and often compared to placebo. These designs are frequently used for FDA registration studies. In contrast, CER addresses the effectiveness question “Does it work?” in the real world, relative to an active comparator treatment group. To successfully address this question, other study designs may be more useful, including: 1) Bayesian and adaptive trial designs, 2) pragmatic clinical trials, 3) prospective registry or observational studies, 4) retrospective observational studies, 5) systematic evidence reviews, and 6) modeling studies. A caveat to the contrast just described is that sometimes a traditional RCT includes a comparator considered relevant for real world decision-making and performed within a research setting that approximates “real world” or usual care conditions. For all intents and purposes, such a study would be considered a CER trial.

Bayesian and Adaptive Trial Designs: Unlike traditional RCTs, Bayesian randomized trials can incorporate existing high quality external evidence (e.g., information from pivotal trials, systematic reviews, observational studies) into CER trial design; subsequently draw upon observed within-trial endpoint relationships^{34,35} and incorporate relevant new evidence that may become available during the

³¹ The Patient Protection and Affordable Care Act. PL 111-148. 3-23-2010. Available at <http://www.gpo.gov/fdsys/pkg/BILLS-111hr3590enr/pdf/BILLS-111hr3590enr.pdf>. (Accessed 8/1/2012)

³² Patient Centered Outcomes Research Institute. Preliminary Draft Methodology Report. Our questions, our decisions: standards for patient-centered outcomes research. June 4, 2012. <http://www.pcori.org/assets/Preliminary-Draft-Methodology-Report.pdf> (accessed 6 July 2012)

³³ Thorpe KE, Zwarenstein M, Oxman AD, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *J Clin Epidemiol*. May 2009;62(5):464-475.

³⁴ Berry DA. Bayesian clinical trials. *Nat Rev Drug Discov*. 2006;5(1):27-36..

course of the trial³⁶. These methods use formal, probabilistic statements of uncertainty to pre-specify how information from various sources will be combined. Coupled with the adaptive feature, the Bayesian analyst pre-specifies how the design will change as evidence accumulates, while controlling the probability of false positive and false negative conclusions. As new interventions become available, they can incorporate new arms and drop less effective ones without restarting the trial.^{35, 37, 38} These methods are becoming more common, and accepted by the FDA,^{36,39} however, they have not yet been tested in CER 'real world' environments.

Pragmatic Clinical Trials: Randomized trials whose explicit purpose is to inform health-care decision makers are called pragmatic clinical trials (PCTs).^{40, 41, 42} PCTs have limited required design features, most notably randomization. Compared to RCTs, pragmatic trials are characterized by less restrictive inclusion/exclusion criteria, resulting in more generalizable study populations and community providers, more relaxed protocol requirements, longer term endpoints, active comparators, and outcome measures of specific relevance to health-care decision-makers, including patients. They are designed to demonstrate how a medical intervention works in typical health care settings and typical patients. From a validity standpoint, PCTs tend to emphasize external validity (relative to RCTs) often at the expense of internal validity. None the less, PCTs have more internal validity than observational CER study designs because the interventions studies are randomized.

Prospective Observational Studies: Prospective observational studies (POSS) are non-randomized clinical studies, e.g. registries or cohort studies, and can be used to compare interventions, treatment strategies, or pathways of care. A POS protocol defines what shall be observed and what data shall be collected over time; it does not normally require any particular clinical intervention or limit a clinician's decision-making. Accordingly, a POS collects data to help understand the real world without limiting clinical practice or requiring any particular intervention or treatment. Specifically, a POS is designed to demonstrate how disease presents and how outcomes manifest themselves over time, in patients with diverse demographic and clinical characteristics, as modified by alternative diagnostic and therapeutic regimens. POSS typically have more generalizable patient and clinician populations, minimal inclusion/exclusion criteria, longer term endpoints than traditional RCTs, and outcome measures of specific relevance to clinicians, health care decision-makers, and patients. While emphasizing external

³⁵ Olsen L, Aisner D, McGinnis JM. The Learning Healthcare System: Workshop Summary (IOM Roundtable on Evidence-Based Medicine). Washington, DC: The National Academies Press; 2007.

³⁶ Berry DA. Bayesian approaches for comparative effectiveness research. *Clin Trials*. 2012;9(1):37-47.

³⁷ Tunis S. Strategies to improve comparative effectiveness research methods and data infrastructure. *Implementing Comparative Effectiveness Research: Priorities, Methods, and Impact*. The Brookings Institution; 2009:35-53.

³⁸ Zhou X, Liu S, Kim ES, Herbst RS, Lee JJ. Bayesian adaptive design for targeted therapy development in lung cancer--a step toward personalized medicine. *Clin Trials*. 2008;5(3):181-193.

³⁹ U.S. Food and Drug Administration. Medical Devices. Guidance for the use of Bayesian statistics in medical device clinical trials, February 5, 2010. Available at:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071072.htm> (accessed 9 December 2011)

⁴⁰ Thorpe KE, Zwarenstein M, Oxman AD, et al. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *J Clin Epidemiol*. May 2009;62(5):464-475.

⁴¹ Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. *JAMA*. Sep 24 2003;290(12):1624-1632.

⁴² Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. *J Chronic Dis*. Aug 1967;20(8):637-648.

validity, relative to randomized designs, POSs exhibit diminished internal validity (e.g. due to possible selection bias) which advanced statistical methods can/should be employed to address.

Retrospective Observational Studies: Retrospective observational studies (ROSs), which are also not randomized, can include cohort or case control designs. These studies typically include large populations followed over time and across different care settings, while retaining patient level data. They support evaluation of long-term disease progression, evolving treatment patterns, and comparisons of long-term treatment effectiveness, safety and other outcomes. Many retrospective studies employ existing administrative, financial, and operational databases. For example, pharmacy, medical, and laboratory claims databases are commonly used. Recent public and private investments are expected to transform the nation's health information technology (HIT) system in a manner that facilitates ROSs.^{43,44} These investments are expected to promote standardization of terms and processes, linking of databases, expand clinical content and to bring a sharper focus on variations in health care delivery and outcomes across larger populations. Similar to POSs, retrospective observational studies emphasize external validity at the expense of internal validity requiring statistical control methods. An important feature is that these retrospective designs can often be performed much more quickly and less expensively than prospective designs.

Systematic Evidence Reviews: Systematic evidence reviews are critical assessments and evaluations of all research studies that fit pre-specified eligibility criteria in order to answer a specific clinical question. Meta-analyses are systematic reviews that employ statistical methods to combine the quantitative results of independent studies. Network meta-analyses, which include indirect treatment comparisons and mixed treatment comparisons, are formal meta-analyses that involve more than two RCTs and more than two interventions. Today, network meta-analyses are becoming more relied on and accepted as valid means to compare interventions. This is important and useful since comparative trials are often not available⁴⁵

Modeling Studies: Modeling studies involve the development of mathematical algorithms that reflect a disease or clinical process. The models incorporate evidence from a variety of sources, including the study designs identified above. These simulation models can be used to compare the harms, benefits, and financial consequences of interventions.

The following table contrasts three general CER study designs with traditional RCTs along a number of relevant dimensions. The table is presented for illustrative purposes only, in part because CER methods are still evolving and they tend to occupy a continuum. For instance individual traditional RCTs and pragmatic trials can be more or less "pragmatic" or real world-focused across many dimensions.³³ Also, the table does not include a number of other useful designs, e.g. especially systematic reviews of evidence.

⁴³ Blumenthal D. Stimulating the adoption of health information technology. *N Engl J Med.* 2009;360(15):1477-1479.

⁴⁴ Blumenthal D. Launching HITECH. *N Eng JMed.* 2010;362(5):382-385.

⁴⁵ Report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: Part 1. *Value in Health* (2011); 14: 417-28)

Comparison of Three Comparative Effectiveness Research Designs with Traditional Randomized Controlled Trials

	Traditional RCT	Comparative Effectiveness Research Designs		
	E.g. Registration Trials	Pragmatic Trial Randomized, Real-World	Prospective Observational Cohort, Registry	Retrospective Observational Cohort, Case Control, Database*
Randomization	Yes	Yes	No	No
Question	Comparative Efficacy <i>Can it work?</i>	Comparative Effectiveness <i>Does it work?</i>	Comparative Effectiveness <i>Does it work?</i>	Comparative Effectiveness <i>Does it work?</i>
Population of Interest / Participants	Highly selected population No/less Comorbidities, similar severity of disease, limited interactive therapies, high adherence	Less selective, more diverse population than RCT Comorbidities, varying severity of disease, use of ancillary therapies, mixed adherence	Least selective population Comorbidities, varying severity of disease, use of ancillary therapies, mixed adherence	Least selective population Comorbidities, varying severity of disease, use of ancillary therapies, mixed adherence
Intervention	Placebo or Active comparator Usually strict protocol	Active comparator More flexible protocol than RCT	Active comparator Flexible or not dictated by protocol	Active comparator Flexible or not dictated by protocol
Outcomes	Any clinical; commonly surrogate clinical; humanistic; partial economic possible	Any clinical, persistence, humanistic and economic	Any clinical, persistence, humanistic and economic	Any clinical, persistence, humanistic (except rarely for database studies); partial economic
Setting	Controlled setting	Usual clinical practice	Usual clinical practice	Usual clinical practice
Relevance to Practice	Indirect	Direct	Direct	Direct
Sample Size	+ to ++	+ to +++	++ to +++	++ to +++
Duration	+ to ++	+ to +++	+ to +++	Not constrained or + to +++
Cost per Subject	+++	++ to +++	+ to ++	+
Internal Validity	Highest			Lowest →
External Validity	← Lowest			Highest

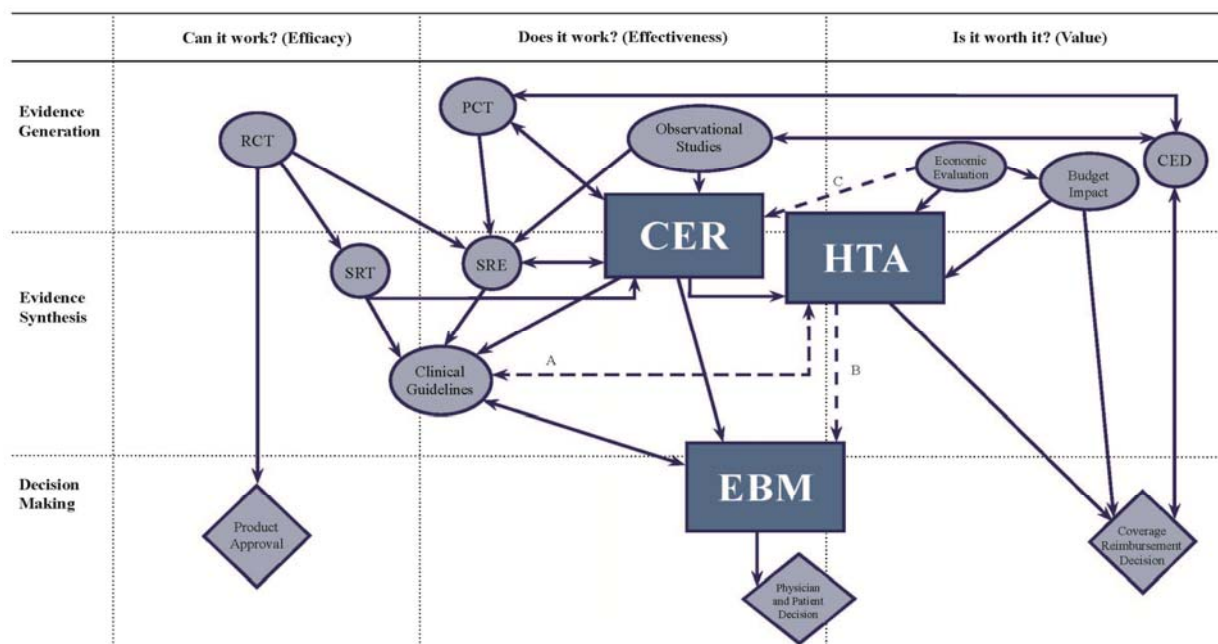
*Database may include administrative claims data, electronic health records, and retrospective registry data. Each “+” symbol is meant to indicate more.

Related CER Activities

It is important to note that CER is related to, but distinctly different, from evidence-based medicine (EBM) and health technology assessment (HTA).⁴⁶ The following chart outlines some of these differences and defines the three concepts as follows: Evidence-based medicine (EBM) is an evidence synthesis and decision process used to assist patients' and/or physicians' decisions. It considers evidence regarding the effectiveness of interventions and patients' values and is mainly concerned with individual patients' decisions, but is also useful for developing clinical guidelines as they pertain to individual patients. Comparative effectiveness research (CER) includes both evidence generation and evidence synthesis. It is concerned with the comparative assessment of interventions in routine practice settings. The outputs of CER activities are useful for clinical guideline development, evidence-based medicine, and the broader social and economic assessment of health technologies (i.e., HTA). Health technology assessment (HTA) is a method of evidence synthesis that considers evidence regarding clinical effectiveness, safety, cost-effectiveness and, when broadly applied, includes social, ethical, and legal aspects of the use of health technologies. The precise balance of these inputs depends on the purpose of each individual HTA. A major use of HTAs is in informing reimbursement and coverage decisions, in which case HTAs should include benefit-harm assessment and economic evaluation.

Readers who wish to better appreciate the complex distinction and relationships involved between these three related concepts are encouraged to refer to Luce et al (2010).⁴⁶

Evidence Relationships HTA-EBM-CER⁴⁶



RCT = Randomized clinical trial, CER = Comparative effectiveness research, HTA = Health technology assessment, EBM = Evidence-based medicine, PCT = Pragmatic clinical trial, SRT = Systematic review of trials, SRE = Systematic review of evidence, CED = Coverage with evidence development (conditional coverage)

⁴⁶ Luce BR, Drummond M, Jonsson B, Neumann PJ, Schwartz JS, Siebert U, Sullivan SD. EBM, HTA, and CER: Clearing the confusion. *The Milbank Quarterly*, Vol. 88, No. 2, 2010: 256–276.

Conclusion

This addendum provides a brief introduction to the evolving field and method related to comparative effectiveness research and its importance to the *Format*. Federal initiatives have stimulated interest among stakeholders in the development and use of comparative evidence to support clinical decision-making. The AMCP *Format* makes clear that comparative evidence is a necessary component of a comprehensive product dossier, regardless of the methodology used to generate the evidence (e.g., systematic reviews or modeling studies).

Additional Reading

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2. Velengtas P, Dreyer NA, Bryant A. **Good ReseArch for Comparative Effectiveness**. GRACE. Available at: <http://www.graceprinciples.org/publications.html>.
3. Dreyer NA, Schneeweiss S, McNeil BJ, et al. GRACE principles: recognizing high-quality observational studies of comparative effectiveness. *Am J Manag Care*. 2010;16(6):467-471.
4. Zwarenstein M, Treweek S, Gagnier JJ, Altman DG, Tunis S, Haynes B, et al; CONSORT group. Pragmatic trials in healthcare (Practice) group. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ* 2008;337:a2390.
5. Dreyer NA, Tunis SR, Berger M, Ollendorf D, Mattox P, Gliklich R. Why observational studies should be among the tools used in comparative effectiveness research. Appendix Table 1. Exemplary Guidelines and Good Practices for Comparative Effectiveness Research Evidence. *Health Aff* (Millwood). 2010;29(10):1818-25. Available at: http://content.healthaffairs.org/content/suppl/2010/09/30/29.10.1818.DC1/2010-0666_Dreyer_Appendix.pdf
6. Dubois RW, Kindermann SL. Demystifying comparative effectiveness research: A case study learning guide. November 2009. Available at: http://www.npcnow.org/App_Themes/Public/pdf/Issues/pub_ebm/NPC-Cerner_CER_full_report_WEB_final2009.pdf
7. Agency for Healthcare Research and Quality. What is comparative effectiveness research. Available at: <http://www.effectivehealthcare.ahrq.gov/index.cfm/what-is-comparative-effectiveness-research1>
8. Berger ML, Grainger D. Comparative effectiveness research: The view from a pharmaceutical company. *Pharmacoeconomics*. 2010; 28 (10):915-922.
9. Agency for Healthcare Research and Quality. Methods guide for effectiveness and comparative effectiveness reviews. 2010. Available at: <http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=318&pageaction=displayproduct>
10. Oregon Health and Science University. Drug Effectiveness Review Project. Systematic review methods and procedures. 2011; Available at: <http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm>

AMCP *FORMAT* Addendum: Specialty Pharmaceuticals

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Purpose

This addendum addresses the application of the AMCP *Format for Formulary Submissions*, Version 3.1 to specialty pharmaceuticals. It intends to explain where the particular characteristics of these drugs fit into the existing *Format*, and where special considerations, if any, are needed. Most specialty pharmaceuticals undergo the same general U.S. Food and Drug Administration (FDA) approval process and evidence requirements as traditional drugs. The existing *Format* discusses this evidence, and provides a template for detailed information describing the value of products to members of the health care system. This current framework for sharing evidence has been designed to communicate clinical and economic value for most technologies and is flexible enough to cover both traditional and specialty drugs. While additional information on specialty pharmaceuticals, such as Current Procedural Terminology (CPT) codes, administration issues, distribution channels, and care management, may be required by decision-makers for purposes of coverage and reimbursement, these constitute minimal expansions. In addition, one primary goal of the *Format* is to standardize the communication of product and supporting program information. Wholesale changes in the evidentiary requirements for specialty pharmaceuticals are not required and would thwart the goal of standardization. AMCP recommends that specialty medications continue to be considered within the current *Format* in a manner largely consistent with traditional drugs in terms of evaluation process, evidentiary requirements, reimbursement, access, and use.

Section I: Background

Specialty pharmacies and pharmaceuticals, despite their growing number and importance to the U.S. health care system, lack a standard or commonly accepted definition.^{47, 48, 49} In many cases, specialty pharmaceuticals have been defined as therapies with a certain subset of frequently cited characteristics, including high cost, administration by injection or infusion, use for chronic or rare diseases, and complex handling, storage, and/or distribution processes. Results of a systematic literature review of the definitions of specialty pharmaceuticals suggest that components of the definition vary substantially across sources.⁴⁸ In this review, the most common element was high cost, which was always noted but not always included in the formal definition. Approximately half of sources identified by the review mentioned special handling and distribution requirements. When definitions vary, this likely reflects actual differences among specialty pharmaceuticals and the pharmacies that have developed to provide these products and related services.^{47, 49} Definitions also may vary based on the perspectives of the entities writing them. While this might offer some flexibility in a changing therapeutic landscape, the lack of a common understanding of what is meant by specialty pharmacy and pharmaceuticals tends to hamper communication.⁴⁸ For example, U.S. health care executives interviewed in 2009 by the Foundation for Managed Care Pharmacy described the absence of a standard definition as an important barrier to access, payment, and delivery of care.⁴⁷ This addendum to the *Format* will define specialty pharmacy and pharmaceuticals for the purpose of creating and using evidence dossiers to support these products. These definitions have been developed solely for use in the *Format*.

⁴⁷ Foundation for Managed Care Pharmacy. Specialty pharmacy initiative: phase I discovery & U.S. environmental scan. October 2009. Available at: <http://www.amcp.org/WorkArea/DownloadAsset.aspx?id=14305> . Accessed August 1, 2012.

⁴⁸ Blaser DA, Lewtas AJ, et al. How to define specialty pharmaceuticals – a systematic review. *Am J Pharm Benefits*. 2010;2(6):371-380

⁴⁹ Schwartz RN, Eng KJ, et al. NCCN task force report: specialty pharmacy. *J Natl Compr Canc Netw*. 2010;8[Suppl 4]:S1–S11. Available at: http://www.jncn.org/content/8/Suppl_4/S-1.long. Accessed August 1, 2012.

‘Specialty Pharmaceuticals’ Definition for Use within the *Format*

Within the current version of the *Format*, a product can be classified as a specialty pharmaceutical if:

- It requires a difficult or unusual process of delivery to the patient (preparation, handling, storage, inventory, distribution, Risk Evaluation and Mitigation Strategy (REMS) programs, data collection, or administration) or,
- Patient management prior to or following administration (monitoring, disease or therapeutic support systems).

In their systematic review of specialty pharmacy definitions (2010), Blaser et al proposed these two categories, as well as a third (high cost), which is the most common element the authors identified among these definitions.⁴⁸ Cost is one of many factors that health care decision-makers consider when evaluating specialty pharmaceuticals. Cost will not be included as a required element in the current definition of specialty pharmaceuticals; managed health care systems will define cost criteria that meet their specific needs. High cost is not enough to define a product as a specialty pharmaceutical, as this definition alone would potentially capture an expensive branded drug with no other special needs for delivery or patient management. It should be noted that the definition above also does not specify whether a drug is injected or infused, is recombinant or biologically derived, or used to treat cancer or rare conditions. Drugs for any disease, and with any derivation or form of administration, may carry complex and demanding requirements that create the need for specialty pharmacy.

‘Specialty Pharmacy’ Definition for Use within the *Format*

Specialty pharmaceuticals, as defined in this addendum, may be supplied and managed by specialty pharmacies, which provide a range of services that should be addressed within a dossier. Specialty pharmacies are distinct from traditional pharmacies in coordinating many aspects of patient care and disease management. They are designed to efficiently deliver medications with special handling, storage, and distribution requirements with standardized processes that permit economies of scale. Specialty pharmacies are also designed to improve clinical and economic outcomes for patients with complex, often chronic and rare conditions, with close contact and management by clinicians. Health care professionals employed by specialty pharmacies provide patient education, help ensure appropriate medication use, promote adherence, and attempt to avoid unnecessary costs. Other support systems coordinate sharing of information among clinicians treating patients and help patients locate resources to provide financial assistance with out-of-pocket expenditures.^{47, 49, 50} Manufacturers sometimes collaborate with specialty pharmacies to provide these services along with the medication. Thus, as an integrated program for patients with complex medical, administrative, and financial needs, specialty pharmacy services should be described within a dossier as the context for the provision of a product.

Of note, specialty pharmaceuticals may also be dispensed by retail, hospital, or infusion pharmacies, which may provide some (or all) of the services that specialty pharmacies provide.

Section II: Application of the *Format* for Specialty Pharmaceuticals

As noted above, the current *Format* has been designed to cover a variety of products with diverse characteristics. However, AMCP recognizes that specialty pharmaceuticals may offer unique considerations requiring additional guidance. This addendum provides guidance for manufacturers creating an evidence dossier for a specialty pharmaceutical. Please refer to the below recommendations when completing each indicated section of the *Format* for these products. Lengths of entries specified in the current *Format* should continue to be used unless otherwise note

⁵⁰ Eng K. The role of specialty pharmacy in the treatment of myelodysplastic syndromes. *Manag Care*. 2009 Nov; 18(11 Suppl 9):21-23; discussion 24.

1.2. Economic Benefits

Include the economic impact of special handling, delivery, route and site of administration, REMS programs, and other administrative offsets that would be above and beyond the cost of the drug.

2.1. Product Description

2.1.c. The National Drug Code (NDC) for all formulations

For specialty pharmaceuticals that may be covered under the medical or pharmacy benefit, additional codes are required in this section. Provide Healthcare Common Procedure Coding System (HCPCS) codes⁵¹ applicable to these products, as well as any Current Procedural Terminology (CPT) codes⁵² that are relevant to reimbursement. International Classification of Diseases (ICD)-9 codes⁵³ are also advisable to include for any indications specified in the package insert.

2.1.d. The ASP and WAC cost per unit size

Provide cost for specialty pharmaceuticals in this section.

2.1.k. Dosing and Administration

Include any instructions for preparation, administration, and a description of any unique type of delivery devices that do not appear in the package insert, as well as information on setting of care. Verbatim language from the package insert should not be supplied here.

2.1.l. Access, e.g., restrictions on distribution, supply limitations, anticipated shortages, and/or prescribing restrictions

For a specialty pharmaceutical, this section should be expanded up to five paragraphs to cover the following information:

1. Considerations for the product around its distribution channels
2. Prescribing restrictions for the product if applicable
3. Handling instructions
4. Ordering instructions for the product
5. Access assistance information (if a multi-faceted program offers access assistance alongside other services describe it in section 2.2.2.d and note in 2.1.l that the program contains access assistance)

2.1.m. Co-prescribed/concomitant therapies

Explain the rationale and clinical benefit associated with the co-prescribed/concomitant therapies.

2.1.n. Concise comparison of PI information with the primary comparator products

Many specialty pharmaceuticals may not have comparator products in a similar therapeutic class or with a similar mechanism of action that can be directly compared in tabular form. In these circumstances, the material should include a short text description explaining the new technology, the current services or products the

⁵¹ Healthcare Common Procedure Coding System (HCPCS) codes. Available at: <https://www.cms.gov/Regulations-and-Guidance/HIPAA-Administrative-Simplification/TransactionCodeSetsStands/CodeSets.html>, <http://www.icd9data.com/HCPCS/2012/default.htm>. Accessed August 1, 2012.

⁵² Current Procedural Terminology (CPT) codes. Available at: <http://www.ama-assn.org/ama/pub/physician-resources/solutions-managing-your-practice/coding-billing-insurance/cpt.page>. Accessed August 1, 2012.

⁵³ International Classification of Diseases (ICD)-9 codes. Available at: <http://www.cdc.gov/nchs/icd/icd9cm.htm>. Accessed August 1, 2012.

new specialty pharmaceutical will augment or replace, and the merits of the new therapy in comparison (e.g., a drug for a condition that was previously only treatable with surgery). This text description should not exceed three paragraphs and should include as much information as possible from the table normally included in this section (i.e., to include indications, safety, efficacy, etc.). Include any studies meeting the standards set in the addendum to the *Format* on Comparative Effectiveness Research (CER).

2.2. Place of the product in therapy

2.2.1. Disease description

Specialty pharmaceuticals often treat rare diseases that may be unfamiliar, with relatively little information available in the public domain. The current two-page limit for this section may be expanded to three pages to provide greater detail for rare conditions treated with specialty pharmacy.

2.2.2.c. The place and anticipated uses of the proposed therapy in treatment

If the package insert does not provide sufficient information regarding delineation of use in specific care settings, additional description or evidence of use in other settings can be included in this section. Settings may include administration by the patient, by a health care professional in the home, in an infusion therapy clinic, in a physician office, or in a hospital.

2.2.2.d. Proposed ancillary disease or care management intervention strategies

Services intended to accompany a specialty pharmaceutical at launch should be described in this section. These may include any of the following: patient education services, nursing administration support services, programs intended to promote adherence, coordination of information among providers or facilities, sharps disposal, and financial assistance to patients. Specific claims made regarding benefits of these services should be documented in this section. These claims should ideally be supported by scientific evidence and the supporting evidence should be briefly described. It should be clearly stated when there is no scientific evidence to support claims of benefits for these services. For patient assistance programs, it is optimal to include the terms of the program and the expected number of beneficiaries. (A single program that offers multiple facets should be described in this section in its entirety; if it contains access assistance, note this in section 2.1.1, and if it contains a REMS component, note this in section 2.2.2.f.). Expand the page limit of section 2.2.2 by up to one page per indication for specialty pharmaceuticals that will be accompanied by more than one of these programs.

2.2.2.f. Description of other drug development or post-marketing obligations

In addition to the existing instructions for this section, if a multi-faceted program intended to accompany the product at launch will include REMS alongside other elements, describe it in section 2.2.2.d and note in 2.2.2.f that the program contains a REMS component.

3.1. Summarizing key clinical studies

Summaries should include any studies identified for inclusion by the CER addendum to AMCP *Format*.

3.1.4. Summary of evidence from secondary sources

This section should summarize technology assessments for specialty pharmaceuticals available from payers in the U.S. and outside the U.S., such as National Institute for Health and Clinical Effectiveness (NICE) and Canadian Expert Drug Advisory Committee (CEDAC).

4.2. Modeling Approaches and Methods

4.2.2. Data Sources

Economic Data. Unit costs ideally would be based on health care system data, although costs vary among health care organizations and data will not necessarily be available from the system expected to use the model. A model with default numbers for things like cost, epidemiology, etc. that allows the user to insert their own numbers is ideal. To promote standardization, a single pricing benchmark, ideally Wholesale Acquisition Cost, is encouraged. Since the costs of infused and injected drugs may also depend on the site of care, models should take these costs into consideration.

4.3. Modeling report and interactive model

4.3.2. Modeling report format

The modeling report abstract should include the rationale and justification for the type of model selected (e.g., CEA, BIM, CMA, CBA, etc.). Table 2 should include assumptions about care management, delivery, administration, and setting of care. Table 3, item d, should include all anticipated costs of care management, delivery, administration, and setting of care.

Biologicals, Biosimilars and the AMCP Format

Many specialty pharmaceuticals are classified as biologicals which are typically large protein molecules or blood products. Due to the nature of biologicals, the current FDA evaluation process for authorizing a generic version of the innovator product is impractical. The exact chemical structure of the biological is likely unknown, thus preventing FDA from analyzing exact comparison data between the two products. Therefore, biosimilars do not fit the definition of a generic equivalent product, i.e., identical -- or bioequivalent -- to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use. In summary, biosimilars are not generic biologics.

What is a biological product?

The FDA defines biological products as therapies used to treat diseases and health conditions. They include a wide variety of products including vaccines, blood and blood components, gene therapies, tissues, and proteins. Unlike most prescription drugs made through chemical processes, biological products generally are made from human and/or animal materials.⁵⁴

What is a biosimilar product?

According to the FDA, a biological product may be demonstrated to be “biosimilar” to an already-licensed FDA biological product (the “reference product”) if data show that the product is highly similar to the reference product notwithstanding minor differences in clinically inactive components and there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency of the product.⁵⁴

In the future, when the patent expires on an innovator biologic, one or more manufacturers may apply for FDA authorization for a biosimilar product. The Patient Protection and Affordable Care Act amended the Public Health Service Act to include an abbreviated licensure pathway for biosimilars. FDA has announced the issuance of three draft guidance documents on biosimilar product development. These FDA documents provide general, overarching guidance describing the general principles for biosimilar

⁵⁴ Food and Drug Administration. Questions and answers: Issuance of three draft guidance documents on biosimilar product development. Available at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm291186.htm>. Accessed December, 2012.

product development. They detail FDA’s current thinking on approaches to demonstrating that a proposed biological product is biosimilar to an FDA-licensed biological product (the “reference product”) for the purposes of obtaining licensure by submitting a marketing application through the abbreviated licensure pathway under section 351(k) of the Public Health Service Act (PHS Act). The abbreviated licensure pathway was established by the Biologics Price Competition and Innovation Act of 2009 (BPCI Act).⁵⁵ Any proposed biosimilar product that seeks to be marketed in the United States needs to meet the requirements set forth in the BPCI Act.

[CLICK HERE for links to the three FDA draft guidances and FAQs](#)

The extent and scope of animal and human studies needed for biosimilar product development programs may differ markedly from those of generic versions of non-biological products. In addition, FDA has stated that the type and amount of analyses and testing that will be sufficient to demonstrate biosimilarity will be determined on a product-specific basis. Thus, as FDA-approved biosimilars reach the market, formulary decision makers may require a body of efficacy, safety, economic, and comparative effectiveness data similar to that of the innovator product in order to make rational, evidence-based decisions regarding coverage and reimbursement. In response to unsolicited requests, manufacturers may need to provide product dossiers like those of the innovator products.

As FDA regulations for biosimilar product approval evolve, the Academy of Managed Care Pharmacy will provide updated guidance for health system decision makers in assessing evidence for these products.

Conclusion

There are unique considerations for decision makers when evaluating specialty pharmaceuticals for formulary decisions. This addendum provides an overview of additional factors that should be considered when decision makers request evidence from manufacturers using the *Format*.

⁵⁵ The Patient Protection and Affordable Care Act, PL 111-148, 3-23-2010. Sections 7001-7003 (Biologics Price Competition and Innovation Act of 2009). Available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf>. Accessed December 2012.

APPENDICES

- Appendix A – Principles of a Sound Drug Formulary System
- Appendix B: Sample Unsolicited Request Letter
- Appendix C: Unsolicited Request Requirements
- Appendix D – *Guidelines for Authors and Peer Reviewers of Economic Submissions to the British Medical Journal* (M.F. Drummond)
- Appendix E - Principles of Good Practice for Decision Analytic Modeling in Health-Care Evaluation: Report of the ISPOR Task Force on Good Research Practices – Modeling Studies
- Appendix F – Sample P & T Committee Monograph
- Appendix G - Formulary Leveraged Improved Prescribing: Evaluation Tool for Guiding Critical Formulary Decision Making

Appendix A

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.

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

- ❖ 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:
 - ♦ 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.

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

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.

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

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

- ❖ 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:
 - ♦ 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.

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.

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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 B:

Sample Unsolicited Request Letter

Date

Name of Acct Manager/Medical Science Liaison

Name of Company

Address

Address

Dear...:

[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 formulary consideration. Please consider this letter as an unsolicited request for an AMCP *Format*-based dossier for your product [[Name of Product or Products here](#)]. Per the AMCP *Format* the dossier should contain all available 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 comparator products that we consider for formulary inclusion or as part of therapeutic class reviews.

In addition, we request that you provide, for a period of 6 months, any new published or unpublished information on labeled or unlabeled uses that is specific to the information requested herein that may serve to further inform our decisions on the use of this product.

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 we recognize that confidential information may be provided. We also recognize the need to respect and honor commercial-in-confidence information and may be willing to sign necessary confidentiality agreements under agreed circumstances.

If you require additional information, please call

Sincerely,

Appendix C:

UNSOLICITED REQUEST GUIDELINES

NOTE UPDATE FROM FDA: In December 2011, the FDA issued a draft guidance called "Guidance for Industry: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices". Please refer to the FDA document for full details at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM285145.pdf>

A drug manufacturer's promotional activities are heavily regulated by the FDA under the Food, Drug, and Cosmetic Act (FDCA) enacted in 1938, and amended in 1962.^{56,57,58} Product information contained in promotional mediums such as print, television, radio, internet and sales representative discussions with customers must be consistent with the FDA-approved labeling, i.e., prescribing information or package insert. Dissemination of product information that has not been approved by the FDA may be considered mis-branding or constitute off-label promotion. Although physicians may prescribe drugs for off-label use, drug companies may not promote or market products for off-label use. "Off-label" product information is any information or claim that is not contained in or consistent with the FDA-approved prescribing information, and may pertain to any aspect of the drug such as therapeutic use or indication, dosage, route of administration, duration, and special populations.

There exist two specific FDA provisions for industry activities that may involve off-label information.^{59,60} First, the FDA published guidance on industry-supported continuing medical education (CME) in 1997.⁴ Under this guidance, the FDA will not subject industry-supported scientific and educational activities under the FDCA labeling and advertising rules if the requirements for independence and being non-promotional in nature are met. A second provision involves the proactive dissemination of reprint articles from peer-reviewed scientific journals.⁵ In January 2009, the FDA provided its current thinking and guidance on "Good Reprint Practices" replacing a previous provision under the FDA Modernization Act (FDAMA) of 1997 that ceased to be effective on September 30, 2006.^{61,62,63,64}

While manufacturers can not proactively communicate off-label information beyond the limited provisions described above, the FDA has long acknowledged the need for health care professionals to access medical

⁵⁶ Federal Food, Drug, and Cosmetic Act, Section 502, Misbranded drugs and devices. Available at <http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapV-partA-sec352.htm>. Accessed on 5/3/09.

⁵⁷ Code of Federal Regulations, Title 21, Section 202.1. Prescription-drug advertisement. Available at http://edocket.access.gpo.gov/cfr_2001/aprqr/pdf/21cfr202.1.pdf. Accessed on 5/3/09.

⁵⁸ US Code, Title 21, Section 352. Misbranded drugs and devices. Available at <http://www.gpo.gov/fdsys/pkg/USCODE-2010-title21/html/USCODE-2010-title21-chap9-subchapV-partA-sec352.htm>. Accessed on 5/3/09.

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⁶¹ Food and Drug Administration Modernization Act of 1997, Section 401. Available at: <http://www.fda.gov/downloads/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAAct/SignificantAmendmentsToTheFDCAAct/FDAMA/FullTextofFDAMALaw/UCM089145.pdf>. Accessed on 5/3/09.

⁶² Federal Food, Drug, and Cosmetic Act, Section 551[§360-aaa]. Requirements for dissemination of treatment information on drugs and devices. Available at <http://www.gpo.gov/fdsys/pkg/USCODE-2003-title21/pdf/USCODE-2003-title21-chap9-subchapV-partD.pdf>. Accessed on 5/3/09.

⁶³ Code of Federal Regulations, Title 21, Section 99.101. Information that may be disseminated. Available at http://edocket.access.gpo.gov/cfr_2001/aprqr/pdf/21cfr99.101.pdf. Accessed on 5/3/09.

⁶⁴ US Code, Title 21, Section 360aaa Requirements for dissemination of treatment information on drugs and devices. Available at <http://www.gpo.gov/fdsys/pkg/USCODE-2003-title21/pdf/USCODE-2003-title21-chap9-subchapV-partD.pdf>. Accessed on 5/3/09.

information that is not contained in the four corners of the drug package insert. Thus, the FDA recognizes and allows for a “safe harbor” for the pharmaceutical industry to respond to unsolicited requests for information not addressed in the prescribing information. The FDA has previously opined their general support and guidance regarding industry responses to unsolicited requests for product information in various informal letters and communications.^{65,66,67} However, these earlier opinions and statements can not be found in any official FDA document or website, and today there exist no explicit regulations that clearly define or address the safe harbor for unsolicited requests.

Despite the regulatory ambiguity, the field of industry-based drug information for handling unsolicited requests has evolved into a specialized discipline grounded by certain key principles and practices that are based on the previous informal FDA positions as well as the industry’s unique regulatory, legal and corporate landscape.⁶⁸

The practice of industry-based drug information may vary slightly from company to company due to specific policies and procedures. **However, key general principles and well-accepted standards that have been established in this field, which include: 1) the manufacture does not prompt or encourage requests, 2) responses focus on data rather than company-generated discussions of those data, 3) individuals with the appropriate scientific and medical training prepare responses, 4) responses do not deliberately go beyond the scope of the request, 5) responses do not include promotional materials, and 6) responses are objective, balanced and scientifically rigorous.**⁶⁹

At many companies, responding to unsolicited requests is the responsibility of functional groups or departments known as Medical Communications, Medical Information or Medical Affairs. Within these departments, scientific or clinical professionals must own the role and responsibility of responding to unsolicited requests. Because the FDA considers responding to unsolicited requests as peer-to-peer scientific discussions or exchanges, inquiries must be handled by company employees who are well qualified and competent in evaluating and communicating scientific evidence in the peer-reviewed medical literature. Pharmacists are common and ideally qualified for this role but other professionals may also be appropriate (MD, RN, PhD, etc).

Requesters may contact the drug manufacture’s Medical Communications Department directly (by phone, mail, fax, email or internet) or a company field representative may facilitate the request from the requester to the appropriate department. Unsolicited requests must be documented by Medical Communications, usually in a computer database system. Responses to unsolicited requests must be relevant, accurate and balanced. Information provided is objective, data-driven, and non-promotional in content and tone. Information is based mainly on the primary peer-reviewed medical literature which may include off-label information if it is relevant to the question. The response is tailored to the specific request without going beyond the scope of the inquiry. Therefore, if a request is too broad or general, the Medical Communications professional may contact the requester to clarify and narrow down the question so as to provide more meaningful and manageable information. The response may be communicated verbally over the phone, via mail, fax, in-person, email, etc. Medical Communication’s response to unsolicited requests may NOT contain promotional or marketing materials, be delivered or disseminated by sales or field representatives, or provided to customers in the presence of sales and marketing personnel.

Most importantly, to qualify as an unsolicited request, the request for information must be truly *unsolicited*. Specifically, the inquiry must be initiated by the requester (formulated in his/her own mind) without prompting, suggestion or solicitation by the drug manufacturer or its employees. Medical Communications should monitor inquiries received for trends and patterns that may suggest evidence of solicitation and prompting by company personnel. Providing product information in response to questions that

⁶⁵ Informal Letter: Position on the Concept of Solicited and Unsolicited Requests, FDA Division of Drug Marketing, Advertising, 1982.

⁶⁶ Informal Communication: Current Issues and Procedures, FDA Center for Drug Evaluation and Research, 1994.

⁶⁷ Drug Company Supported Activities in Scientific or Educational Contexts - Draft Concept Paper, FDA, 1991.

⁶⁸ Graves DA, Baker RP. The core curriculum for medical communications professionals practicing in the pharmaceutical industry. *Drug Information Journal* 2000;34:995-1008.

⁶⁹ Salter FJ, Kramer PF, Palmer-Shevlin NL. Pharmaceutical industry medical communications departments: regulatory and legal perils and pitfalls. *Drug Information Journal* 2000;34:1009-1015.

are solicited is deemed promotional and subject to FDA promotional regulations. Hence, providing off-label information in response to solicited inquiries is considered off-label promotions.

The Academy of Managed Care Pharmacy (AMCP) *Format for Formulary Submissions* is a guideline that calls for extensive clinical and economic information for a product to be included in a dossier submission. Since dossier content includes non-FDA-approved information, the provision of an AMCP dossier by a manufacturer to a health system should fall under the operating assumptions of the Medical Communications safe harbor for unsolicited requests. In other words, manufacturers must receive an explicit unsolicited request for a product dossier in the AMCP *Format* from health systems before an AMCP dossier can be delivered. This premise aligns with the dialogue between the Academy and the FDA regarding the AMCP *Format*, i.e., “the AMCP *Format* represents an unsolicited request from a health system to a pharmaceutical company” for both on-label and off-label product information.⁷⁰ Further, the FDAMA of 1997 Section 114 provides another safe harbor whereby health care economic information provided to a formulary committee or similar entity responsible for selection of drugs for managed care organizations shall not be considered false or misleading (hence, not subject to FDA promotional regulations) if the information is based on competent and reliable scientific evidence.⁷¹ In general, industry considers the economic requirements of the AMCP *Format* under Section 114. However, each company may have different approaches to meeting those requirements depending on its own legal, regulatory and business perspectives and concerns. As described above, all general principles and standards on handling unsolicited requests must be fulfilled by manufacturers in the course of providing the AMCP dossier, e.g., information is relevant, accurate and balanced, responses may not go beyond the scope of the inquiry, sales representatives must not deliver dossiers to customers, etc.

A health system’s request for the AMCP dossier must be truly unsolicited and unprompted by the drug company or its representatives. The accepted process for the receipt of a request may vary from company to company (formal letter, by phone, signed business reply card, etc.). However, the request should be explicit and specific for a product dossier in the AMCP *Format* as other formats exist^{72,73,74} and the FDA has previously opined that “formulary kits” or other similar materials intended for formulary committees are in fact promotional labeling.⁷⁵ While many drug companies may allow sales representatives to facilitate unsolicited requests to the Medical Communications Department, sales and marketing representatives and other company employees without the appropriate role and responsibilities should not disseminate or deliver AMCP dossiers to health systems (even if there is an unsolicited request). The Medical Communications Department should provide dossiers directly to customers in the company’s established media (hardcopy or electronic) and with consideration of the requester’s preference.

At no time, shall a product dossier in the AMCP *Format* be sent to a health system without an authentic unsolicited request from the payer directly to the manufacturer. Any violation of this rule, intentional or not, jeopardizes the regulatory safe harbor for unsolicited requests that allows industry to prepare and respond to requests for product dossiers in the AMCP *Format*, as well as the Academy’s original intent and mission for the AMCP *Format*.

⁷⁰ The AMCP Format for Formulary Submissions, Version 2.1. Academy of Managed Care Pharmacy, April 2005. Available at <http://www.amcp.org/AMCPFormatforFormularySubmissions>. Accessed on 5/3/09.

⁷¹ Food and Drug Administration Modernization Act of 1997, Section 114. Health care economic information. Available at <http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticAct/FDCAAct/SignificantAmendmentstoheFDCAAct/FDAMA/FullTextofFDAMALaw/default.htm>. Accessed on 5/3/09.

⁷² The Center for Evidence-based Policy at Oregon Health & Science University. The Drug effectiveness review project evidence submission protocol – A format for submission of clinical evidence for systematic evidence-based reviews of drug classes, Version 2.5, July 2010. Available at <http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/pharmaceutical-manufacturers/dossier-process.cfm>. Accessed on 11/3/12.

⁷³ WellPoint Health Technology Assessment Guidelines – Drug Submission Guidelines for New Products, New Indications, and New Formulations. WellPointNextRx, September 2008. Available at http://www.anthem.com/shared/noapplication/f0/s0/t0/pw_b155849.pdf?refer=ahprovider&state=in. Accessed on 11/3/12.

⁷⁴ WellPoint Health Technology Assessment Guidelines – Drug Submission Guidelines for Re-evaluation of Products, Indications, and Formulations. WellPointNextRx, September 2008. Available at http://www.anthem.com/shared/noapplication/f0/s0/t0/pw_b155850.pdf?refer=ahprovider&state=in. Accessed on 11/3/12.

⁷⁵ Informal Communication: Current Issues and Procedures, FDA Center for Drug Evaluation and Research, 1994.

APPENDIX D —

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 YO1 5DD, ^b Ministry of Defence, Army Medical Directorate 5, Keogh Barracks, Ash Vale, Hampshire GU12 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-

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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

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

<i>Different forms of economic evaluation</i>		
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.

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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

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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.

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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.

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- 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).

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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.

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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 off) 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,

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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.

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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 pre-specified 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

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patients with asymptomatic AIDS³³; (b) to transform final outcomes from intermediate measures — for example, survival and coronary heart disease events from cholesterol concentrations³⁴; (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 care³⁵; (d) to use data from a variety of sources to undertake a decision analysis — for example, of screening options for prostate cancer³⁶; (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

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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.

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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-

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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
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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 disaggregated 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

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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?				

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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 foresee 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.

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Conflict of interest: None.

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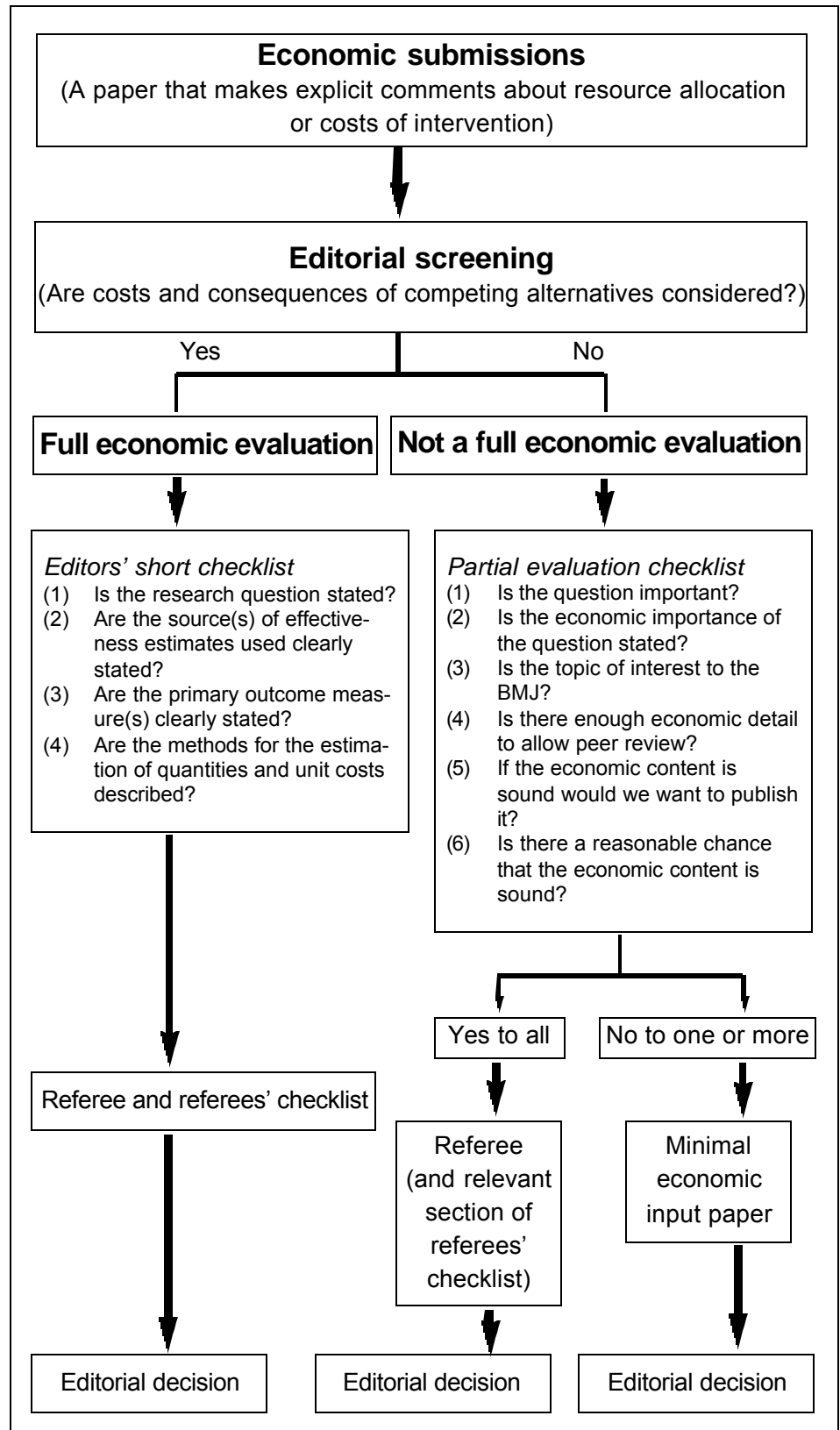
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APPENDIX E

A Report of the ISPOR Health Science Committee – Task Force on Good Research Practices – Modeling Studies

Task Force Chair

- Milton C. Weinstein PhD, Center for Risk Analysis, Harvard School of Public Health, Boston, Massachusetts, and Innovus Research, Inc., Medford, Massachusetts, USA.

Core Group

- Chris McCabe MSc, Senior Lecturer in Health Economics, Trent Institute for Health Services Research, University of Sheffield, Sheffield, UK. John Hornberger MD, MS, Acumen, LLC, and Stanford University School of Medicine, Stanford, California, USA.
- Joseph Jackson PhD, Group Director, Pharmaceutical Research Institute, Bristol-Myers Squibb, Princeton, New Jersey, USA.
- Magnus Johannesson PhD, Associate Professor, Centre for Health Economics, Stockholm School of Economics, Stockholm, Sweden.
- Bryan R. Luce PhD, Senior Research Leader and CEO, MEDTAP International, Bethesda, Maryland, USA.
- Bernie O'Brien PhD, Professor, Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada

Reference Group

- Andrea K. Biddle MPH, PhD, Associate Professor, Department of Health Policy and Administration, School of Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA.
- Donald Chafin MD, MS, Director, SICU/Associate Professor of Medicine & Epidemiology, Beth Israel Medical Center/Albert Einstein College of Medicine, New York, NY, USA.
- Daniel Halberg PhD, Assistant Professor, University of Arkansas for Medical Sciences, Little Rock, AK, USA.
- Matthew Rousculp MPH, The University of Alabama at Birmingham, Birmingham, AL, USA.
- Phantipa Sathkong MS, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Pathumwan, Bangkok, Thailand.
- Daniel Sarpong PhD, Associate Professor of Biostatistics, College of Pharmacy, Xavier University of Louisiana, New Orleans, LA, USA.
- Hemal Shah PharmD, Director, Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CN, USA.
- Mendel Singer PhD, Assistant Professor, Case Western Reserve University, Cleveland, OH, USA.
- Dong-Churl Suh PhD, Assistant Professor, Rutgers University, College of Pharmacy, Piscataway, NJ USA.
- John Walt MBA, Manager, Global Pharmacoeconomic Strategy & Research, Allergan, Irvine, CA, USA.
- Leslie Wilson PhD, MS Adjunct Assistant Professor, University of California San Francisco, San Francisco, California, CA, USA.

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Principles Of Good Practice For Decision Analytic Modeling In Health Care Evaluation: Report of the ISPOR Task Force on Good Research Practices – Modeling Studies

Milton C. Weinstein PhD¹ (Chair), Bernie O'Brien PhD², John Hornberger MD, MS³, Joseph Jackson PhD⁴, Magnus Johannesson PhD⁵, Chris McCabe MSc⁶, Bryan R. Luce PhD⁷

1 Center for Risk Analysis, Harvard School of Public Health, Boston, Massachusetts, and Innovus Research, Inc., Medford, Massachusetts, USA.

2 Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada.

3 Acumen, LLC, and Stanford University School of Medicine, Stanford, California, USA.

4 Pharmaceutical Research Institute, Bristol-Myers Squibb, Princeton, New Jersey, USA.

5 Centre for Health Economics, Stockholm School of Economics, Stockholm, Sweden.

6 Trent Institute for Health Services Research, University of Sheffield, Sheffield, UK.

7 MEDTAP International, Bethesda, Maryland, USA.

ABSTRACT

OBJECTIVES: Mathematical modeling is used widely in economic evaluations of pharmaceuticals and other health care technologies. Users of models in government and the private sector need to be able to evaluate the quality of models according to scientific criteria of good practice. This report describes the consensus of a task force convened to provide modelers with guidelines for conducting and reporting modeling studies.

METHODS: The task force was appointed with the advice and consent of the Board of Directors of ISPOR. Members were experienced developers or users of models, worked in academia and industry, and came from several countries in North America and Europe. The task force met on three occasions, conducted frequent correspondence and exchanges of drafts by electronic mail, and solicited comments on three drafts from a core group of external reviewers and more broadly from the membership of ISPOR.

RESULTS: Criteria for assessing the quality of models fell into three areas: model structure, data used as inputs to models, and model validation. Several major themes cut across these areas. Models and their results should be represented as aids to decision making, not as statements of scientific fact; therefore, it is inappropriate to demand that models be validated prospectively prior to use. However, model assumptions regarding causal structure and parameter estimates should be continually assessed against data, and models revised accordingly. Structural assumptions and parameter estimates should be reported clearly and explicitly, and opportunities for users to appreciate the conditional relationship between inputs and outputs should be provided through sensitivity analyses.

CONCLUSIONS: Model-based evaluations are a valuable resource for health-care decision makers. It is the responsibility of model developers to conduct modeling studies according to the best practicable standards of quality and to communicate results with adequate disclosure of assumptions and with the caveat that conclusions are conditional upon the assumptions and data upon which the model is built.

INTRODUCTION

Mathematical modeling is used widely in economic evaluations of pharmaceuticals and other health care technologies. The purpose of modeling is to structure evidence on clinical and economic outcomes in a form that can help to inform decisions about clinical practices and health-care resource allocations.

Models synthesize evidence on health consequences and costs from many different sources, including data from clinical trials, observational studies, insurance claim databases, case registries, public health statistics, and preference surveys. A model is a logical mathematical framework that permits the integration of facts and values, and that links these data to outcomes that are of interest to health-care decision makers. For decisions about resource allocation, the end result of a model is often an estimate of cost per quality-adjusted life year (QALY) gained or other measure of value-for-money.

Although evidence from randomized clinical trials (RCTs) remains central to efficacy testing, taken alone it can be misleading if endpoints are not translated into measures that are valued by patients, providers, insurers, and the general public. For example, suppose that an RCT demonstrates that a treatment reduces the risk of a rare sequela of a chronic disease by 50%. Further, suppose that another trial shows that a different treatment reduces the risk of a different, more common, sequela by 10%. The latter intervention may well be more effective, and cost-effective, than the former, but a simple comparison of the trial results would not suffice. However, a model could be helpful in revealing that fact to decision makers. The comparison between the two interventions would depend on a synthesis of evidence on the incidence of the sequelae in the target population, the relative risk reductions offered by treatment, survival and quality of life with and without the sequelae, and the costs of the interventions and the medical care required to diagnose and treat the sequelae.

The value of a model lies not only in the results it generates, but also in its ability to reveal the logical connection between inputs (i.e., data and assumptions) and outputs in the form of valued consequences and costs. For this reason, a model should not be a “black box” for the end-user but be as transparent as possible, so that the logic behind its results can be grasped at an intuitive level. Also for this reason, model results should never be presented as point estimates, or as unconditional claims of effectiveness or cost. Instead, the outputs of models should be represented as conditional upon the input data and assumptions, and they should include extensive sensitivity analysis to explore the effects of alternative data and assumptions on the results.

The purpose of this document is to state a consensus position of the ISPOR Task Force on Good Research Practices – Modeling Studies. Like models themselves, this position represents the best judgment of the Task Force at this time, and is subject to change as new technologies for modeling emerge, through advances in computing and analysis, and as fundamentally new dimensions of health care technology and the environment, such as genomic or microbial resistance to drugs, become more pervasive.

TASK FORCE PROCESS

The Chair of the ISPOR Task Force on Good Research Practices -- Modeling Studies, Milton C. Weinstein, was appointed in 2000 by the Chairman of the ISPOR Health Sciences Committee, Bryan R. Luce. The members of the Task Force were invited to participate by the Chair, with advice and consent from the ISPOR Board of Directors. We sought individuals who were experienced as developers or users of pharmacoeconomic models, who were recognized as scientific leaders in the field, who worked in academia, industry, and as advisors to governments, and who came from several countries. A reference group of ISPOR members was also identified as individuals from whom comments would be sought. The Task Force held its first meeting at the Annual North American Scientific Meeting of ISPOR in Arlington, Virginia, May 2000. The Task Force utilized electronic mail to exchange outlines and ideas during the subsequent months. A draft report was prepared by the Chair, and circulated to the Task Force members for revision and additional comment. The revised draft was circulated to the reference group, and after receiving their comments, another draft was prepared. A summary of this draft was presented at a plenary session of the Annual North American Scientific Meeting of ISPOR in Arlington, Virginia, May 2001. Comments from the audience were incorporated into a newly revised draft, which was posted on the ISPOR web site for general comment. The next draft was presented at the Annual European Scientific Meeting of ISPOR in Cannes, France, November, 2001, and a revised draft was posted for

further comment on the ISPOR website. This report reflects the input from all of these sources of comment.

Model Defined

The National Research Council, in its report on the uses of microsimulation modeling for social policy, offered this definition of a simulation model: "... a replicable, objective sequence of computations used for generating estimates of quantities of concern...[1]." We define a health-care evaluation model as an analytic methodology that accounts for events over time and across populations, that is based on data drawn from primary and/or secondary sources, and whose purpose is to estimate the effects of an intervention on valued health consequences and costs.

As part of our working definition, we assume that cost-effectiveness models are meant to be aids to decision making. This means that their purpose is not to make unconditional claims about the consequences of interventions, but to reveal the relation between assumptions and outcomes. These assumptions include structural assumptions about causal linkages between variables; quantitative parameters such as disease incidence and prevalence, treatment efficacy and effectiveness, survival rates, health-state utilities, utilization rates, and unit costs; and value judgments such as the nature of the consequences that are valued by decision makers. A good study based on a model makes all of these assumptions explicit and transparent, and states its conclusions conditionally upon them.

Model Evaluation

Models should be used only after careful testing to ensure that the mathematical calculations are accurate and consistent with the specifications of the model (internal validity), to ensure that their inputs and outputs are consistent with available data (calibration), and to ensure that their results make sense and can be explained at an intuitive level (face validity). To the extent that different models of the same decision come to different conclusions, modelers should also be expected to explain the sources of the differences (cross-validation). The description of the model should be sufficiently detailed that the model can be replicated mathematically.

Tests of predictive validity – the ability of the model to make accurate predictions of future events -- are valuable, but not absolutely essential. Since future events convey information that is not available at the time the model is developed and calibrated, a model should not be criticized for failing to predict the future. However, a good model should be susceptible to recalibration or respecification to adapt to new evidence as it becomes available. The criterion for determining whether, and to what degree, tests of predictive validity are required prior to model use depends on the benefits in terms of improving the model for decision making, and the costs of delaying the flow of information while obtaining the additional data [2].

ASSESSING THE QUALITY OF MODELS

The remainder of this statement describes the consensus of the Task Force regarding the attributes that define a good health-care decision model. We borrow heavily from several excellent papers that propose criteria for assessing the quality of models [3-6]. The attributes are organized under the major headings of structure, data, and validation.

Structure

1. The model should be structured so that its inputs and outputs are relevant to the decision-making perspective of the economic evaluation. Both costs and health consequences should reflect the

chosen decision-making perspective. For example, if the study is meant to assist decision makers in allocating resources across a broad range of health interventions at the societal level, then the outputs of the model should be broadly applicable, and important costs and consequences for all members of the affected population should be included. If a perspective narrower than societal is used, then the report should discuss, at least qualitatively, the implications of broadening the perspective to the societal perspective.

2. The structure of the model should be consistent both with a coherent theory of the health condition being modeled and with available evidence regarding causal linkages between variables. This does not mean that all causal linkages must have been proven, as is commonly understood in tests of hypotheses by showing that the effect size is statistically significant at a generally accepted level of significance (e.g., $p < .05$). Instead, it does mean that the linkages assumed are not contradicted by available evidence and are consistent with widely accepted theories.
3. If evidence regarding structural assumptions is incomplete, and there is no universally accepted theory of disease process, then the limitations of the evidence supporting the chosen model structure should be acknowledged. If possible, sensitivity analyses using alternative model structures – for example, using alternative surrogate markers or intermediate variables – should be performed.

Items 4-8 relate to state-transition (or compartmental, or Markov) models:

4. Health states may be defined to correspond either to the underlying disease process, which may be unobserved or unobservable, or to observed health status, or to a combination of both. For example, screening models may define health states based on underlying pathology, or on clinical status, or both. However, care should be taken to avoid structural bias when interventions modify both the underlying disease and the clinical presentation, as, for example, in models of cancer screening where cases of detected cancer may have different prognoses depending on the method or frequency of screening. In general, structural bias is avoided by modeling underlying disease states, and then by calibrating outputs to data on observed clinical status.
5. When transition rates or probabilities depend on events or states that may have been experienced in prior time periods, this dependence, or “memory”, should be reflected in the model. This may be done either by incorporating clinical or treatment history in the definition of health states, or by including history as a covariate in specifying the transition probabilities.
6. States should not be omitted because of lack of data. Examples might be chronic health states corresponding to uncommon adverse events, or disease sequelae that are not observed within clinical trials. However, inclusion of a health state should be based on evidence consistent with recommendation # 2 above.
7. Reasons to include additional subdivisions of health states may be based on their clinical importance, their relation to mortality, their relation to quality of life or patient preferences, their relation to resource costs, or any combination. Disease states that may not be considered clinically important may well be important to include separately in the model for these other reasons. Conversely, health states that are regarded as having clinical importance may be included to enhance face validity, even if they do not materially affect the model’s results.

8. The cycle length of the model should be short enough so that multiple changes in pathology, symptoms, treatment decisions, or costs within a single cycle are unlikely. The choice of cycle length should be justified.
9. The structure of the model should be as simple as possible, while capturing underlying essentials of the disease process and interventions. It is not necessary to model the full complexity of a disease if the decision can be informed by a more aggregated structure, in terms of disease states or population subgroups. If simplifications are made, these should be justified on grounds that they would be unlikely to materially affect the results of the analysis. Sometimes a structural sensitivity analysis that uses a less aggregated model can provide reassurance that the simplifications do not materially affect the results.
10. Options and strategies should not be strictly limited by the availability of direct evidence from clinical trials. Neither should the range of modeled options and strategies be limited by currently accepted clinical practice. There should be a balance between including a broad range of feasible options and the need to keep the model manageable, interpretable, and evidence-based.
11. While the structure of the model should reflect the essential features of the disease and its interventions irrespective of data availability, it is expected that data availability may affect choices regarding model structure. For example, if a particular staging system has been used most frequently in clinical studies, then health states might well be defined according to that staging system even if other staging systems perform better in terms of predicting outcomes or in terms of differentiating quality of life and cost.
12. Failure to account for heterogeneity within the modeled population can lead to errors in model results. When appropriate, modeled populations should be disaggregated according to strata that have different event probabilities, quality of life, and costs. This is particularly important when recurrent event rates over time are correlated within subpopulations that have different event rates, since failure to do so can lead to biased estimates of long-term outcomes.
13. The time horizon of the model should be long enough to reflect important and valued differences between the long-run consequences and costs of alternative options and strategies. Lifetime horizons are appropriate for many models, and are almost always required for models in which options have different time-varying survival rates. Shorter horizons may be justified if survival and long-term chronic sequelae do not differ among options, or based on an understanding of the disease process and the effect of interventions. In any case, the lack of long-term follow-up data should not be used as a rationale for failing to extend the time horizon as long as is relevant to the decision under analysis.

Data

Our recommendations on data inputs to models are grouped into three categories: data identification, data modeling, and data incorporation.

Data Identification

1. A model should not be faulted because existing data fall short of ideal standards of scientific rigor. Decisions will be made, with or without the model. To reject the model because of incomplete evidence would imply that a decision with neither the data nor the

model is better than a decision with the model but without the data. With the model, the available evidence can be used in a logical way to inform the decision; without the model, an opportunity to utilize the available evidence within the logical framework will have been forgone.

2. Systematic reviews of the literature should be conducted on key model inputs. Evidence that such reviews have been done, or a justification for failing to do so based on the adequacy and generalizability of readily obtained data, should accompany the model.
3. Ranges (i.e., upper and lower bounds) should accompany base-case estimates of all input parameters for which sensitivity analyses are performed. The choice of parameters for sensitivity analysis is a matter of judgment by the analyst, but failure to perform sensitivity analysis on a parameter whose value could be disputed leaves the conclusions open to question.
4. Specification of probability distributions for input parameters based on sampling uncertainty and/or between-study variations may be incorporated into formal probabilistic sensitivity analysis. This is not always necessary or cost-effective, however. For purposes of assessing input distributions, the preferred methodology is to use posterior distributions obtained from formal meta-analyses and Bayesian analysis, but practical considerations may lead to the use of expert judgment (see item 7 below).
5. If known data sources are excluded from consideration in estimating parameters, the exclusion should be justified.
6. Data sources and results should not be rejected solely because they do not reach generally accepted probability thresholds defining “statistical significance” (e.g., $p > .05$). All evidence, even if insufficient to rule out randomness as a cause, may be legitimately incorporated into models. This is subject to the proviso that uncertainty about the estimates is disclosed and tested in sensitivity analyses, and that conclusions are clearly framed as conditional upon the input estimates used.
7. Expert opinion is a legitimate method for assessing parameters, provided either that these parameters are shown not to affect the results importantly, or that a sensitivity analysis is reported on these parameters with a clear statement that results are conditional upon this (these) subjective estimate(s). If expert opinion is elicited, and the results are sensitive to the elicitations, then the process of elicitation should be disclosed in detail. Expert estimates derived from formal methods such as Delphi or Nominal Group techniques are preferred.
8. A case should be made that reasonable opportunities to obtain new additional data prior to modeling have been considered. “Reasonable” in this context means that the cost and delay inherent in obtaining the data are justified by the expected value of the new information in the analysis. While formal methods of assessing value of information exist, it is sufficient to give a heuristic argument as to why the current body of evidence was optimal from the point of view of informing current decisions. This can often be accomplished using sensitivity analysis, to show that reasonable ranges of data would lead to qualitatively similar findings, or by arguing that the cost and delay in obtaining the data are not worth the forgone benefits of acting on current evidence.

Data Modeling

1. Data modeling refers to the mathematical steps that are taken to transform empirical observations into a form that is useful for decision modeling. Examples include:
 - a. The method for incorporating estimates of treatment effectiveness from clinical trials with estimates of baseline outcomes from epidemiologic or public health data. Effectiveness estimates may be based on either intention-to-treat or on-treatment data, depending on the objectives of the analysis. Often, an appropriate approach is to derive estimates of relative risk (or odds ratios) between treatment options from clinical trials, and to superimpose these on estimates of baseline (e.g., untreated or with conventional treatment) probabilities of survival or other endpoints from population-based sources.
 - b. The method for transforming interval probabilities from the literature or from a clinical trial into an instantaneous rate, and then into a transition probability or event probability corresponding to the time interval used in the model.
 - c. The method for combining disease-specific and all-cause mortality into the model. In general, it is acceptable to derive all-cause mortality probabilities from national life tables, unless an alternative source can be justified. In general, it is not necessary to correct for the fact that all-cause mortality includes disease-specific mortality in the general population, unless the disease represents a major cause of death in the demographic groups being modeled.
 - d. The method for modeling survival (e.g., as an exponential, gamma, Weibull, or Gompertz distribution). The choice of functional form for disease-specific mortality should be specified and justified. In general, all-cause mortality should be modeled non-parametrically based on life table data.
 - e. Modeling risk factors or interventions as having an additive or multiplicative effect on baseline probabilities or rates of disease incidence or mortality. Evidence supporting either the additive or multiplicative form should be sought from studies that examine the effect of the risk factor or intervention in a population stratified by base risk.
 - f. The method for combining domain-specific utilities into a multi-attribute utility function. It is preferable to use validated health-related quality-of-life instruments with pre-specified scoring systems based on “forced-choice” methods (standard gamble, time tradeoff).
 - g. The method for transforming health status values (such as rating scales or health-state classifications) into quality-of-life weights.
 - h. The method for transforming charges to costs.

- i. The method for adjusting for inflation or purchasing power across time and among countries. Adjustment for inflation should be based on the Consumer Price Index (CPI), its health care components, or one or more of its subcomponents such as medical care services or equipment. The choice between the general CPI and its health-care component or subcomponents depends on whether the resources being priced are better represented by the general “market basket” in the CPI or by the health-care “market basket”. A limitation of the health-care CPI is that it reflects not only the prices but also to some degree the quantities of input resources used to produce health care services. The method of choice for making adjustments across countries is to use purchasing power parity. However, a simple currency conversion would be appropriate if there is an international market for an input at a fixed price.
 - j. The method for discounting costs and health effects to present value.
2. Data modeling assumptions should be disclosed and supported by evidence of their general acceptance and, preferably, of their empirical validity. Key steps taken in developing the model should be carefully documented and recorded. Model credibility may be enhanced by showing how a model was conceived, for example, prior to or during a phase III or IV clinical trial, and how its structure and data inputs evolved in light of new evidence (e.g., after completion of a clinical trial) in response to subsequent discussions with clinical, regulatory, and policy experts.
3. When alternative, but equally defensible, data modeling approaches may lead to materially different results, sensitivity analyses should be performed to assess the implications of these alternatives. For example, if a model predicts smaller gains in life expectancy at older ages, but the model uses a multiplicative specification of the effect of an intervention of baseline mortality, then the alternative of an additive model should be tested. If there is stronger empirical evidence in support of one functional form, then that form should be the base case, and the alternative form(s) should be tested in sensitivity analysis.
4. Data modeling methods should follow generally accepted methods of biostatistics and epidemiology. For modeling, meta-analysis is a valid and desirable approach, provided that care is taken to recognize heterogeneity among data sources. Heterogeneity can be considered either by segregating estimates based on different groupings of primary studies, or by estimating formal hierarchical models to combine information from heterogeneous studies can do this either.

Data Incorporation

1. Measurement units, time intervals, and population characteristics should be mutually consistent throughout the model.
2. Either probabilistic (Monte Carlo, first-order) simulation or deterministic (cohort) simulation is acceptable.

3. If first-order, Monte Carlo simulation is used, evidence should be provided that the random simulation error (e.g., the standard deviation of output values per run) is appreciably smaller than the effect sizes of interest.
4. All modeling studies should include extensive sensitivity analyses of key parameters. Either deterministic (one-way and multi-way) or probabilistic sensitivity analyses are appropriate.
5. When possible, sensitivity analyses within models that use Monte Carlo simulations should use fixed random number “seeds” within each sensitivity analysis, in order to minimize random simulation error.
6. If cohort simulation is used, sensitivity analysis may be done using probabilistic (Monte Carlo, second-order) simulation, using the specified probability distributions of parameter inputs. In specifying those parameter distributions, care should be taken to ensure that interdependence among parameters is reflected properly in the joint distribution of parameters.
7. When appropriate, and if the differences in quality-adjusted survival between alternatives are less than one cycle length, the half-cycle correction should be used to adjust time-related estimates in the model.

Validation

Our recommendations on validation of models are grouped into three categories: internal validation, between-model validation, and external validation.

Internal Validation

1. Models should be subjected to thorough internal testing and “debugging”. Evidence that this has been done should be provided. This process should include using null or extreme input values to test whether they produce the expected outputs. It may also include examination of the program code for syntactical errors, and tests of replication using equivalent input values.
2. Models should be calibrated against data when possible. Calibration is possible when there exist data on both model outputs and model inputs, over the time frame being modeled. Calibration data can come from national health statistics, such as aggregate and age-gender-specific numbers of deaths, hospitalizations, procedures, or resource costs. The calibration data should be from sources independent of the data used to estimate input parameters in the model. A model should not be criticized if independent calibration data do not exist. However, a model is subject to criticism if independent data suitable for validation do exist and either the model fails to produce outputs consistent with those data (or discrepancies cannot be explained), or the modeler has not examined the concordance between model outputs and such data.
3. While the source code should generally remain the property of the modeler, reasonable requests for copies of models with adequate user interface should be made available for peer review purposes, under conditions of strict security and protection of property rights.

Between-Model Validation

1. Models should be developed independently from one another, in order to permit tests of between-model corroboration (convergent validity).
2. If a model's outputs differ appreciably from published or publicly available results based on other models, the modeler should make a serious effort to explain the discrepancies. Are the discrepancies due to differences in model structure or input values?
3. Modelers should cooperate with other modelers in comparing results and articulating the reasons for discrepancies. (We applaud funding agencies that support this type of collaboration, e.g., the CISNET program of cancer modeling supported by the U.S. National Cancer Institute.)

External and Predictive Validation

Models should be based on the best evidence available at the time they are built. In areas such as HIV and hyperlipidemia, early models assumed that health consequences are mediated by risk factors (CD4 cell counts, serum cholesterol). Subsequent data from some clinical trials have been found to be at variance with the estimates from initial models, while others are consistent with the model assumptions. Insights from clinical trials have led to a second generation of models in both HIV and hyperlipidemia, the estimates from which track more closely with those of the clinical trials. In HIV, this has been accomplished by incorporating antiretroviral drug resistance into treatment efficacy estimates and HIV-RNA as a marker of disease virulence; in hyperlipidemia, this has been accomplished by modeling the lipid fractions LDL and HDL as risk factors. Remaining discrepancies between direct empirical evidence and model results are unexplained. Whether these relate to artifacts of clinical trial design (e.g., patient selection, treatment crossovers) or underlying biological factors (e.g., C-reactive protein and statins, immunological recovery and antiretroviral therapy) is still unknown. Models therefore not only capture the understanding of the science at the time the model is constructed (at a time when there still might be limited long-term data on new treatment), but they can also provide a basis for contrasting and interpreting information from new studies. The ability of models to adapt to new evidence and scientific understanding should be regarded as a strength, not as a weakness, of the modeling approach.

1. Since models are intended as aids to current decision-making, and since their outputs should be reported as conditional upon the input assumptions, it is not necessary that every data estimate or structural assumption be tested in prospective studies, in advance of model use.
2. The decision to obtain additional data to inform a model should be based on a balance between the expected value of the additional information and the cost of the information.
 - a. The "expected value of information" refers to the decision-theoretic concept which values information in terms of its expected (or average) effect on the consequences of decisions. For example, the expected value of information would be zero for a study of a model parameter whose prior range does not include the threshold for the choice among decision options. Judgment concerning prior probabilities of possible study results is inevitably part of the assessment of "expected value of information".
 - b. The "cost of the information" includes the resource cost of performing an empirical study or trial, as well as the expected forgone benefits of delaying decisions until the study or

trial is completed. Judgment concerning prior probabilities of treatment effects is inevitably part of the assessment of “cost of information”.

- c. Recommendations for the conduct or design of research investigations to guide future decision-making can be based on formal analysis of the value of information or on informal interpretation of the implications of sensitivity analyses.
3. Models should never be regarded as complete or immutable. They should be repeatedly updated, and sometimes abandoned and replaced, as new evidence becomes available to inform their structure or input values. As a corollary, models that have been shown to be inconsistent with subsequent evidence, but that have not been revised to calibrate against or incorporate this new evidence, should be abandoned until such recalibration has been accomplished.

CONCLUDING COMMENTS

While these guidelines represent the views of this Task Force at this time, they should not be regarded as rigid or cast in stone. This is not a “rule book”. Different circumstances will lead to deviations from these guidelines, depending on resources available to the modeler (time, money, and data) and on the purpose of the model.

In our view, the most important thing to keep in mind in evaluating a health-care evaluation model is that its outputs must not be regarded as claims about the facts or as predictions about the future. Rather, its purpose is to synthesize evidence and assumptions in a way that allows end-users to gain insight into the implications of those inputs for valued consequences and costs. Its outputs are always contingent on its inputs, which is why it is so important that its inputs be as transparent and accessible as is practical.

FURTHER READING ON MODELING METHODOLOGY

The purpose of this report is not to provide an overview of modeling methodology, but rather to identify those aspects of methodology that the Task Force regards as good research practice. We recommend the following sources for readers who wish to acquaint themselves with the basics of modeling methods. For an introductory textbook on decision analysis, including decision trees and Markov models, see Hunink et al [7]. For contemporary methods of modeling in economic evaluations, including an overview of methods for modeling survival from trial data, and an overview of deterministic and stochastic approaches to modeling, see Kuntz and Weinstein [8]. For an overview of methods for handling uncertainty in models, see Briggs [9], and chapter 11 of Hunink et al. [7].

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APPENDIX F - - Formulary Monograph Template Individual Drug Review

Generic Name: [Name]
Brand Name: [Name]
Manufacturer: [Text]
Date of Review: Month Year
Reason for Review: [Text].

TABLE OF CONTENTS:

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[Executive Summary](#)

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[Background](#)

[Disease Background](#)

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Abbreviations used in this monograph:

EXECUTIVE SUMMARY

Key Questions/Issues and Results of Investigation:

[Issue 1: What is the evidence of efficacy from clinical trials?](#)

[Text. The answers to key questions should normally be no more than a paragraph of modest length. If no evidence was found to answer a particular question, state “No evidence found.”]

Issue 2: Is there sufficient evidence to assess real world comparative effectiveness?

[Text]

Issue 3: What is the evidence of safety?

[Text].

Issue 4: What is the value proposition for this product?

[Text].

Issue 5: Are there identifiable patient subgroups in which this treatment will be most cost-effective?

[Text]

RECOMMENDATIONS TO THE COMMITTEE

[Summary of findings, key issues & conclusions, 1 or 2 short paragraphs that explain the logic leading to your recommendations.]

Therefore, the following P&T action is recommended:

ISSUE 1: What is the evidence of efficacy from clinical trials?

[Narrative summary of evidence for efficacy.]

ISSUE 2: Is there sufficient evidence to assess real world comparative effectiveness?

[Narrative summary of evidence for comparative effectiveness.]

ISSUE 3: What is the evidence of safety?

[Narrative summary of evidence for safety.]

ISSUE 4: What is the value proposition for this product?

Summary of Product Value

[Text summary statement]

Incremental Cost-effectiveness:

[Discussion of cost-effectiveness analyses]

Table . Summary of incremental cost-effectiveness ratios found by studies included in this review.

Cost/QALY (USD)					
Reference					
Setting or Disease 1					
Setting or Disease 2					

ISSUE 5: Are there identifiable patient subgroups in which this treatment will be most cost-effective?

[Discussion of patient subgroups and the evidence that would indicate improved ICER for them. Include a description of relevant biomarkers or other companion diagnostics that would be used to identify these target populations, and the feasibility of using these markers in routine clinical practice.]

Table . Clinical evidence summary

Ref. and Evidence Grade	Drug Regimens	n	Time	Demographics	Design*	End Points/Results/Comments	NNT
Abbreviations used in this table: AC =active control, CCS = case-control study, DB = double blind, PC = placebo control, PCS = prospective cohort study, PG = parallel group, MA = meta-analysis MC = multicenter, RCS = retrospective cohort study, RCT = randomized controlled trial, XO = crossover							

Table . Validation of instruments used in studies included in this review.

Name of Instrument	Abbreviation	Description	Numerical Scale	Interpretation of Values	M.I.D.*

M.I.D. = minimal important difference, usually determined by the originator or owner of the instrument. This number represents a threshold below which a numerical difference is not considered to be clinically meaningful, even if statistically significant. Differences less than this amount are usually excluded from discussions of incremental clinical effect.

Table . Cost-effectiveness evidence summary (Reviewers may change this table format to better fit the economic study methodology)

Ref. and Sponsor	QHEs Score	Study Design and Treatments Compared	Time Horizon and Demographics	Model Inputs and Data Sources	Results: Base Case, Sensitivity Analysis and Limitations

Abbreviations used in this table: LYS = life-years saved, QALY = quality-adjusted life-year, QOL = quality of life.

BACKGROUND INFORMATION

DISEASE BACKGROUND

[Text]

DISEASE BURDEN

[Text]

PATHOPHYSIOLOGY

[Text]

TREATMENT ALTERNATIVES

[Discussion of other existing pharmacologic alternatives or nonpharmacologic treatments that could be used in place of the drug being reviewed. If there are no existing treatment modalities, indicate “best supportive care” etc. and delete the next two sub-sections.]

Preferred Existing Therapy

[Discuss current treatment standards. If there is a “gold standard” treatment that is endorsed by practice guidelines or specialty society opinion statements, reference these authorities.]

Other Therapeutic Alternatives

[Discuss other generally accepted treatment options, including ‘watchful waiting’ or “best supportive care” if these are considered appropriate.]

PRODUCT BACKGROUND

PHARMACOLOGY

[Brief description of mechanism. If it is a novel mechanism, a longer description may be appropriate.]

PHARMACOKINETICS

[Text summary, if kinetics will factor significantly into the decision.]

Route of Administration:	
Bioavailability:	
Time to Peak:	
Multiple dosing:	
Clearance:	

ADVERSE EFFECT PROFILE

[Brief text summary of known side effects and general tolerability from the package insert or other available sources. If clinically important, include a brief table of side effects from the package insert, listing only side effects with incidence rates significantly different from placebo.

This section is for discussion of routine side effects. Major safety issues should be discussed under Issue 3 above.]

DRUG INTERACTIONS

[Text. List these from the package insert. Include a table if appropriate.]

METHODOLOGY OF THIS REVIEW

DATABASES SEARCHED:

Medline
Embase
Cochrane Controlled Trials Registry
Clinicaltrials.gov
Other: [Name]

SECONDARY SOURCES:

Cochrane Reviews Database
BCBSA TEC
NICE
Other: [Name]

SEARCH STRATEGY:

[text]

INCLUSION CRITERIA:

[text]

Search Results:

Study Type	N
Randomized controlled trials (RCT)	
Meta-analyses of RCTs	
Systematic reviews	
Randomized pragmatic Trials	
Prospective cohort studies	
Retrospective cohort or case-control studies	
Economic modeling studies	
Case Series	

RCT abstracts, not peer-reviewed	
Other abstracts, posters, etc., not peer-reviewed	

Articles Excluded from Evidence Synthesis:

Reason for Exclusion	N

REVIEW PREPARED BY

[Author's Name(s), degrees and organization]

REFERENCES

APPENDIX G

FORMULARY LEVERAGED IMPROVED PRESCRIBING: TOOL FOR GUIDING CRITICAL FORMULARY DECISION MAKING²

The following questions provide an enhanced framework for formulary decision making. They should assist committee members in evaluating claims made about new drugs and in considering whether or not to add new drugs to a formulary. In each of the following areas, emphasis should be placed on the *quality of the available evidence* and on *comparisons* to therapeutic alternatives. The ultimate objective should be to evaluate the role for a given drug in significantly improving patient outcomes. A one page short form checklist is included at the end of this document.

Evidence of need

Is there a compelling need to add the drug to our formulary?

- ❑ What is the prevalence and importance of the condition the drug is intended to treat?
What is the relevance of this drug to our population?
- ❑ Are there demonstrated shortcomings of existing therapy?
Is there evidence that this drug overcomes problems in safety, efficacy, acceptability or convenience that characterize existing therapy?
- ❑ What role does this drug play in addressing this need? What are the FDA approved indications? What other claims are being made?
- ❑ What other therapeutic approaches (including non-drug) might reasonably be pursued instead?
- ❑ Is it needed for all the venues/settings for which it is being requested (e.g., for both inpatient and outpatient formulary use)?

Efficacy

What is the evidence to support the claims for this drug?

- ❑ What is the quality and strength of the evidence supporting the efficacy?
How well designed are these studies?
- ❑ Are the claims (both on and off-label) being made for this drug supported by the data presented?
- ❑ How relevant is the population in the published studies to our population and patients in whom it is likely to be used? Were patients like ours included in the clinical trials used to gain FDA approval?
- ❑ To what extent are the benefits based on surrogate measures (i.e., hemoglobin A1c, LDL, serum sodium) rather than clinically relevant outcomes (e.g., mortality, quality of life, stroke)?
- ❑ Does the published (or unpublished) literature contain conflicting evidence about efficacy?
This is especially important given recent examples of selective publication as well as the practice of marketing via distribution of only favorable studies.
- ❑ What is the “marginal efficacy,” efficacy, above and beyond other therapeutic alternatives?

- ❑ Did the efficacy studies use proprietary or manufacturer-developed scales that may bias the findings to give favorable results (e.g., specialized, manufacturer-developed quality of life instruments targeted to be responsive to the effects of a particular drug)?

Safety

What safety issues need to be considered?

- ❑ Is there a potential for look-alike, sound-alike name errors raised by or reported for this drug?
- ❑ Are there safety issues surrounding the administration or preparation requirements?
- ❑ What is the adequacy of the experience with the drug: what are the number and types of patients studied? How long has the drug been used to assure a demonstrated track record of safety (since many adverse effects only appear after 5-10 years of use)?
- ❑ Are there any early warning signals (either in the literature, unpublished studies or FDA reports, or theoretical concerns based on class effects) of potential safety concerns (e.g., reports of hepatotoxicity, nephrotoxicity or drug-drug interactions) that may be a red flag, cautioning against moving too quickly to approve the drug?
- ❑ What patient monitoring, or other special precautions are needed to use the drug safely? How difficult will it be for practitioners to comply with needed monitoring, and how likely are they to perform adequately?
- ❑ How strong is the evidence of this drug's safety compared to other drugs in its class, or other drugs for the same indication currently on the market? What are the anticipated types of adverse events? How do the frequency, severity, preventability and ameliorability of these adverse events compare across alternative drugs for this indication?

Misuse impact potential

If placed on the formulary, what is the potential for misuse or overuse?

- ❑ Is the drug subject to intensive marketing to either consumers or prescribers for questionable and/or off-label indications that may lead to excessive or inappropriate use?
- ❑ Is there evidence or worry that the drug will be subject to excessive or unrealistic patient demand and expectation? Are there concerns that direct to consumer advertising will play a role in patient demand? Are patient advocacy groups aggressively lobbying for the drug?
- ❑ Is there uncertainty or difficulty in accurately diagnosing the condition that is the indication for this drug, possibly leading to overuse or inappropriate use of the drug?
- ❑ Is there potential for widespread off-label usage?
- ❑ Might the expansion of indications to new manufacturer-promoted syndromes play a role in this drug's usage and potential for overuse?
- ❑ Is there experience (in our institution or published literature) with similar drugs and situations suggesting there may be overuse of this agent?

Cost Issues

Can we justify the cost of this drug?

- ❑ How much will it cost? Are there other relevant costs such as additional preparation, storage,

administration, monitoring costs beyond simple acquisition costs?

- ❑ What is the cost and burden of additional monitoring requirements in safely using this drug?
- ❑ What are the comparative costs of other alternatives (e.g., are generics available?)
- ❑ Is a competitor's drug about to become available generically?
- ❑ If there is an added cost associated with using this drug, is there a significant clinical benefit that justifies the added expense?
- ❑ What are the pricing issues (rebate deals, market share or exclusivity requirements, some of which may not be transparent) related to purchasing this drug? Will the price be raised once we switch over to this drug ("bait and switch" pricing tactics)
- ❑ What costs are involved in switching patients currently on another drug that we may be substituting this medication for (additional visits, monitoring)?
- ❑ Is pill-splitting a possibility for saving costs. Is it easy, safe, desirable?

Decision-making information, calculations, timing and process

What is the strength and quality of evidence and information available to the Committee?

- ❑ What is the source (i.e., from drug rep vs. independent review) completeness, timeliness, and quality of the information the Committee has available to make a decision at this time?
- ❑ Has an independent drug monograph review been prepared for the Committee (i.e. by pharmacist or drug information center/service)? If yes: Are the monograph and other information upon which decisions are being made adequate, or are there unanswered questions (such as those raised in this document) that require more information?
- ❑ Are there reviews by other formulary or guideline committees (local, national, international) whose judgments and decisions can help inform our discussion and decision?
- ❑ Are there outstanding questions that may be answered by additional information (or pending research trials) that may warrant deferring a decision?

What is status and quality of the review process at our institution?

- ❑ Has the drug previously been considered/reviewed by our P&T Committee?
If yes what were the issues raised in prior review, discussion and decision?
- ❑ Have there been significant numbers of non-formulary requests for this drug?
If yes, what are utilization and safety experiences and issues surrounding its non-formulary use? What are the pros and cons of keeping drug non-formulary for now?
- ❑ Have the requisite subcommittees and key and knowledgeable specialists been consulted, and have they weighed in on the decision?
- ❑ Has there been undue influence or bias impacting the decision making process? Are there conflicts of interest involved with evaluating this drug's formulary status (e.g. desire to please a high income generating clinician)?
- ❑ What is desirability of approval now, vs. delaying approval pending additional information?
- ❑ Which clinicians should be permitted to use this drug and in what clinical venue?
- ❑ Should there be restrictions (e.g., clinical prior approval or other mechanisms) placed on this medication (based on indication, safety or cost)? If so, what should they be and how can they be easily operationalized?
- ❑ Are their guidelines and/or electronic alerts that could help ensure safe and appropriate use of this medication?

Formulary (New) Drug Evaluation Tool Short Form

A. Evidence of need

Is there a compelling need to add this drug to our formulary?

B. Efficacy

What is the evidence to support the claims for this drug?

C. Safety

What safety issues need to be considered?

D. Misuse impact potential

If placed on the formulary, what is the potential for misuse or overuse?

E. Cost Issues

Can we justify the cost of this drug?

F. Decision-making information, calculations, timing and process

What is the strength and quality of evidence and information available to the Committee?

What is the status and quality of the review process at our institution?

¹ Institute of Medicine. Initial National Priorities for Comparative Effectiveness Research. Report Brief. June 2009. Available at: <http://www.iom.edu/~media/Files/Report%20Files/2009/ComparativeEffectivenessResearchPriorities/CER%20report%20brief%2008-13-09.pdf>. (Accessed 9/1/2012)

² The Formulary Leveraged Improved Prescribing (FLIP) Tool for Guiding Critical Formulary Decision Making was originally developed under a grant from the Attorney General Consumer and Prescriber Education Grant Program (Principal Investigator, Gordon Schiff, MD). It was revised with support from grant number U18HS016973 from the Agency for Healthcare Research and Quality (Principal Investigator, Bruce Lambert, PhD). The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality. The following individuals contributed to the development of the tool: William Galanter, MD, PhD, Michael Koronkowski, PharmD, Amy Lodolce, PharmD, James Duhig, MS, Marcia Edison, PhD, John Busker, PharmD, Pam Pontikes, PharmD, Surrey Walton, PhD., Daniel Touchette, PharmD.