



The LEWIN GROUP

Cost-effectiveness Considerations in the Approval and Adoption of New Health Technologies

Final Report and Case Studies

HHSP23300005T

Submitted to:

Department of Health and Human Services
Assistant Secretary for Planning and Evaluation

Submitted by:

The Lewin Group, Inc.

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This report was produced under the direction of Laina Bush, Task Order Officer, Office of the Assistant Secretary for Planning and Evaluation, Office of Science and Data Policy, Jim Scanlon, Deputy Assistant Secretary for Planning and Evaluation (Science and Data Policy), Don Young, Acting Assistant Secretary for Planning and Evaluation. This report is available online at: <http://aspe.hhs.gov/sp/reports/2007/CECHT>.

This report was prepared by The Lewin Group, Inc. under contract to the Assistant Secretary for Planning and Evaluation. The findings and conclusions of this report are those of the author(s) and do not necessarily represent the views of ASPE or HHS.

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I. Executive Summary

A. Background and Purpose

The Office of the Assistant Secretary for Planning and Evaluation (ASPE) commissioned The Lewin Group (Lewin) to determine how and to what extent cost-effectiveness (CE) considerations are incorporated in the approval and adoption of new health technologies and the implications of not incorporating such considerations. This report examines the use of CE and other cost-health tradeoff evidence by federal and nonfederal health stakeholders, paying particular attention to the scope of authority, range and/or circumstances of use, and responsibilities for regulating CE and other economic information by the Food and Drug Administration (FDA). The role of economic evidence in decision-making also is explored in case studies of four contemporary health technologies.

B. Methodology

Lewin completed two stages of research and analysis culminating in this report. The first was an environmental scan of the current application of economic evidence in decision-making for new health technologies. The second consisted of four case studies conducted to illustrate the use of this evidence for four technologies: nucleic acid testing; Relenza (zanamivir); drug-eluting stents; and implantable cardioverter-defibrillators.

Lewin conducted primary and secondary data collection and analysis for this report. For the environmental scan, primary data were collected during semi-structured discussions with senior staff and other experts representing key federal agencies; private payers; manufacturers; and other health stakeholders from the business, academic and policy community (e.g., health economists, technology assessment organizations) involved in the innovation, adoption and diffusion of new health technologies. Secondary data collection included a review of published and unpublished peer-reviewed and other substantive literature using relevant bibliographic databases (e.g., MEDLINE/PubMed) and web-based search engines. For each case study, semi-structured discussions also were held with stakeholders with relevant expertise. Findings from these discussions were supplemented with secondary data collected from the literature and web-based resources.

After gathering data for the environmental scan and case studies, we conducted a qualitative assessment of interview responses and perspectives in the literature to perceive trends, to characterize use of evidence on CE and other health and economic tradeoffs and to compile potential options for application of cost-effectiveness analysis (CEA) as suggested by some of our sources.

C. Summary of Key Findings and Stakeholder Suggestions

Key Findings

Citing an environment of rising health care costs and insufficient access to care for many Americans, nearly all interviewees recognized potential value of using CE or other cost-health tradeoff evidence in decision-making pertaining to new health technology. At the same time, interviewees expressed caution regarding how economic evidence is and could be incorporated into policymaking. Many stressed that economic evidence should not be applied for cost control alone or rationing of safe and effective interventions, and that any considerations of

cost-health tradeoffs should be inputs to a broader set of important factors mediating the introduction and use of new health care technology. Interviewees acknowledged tension in relationships among certain stakeholder groups concerning matters such as transparency, openness and clarity of the process for incorporating economic evidence.

Regarding the point in the technology lifecycle at which use of cost-health tradeoff evidence is most appropriate, interviewees offered responses ranging from the early stages of innovation to the postmarket phase. While interviewees generally were familiar with the use of CEA in one or more federal agencies, the one most frequently cited was the Agency for Healthcare Research and Quality (AHRQ), although most interviewees were aware that this agency conducts or supports these analyses but does not have regulatory or payment responsibilities. While many interviewees expressed interest in expansion of certain CE applications in the public and private sectors, none suggested that FDA incorporate CE or other cost-health tradeoff considerations in the agency's premarket or postmarket regulatory decisions. A few interviewees for the environmental scan and case studies saw some merit in having the FDA expand processes to determine the economic impact of its guidances.

Responses about the development, current use and potential use of CE and other cost-health tradeoff evidence tended to differ by the type of stakeholder interviewed. Among federal stakeholders, perspectives about the role of FDA were influenced by the extent of interaction between the interviewee's agency and FDA. The following represent the most significant findings regarding development and use of CE and other cost-health tradeoff evidence in decision-making pertaining to new health care technology. The subsequent section includes stakeholder suggestions for improving current systems or structures pertaining to the use of economic information.

1) The types and scope of health economic analysis are diverse

There is no single appropriate method of conducting CE or other cost-related analysis for health care decision-making.

- The intended use of an economic analysis should inform the most appropriate type of analysis to employ in any given instance. For instance, CEA may be most useful to a major payer considering the circumstances for covering a new technology, whereas cost-consequences analysis might be more useful to a hospital staff weighing the pros and cons of using a particular technology.
- Apart from selecting an appropriate type of economic analysis for a given circumstance, our interviewees concurred that patient health considerations are most important and that economic factors can be among multiple considerations in health policy or clinical decisions.

2) Formal use of CE evidence has been less common in the US than in certain other nations (e.g., Australia, Canada, UK)

- Australia and Canada have formal systems to request and incorporate economic evidence into pharmaceutical and other technology payment decisions. The UK's National Institute for Health and Clinical Excellence (NICE) reviews economic evidence pertaining to many types of health technologies as part of the guidance that it issues to the National Health Service. Stakeholders in these systems have expressed concerns about the relatively closed

nature of the Australian system, while generally commending the more accessible and transparent process of NICE.

- There are many potential explanations for the differential uptake of CE evidence in the US and abroad. The literature in this area cites potential obstacles such as methodological concerns, insufficient training, legal concerns, insufficient trust and social acceptance and health system and political barriers.

3) Among DHHS agencies and other federal agencies that influence the climate for innovation, adoption and diffusion of new health technologies, there is great variability in the ways that CE and other cost-health tradeoff information is used and in the authority to use such information

- Stakeholders repeatedly identified certain federal health agencies (e.g., AHRQ) as being involved in CE and other cost-health tradeoff studies, but were less certain about the roles of others, especially with regard to how economic evidence is used in decision-making.
- Federal agencies involved in the development of CE or other cost-health tradeoff evidence include AHRQ, the Centers for Disease Control and Prevention (CDC), Centers for Medicare & Medicaid Services (CMS), National Institutes Health (NIH) and the Veterans Administration (VA). In diverse ways, these agencies sometimes consider, review or use CE or other economic evidence to inform certain decisions (e.g., payment level, benefit structure, program impact). These agencies include AHRQ (and its US Preventive Services Task Force), CDC, CMS, Department of Defense (DoD), FDA and the VA.
- Although these agencies occasionally have some role in the development or use of CE or other economic evidence, the overall level of use of economic evidence in decision-making for new health technologies is relatively low. Across the four case studies, none of these agencies appears to have explicitly incorporated economic considerations into their decision-making processes for the four case study technologies. When economic factors were involved, stakeholders indicated that these factors were more tangential to decision-making, or that it was unclear if economic factors were considered at all.
- The extent of current and future use of CE and other cost-health tradeoff evidence by federal agencies is limited by their respective legislated missions and applicable regulations.

4) Health economists and other stakeholders suggest that, given rising health care costs and system constraints, CE and other economic evidence can provide important input to inform more effective and efficient health decision-making in the US

- Continued growth in domestic health spending of nearly 8% per year, now amounting to 16% of the gross domestic product with double-digit increases in annual health insurance premiums in each of the past four years, is adding to concerns of government, industry and consumers.
- Health care providers, payers, consumers and others increasingly are intent on achieving quality care and value for their health care dollar. Initiatives such as pay-for-performance are prominent examples of this trend.

- Many interviewees expressed that greater and more explicit adoption of CEA or other forms of economic analysis by CMS, other federal entities and private sector payers would inform more credible resource allocation and contribute to better value in health care.

5) Although both public and private stakeholders recognize the potential value of using CE or other cost-health tradeoff evidence, currently, there is no standard set of criteria for determining when economic factors are relevant and how they are to be used in decision-making

- Technology manufacturers expressed that, when they submit economic data to federal agencies like CMS, they are uncertain regarding how the information will be used and how it will affect adoption and payment of their technology.
- These industry stakeholders expressed concerns that economic evidence may be weighted too high relative to other important factors, thereby diminishing matters of clinical utility and patient access.
- Many stakeholders, particularly those from industry, perceived that current applications of CEA in health care delivery and policy decisions are lacking in transparency and resulting in somewhat unpredictable outcomes.
- Interviewees for one of the case studies also suggested that some industry and professional association stakeholders perceive that economic factors were at the root of new technology decisions, even when the decision-makers maintain that clinical evidence was the main consideration.

6) Currently, there is not a uniformly accepted standard for information included in CEAs

- Manufacturers expressed that payers provide little or no guidance regarding what should be included in CEAs to support payment decisions. As a result, manufacturers use varying assumptions and endpoints in these analyses and then, when they submit these analyses to payers, the payers find that the CEAs did not employ desired endpoints or assumptions.
- From the standpoint of public and private payers, CE models submitted by manufacturers often are insufficiently relevant to decision-making. For instance, payers indicated that manufacturers are not always explicit about assumptions used in CE models, and that these models often are not designed for interactive use by payers.

7) In the large and fragmented US health care system, there is no national, standardized process for setting priorities among health issues that could merit CEA

- Many federal and nonfederal stakeholders emphasized that the US lacks a systematic approach to determining priorities for CE research applying to interventions across a range of health conditions.
- As a result, current allocations of CE research may not address the most pressing health topics, and reviews of CE evidence may not account systematically for variations in the quality of this evidence.

8) The current role of FDA in development or use of CE evidence is very limited

- FDA's mission pertaining to health care technology focuses on reviewing evidence of safety and effectiveness pertaining to market approval and postmarket surveillance. Consideration of CE or other economic evidence in market clearance or approval of regulated technologies is not pursuant to FDA's mission, limiting the agency's purview to address these topics.
- FDA does have the responsibility to regulate claims of CE made by manufacturers about particular technologies. Many interviewees believe that FDA's regulation of such claims may stifle the availability of useful CE evidence for new health technologies unnecessarily.
- If FDA, or any other federal agency, issues new regulations meeting certain criteria, it is required to conduct a regulatory impact analysis, including analysis of the CE of such regulations, as mandated by Executive Order 12866 and Circular A-4. However, these analyses primarily gauge the impact of an entire regulation and rarely, if ever, pertain to particular health technologies that may be subject to these regulations.

9) In contrast to the impact analysis pertaining to new regulations, FDA has no statutory authority or mechanism for evaluating the economic impact of guidances

- Periodically, FDA issues guidance documents to address clinical trial design, good manufacturing practices (GMPs) or use of new technologies within the blood industry. A 2005 FDA guidance on the use of a particular type of nucleic acid testing to screen the blood supply received attention from some economists and other stakeholders. Despite the considerable additional cost of this testing and its marginal improvement in detection of pathogens, FDA did not consider the economic impact of this guidance formally.
- While FDA has no statutory authority to perform economic impact analyses of guidances, and its mission specifies evaluating safety and effectiveness, some stakeholders noted that there are no prohibitions for FDA to consider economic evidence when drafting guidance. Therefore, with no explicit restriction against doing so, it may be possible for FDA to incorporate economic evidence in this capacity.
- Stakeholders expressed openness to developing a mechanism for review of guidance documents. Stakeholders indicated that, if such a mechanism were developed, the reviewing agency would have to establish criteria for evaluating CE or economic impact, determine which stakeholders should be involved and identify an appropriate source of funding.

10) While FDA does not require economic evidence in market approval, FDA, CMS and other stakeholders (including manufacturers) are communicating more often during the review phase for new health technologies

- During internal reviews and as a result of this type of communication, FDA may consider resource utilization or other potentially cost-related endpoints (e.g., average length of stay in hospitals) if these endpoints relate directly to safety and effectiveness (e.g., associated with elevated risk of developing secondary/nosocomial infections).

- Despite increased communication among FDA and these parties, and some greater interest in CEA on the part of payers and some other stakeholders in CE evidence, this does not appear to be broadening the scope of FDA's focus beyond matters of safety and effectiveness.

11) Virtually all interviewees expressed that consideration of CE or other cost-health tradeoff evidence during market approval or postmarket surveillance could compromise or distract from the FDA's core mission of ensuring safety and effectiveness of regulated health care products

- Many stakeholders emphasized how resource-intensive FDA's responsibilities are regarding ensuring safety and effectiveness of health care technology, and that the agency currently lacks the internal capacity and statutory authority to incorporate economic evidence into its decisions.
- Some stakeholders expressed concern that weighing economic evidence at the approval phase for a new technology might result in withholding or delaying market entry of beneficial technologies. Similar concerns were expressed in stakeholder interviews conducted for the case studies. These concerns also were expressed in stakeholder interviews conducted for the case studies.

Health Stakeholder Suggestions

Stakeholders interviewed were forthcoming about contemporary development and use of CE and other economic evidence, as well as perceived limitations to potentially beneficial applications of such evidence. Some interviewees suggested ways of remedying these limitations. Themes and individual suggestions for using evidence on CE or other health and economic tradeoffs of new technologies are compiled here. Stakeholder suggestions are divided into two broad headings: 1) process and implementation considerations and 2) considerations specific to the FDA.

1) Process and Implementation Considerations

The great majority of interviewee suggestions relate to modifying the current system to better incorporate CE and other economic evidence into open and transparent policymaking processes. Overarching questions inherent to implementing such provisions address which entities might coordinate the process and potential sources of funding.

Several options emerged from stakeholder suggestions about the proper entities to coordinate a system for review and use of CE and other economic evidence. Among the federal agencies, stakeholders were most likely to identify AHRQ as the most appropriate and best equipped agency to take on this role. Many stakeholders emphasized that AHRQ currently is acting as a facilitator of CE evidence development and use already and, hence, would be a natural choice. However, others suggested that any federal entity coordinating such a process would be susceptible to political pressures that might introduce bias into activities. As such, stakeholders also suggested creating new entities to fill this role, as described below.

- ***Independent entity within government.*** Stakeholders repeatedly referenced establishing a body in the US with a role similar to that of NICE in the UK, which acts independently as a Special Health Authority to the National Health Service, providing guidance informed by

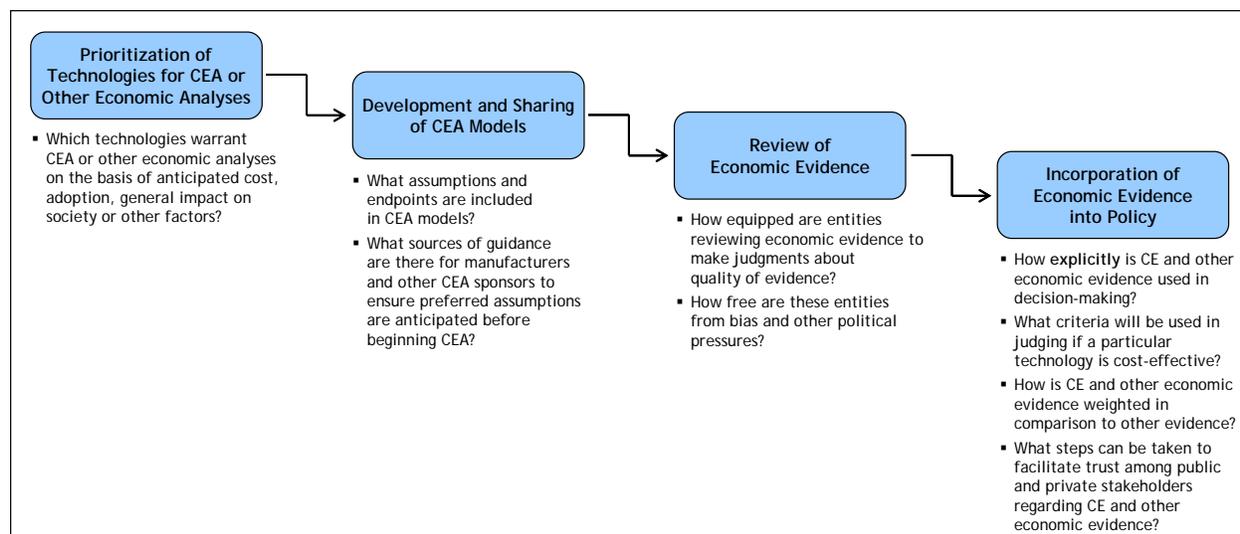
clinical and economic evidence. Some stakeholders referenced the Federal Reserve (the central bank of the US) as a similar arrangement that could serve as a potential model.

- **Fully independent entity.** Some stakeholders favored establishing an entity that would act independently of government or industry. Among those discussed was an organization with a status similar to that of the Institute of Medicine, which would be responsible for coordinating the steps involved in setting priorities for and conducting or sponsoring CEAs. Other independent models were offered, including the Pharmacoeconomic Research Institutes (PERIs) model (which has been suggested by Princeton economist Uwe Reinhardt). PERIs would be funded to conduct economic research on drugs using funding from a small surcharge on the pharmaceutical industry.

Aside from the PERIs strategy, few suggestions emerged from this environmental scan related to funding new systems for incorporating CE or other economic evidence into policymaking. Nevertheless, stakeholders emphasized that responsibility for funding should be shared by public and private stakeholders, ideally in some form of partnership.

Stakeholder suggestions about individual steps in the process of incorporating CE or other economic evidence into decision-making fall roughly into four main categories, as depicted in Exhibit 1, along with relevant questions at each step. Suggestions are summarized according to these four categories.

Exhibit 1:
Key Considerations for Integrating CE and Other Economic Evidence into Policy



Setting Priorities among Technologies for CEA or Other Economic Analyses

Stakeholders emphasized the importance of instituting means to set priorities for determining which technologies warrant CEA or other forms of economic analysis. In suggesting approaches, some stakeholders noted that AHRQ already has instituted a process for identifying topics for clinical evidence assessments as part of its Evidence-based Practice Centers (EPC) program. Similar to the process used by NICE in the UK, the EPC program selects from among topics nominated for systematic evidence review by professional associations, payers, patient groups and other organizations. Some stakeholders suggested that

this portion of the EPC process might be expanded to provide a systematic priority-setting process for implementing economic studies.

Development and Sharing of CEA Models

Manufacturers often conduct or sponsor CEAs for internal purposes and to share with decision-makers such as payers and providers. Stakeholders reported that manufacturers often submit CEA models, only to learn from payers that the models do not incorporate assumptions or endpoints preferred by the payers. From their standpoint, payers often find that models submitted by manufacturers are not interactive and that assumptions used in the models are not readily apparent. As such, stakeholders suggest the need for an objective entity or entities to help set standards about assumptions to be used in CEAs and guidelines for manufacturers to help increase transparency of models submitted to payers. Increased clarity may help to guide CEAs conducted or sponsored by technology manufacturers, so that they may be aligned better with payer expectations. This may mitigate manufacturer risk and improve timeliness of market approval and payment decisions.

Review of CE and Other Cost-health Tradeoff Evidence

In addition to establishing guidelines for developing and sharing CEA models, stakeholders suggested that an objective entity might have a role in reviewing cost-health tradeoff evidence. Some stakeholders proposed that an agency such as AHRQ could have a role in coordinating economic analyses, including evaluating the quality of available evidence and synthesizing findings from existing literature, in the current manner of AHRQ's Evidence-based Practice Centers (EPCs). Well-recognized technology assessment groups such as the Blue Cross Blue Shield (BCBSA) Technology Evaluation Center (TEC), ECRI or HAYES may have similar roles.

Incorporation of CE and Other Economic Evidence into Policy

To improve the clarity and transparency of current CEA efforts, stakeholders suggested that the private and public sector payers could facilitate greater trust among industry stakeholders by clearly establishing how economic evidence will be used (e.g., for what types of decisions) and its role relative to other technology attributes or criteria. Some stakeholders suggested that establishing a public-private partnership to develop a standard framework for use of CE and other economic evidence may enhance transparency and strengthen trust in these processes.

2) Considerations Specific to FDA

The clear consensus of the stakeholders whom we interviewed for the environmental scan and the case studies was that FDA should not consider CE or other economic factors in matters pertaining to market approval or postmarket surveillance. No stakeholder raised suggestions for using these approaches at FDA. However, stakeholders did offer suggestions pertaining to other ways in which FDA authority might affect CE or other economic evidence directly or indirectly, as follows.

- Some stakeholders have proposed ways to respond to concerns that FDA regulation of economic claims made by manufacturers can inhibit availability of CE evidence for new technologies. One health economist has suggested that FDA consider adding disclaimers about assumptions used in CEAs to products advertised using CE claims. An example of

such a disclaimer could be, “This claim of cost-effectiveness is based on assumptions and simulations that may not meet the FDA criteria for claims of efficacy and safety.”¹

- Certain interviewees raised the potential importance of evaluating the economic impact of FDA’s guidance documents. They noted that the agency formally has not been granted legislative authority to conduct analyses of guidance documents. However, there are no apparent restrictions upon the agency for considering economic factors in developing guidances, suggesting that FDA may be able to consider these factors. In any case, it would be necessary to allocate funding for this purpose.

The few stakeholder suggestions pertaining to use of CEA or other economic analyses by the FDA reflects their general concurrence that CEA is beyond the realm of FDA’s responsibilities pertaining to marketing and postmarket surveillance of regulated health care technologies. Stakeholders emphasized that expanding the purview of the agency to include matters of CE or other economic evidence, even given a new legislative mandate, would compromise the importance of the agency’s core mission pertaining to the regulated technologies.

To the extent that CMS, other public and private sector payers or health care providers become involved in using CE information in ways that increase market pressure for more cost-effective health care, this would further diminish any rationale for FDA to use CE information in regulating health technologies.

D. Conclusions and Policy Implications

At present, the level of use of economic evidence in health care decision-making is relatively low. There are several important potential implications of using, and not using, this evidence. If cost-effectiveness or other economic evidence is incorporated more in decision-making for new health technologies, the following may be relevant:

- ***Greater use by one party could stimulate broader use of economic evidence.*** If certain stakeholders, especially FDA or CMS, incorporate economic considerations to a greater extent, this could encourage more use among other stakeholders.
- ***If certain stakeholders adopt economic evidence into decision-making, this could encourage further economic studies to be conducted.*** In particular, if FDA or CMS were to begin considering explicitly such evidence, manufacturers of drugs, devices and other health technologies may be more inclined to sponsor or conduct CEAs or other economic studies in coordination with clinical data collection.
- ***To address concerns regarding the use of economic factors in decision-making, stakeholders may need to consider how to ensure that economic evidence is used appropriately and accounts for societal values.*** This could include formalizing ways of using economic evidence and ensuring transparency in relevant decision-making processes.

¹ Luce BR. What will it take to make cost-effectiveness analysis acceptable in the United States? *Med Care* 2005;43(7):II-44-8.

If the use of economic evidence in health care decision-making is not altered substantially, another set of implications could arise:

- ***If CEA or other economic analyses are not adopted into health technology decision-making, the need for some means of informing health care resource allocation will remain.*** As rising health care costs account for a larger portion of the GDP, the cost of health care technology, particularly new “high-ticket” technologies, will draw stakeholder and public attention.
- ***Aside from resource allocation, not using economic evidence could place financial burden upon certain stakeholders.*** For example, stakeholders interviewed expressed the view that, while FDA guidance documents technically are not binding, often, they are perceived that way. If economic factors are not considered during the guideline development process (e.g., costs for various stakeholders of implementing a particular technology), those responsible for implementing the technology may have trouble managing additional expenses.
- ***Stakeholders, including the public, may seek to become more familiar with and interested in incorporating economic factors into health care decision-making.*** Currently, there are concerns regarding the use of economic evidence in this context. These concerns can be addressed, at least in part, to the extent that stakeholders continue to standardize the methodology for incorporating this evidence in a transparent way.

This report provides a basis for understanding the implications of greater or lesser use of economic evidence in decision-making regarding new health technologies. These insights may be useful in informing future policymaking or other initiatives in this area.

II. Introduction

A. Background

With mounting health care costs, continued advances in health care technology and concerns and evidence of inappropriate use of some technologies, there is increased demand for evidence to demonstrate the safety, effectiveness and, increasingly, the cost-effectiveness of health care technology. During the lifecycle of any health care technology – whether an asthma medication, cardiac pacemaker, molecular diagnostic or electronic health record – its development, adoption, diffusion and use are mediated by a diverse set of decision-makers. In the US, the most prominent decision-making hurdles for new technology involve market approval by the FDA and reimbursement by Medicare and other large payers. These are among a broader set of parties that weigh some combination of technology benefits, harms and costs to inform decisions affecting health care technology, as follows.

- ***Health care technology companies:*** product development and marketing decisions.
- ***Investors and health care product companies:*** venture capital funding, acquisitions and divestitures and other transactions concerning health care products and services.
- ***FDA and other regulatory agencies:*** regulating the commercial use of a drug, device or other technology and related standards.
- ***Health care payers, plans and employers:*** including technologies in health benefits plans or disease management programs, addressing coverage (whether or not to pay) and payment levels.

- **Clinicians and patients:** determining appropriate use of health care interventions for a particular patient's clinical needs and circumstances.
- **Hospitals, health care networks, group purchasing organizations:** making decisions regarding technology acquisition, deployment and management.
- **Health professional associations:** determining the role of a technology in clinical protocols or practice guidelines.
- **Health technology assessment groups:** assessing the strength of evidence and conducting systematic reviews and other analyses of clinical and economic data.
- **Standards-setting organizations:** applying to manufacture, use, quality of care, etc.
- **Government health departments:** implementing public health programs (e.g., vaccination, screening and environmental protection).
- **Legislators and other policymakers:** policies concerning technological innovation, research and development, regulation, payment and delivery of health care.²

In part to serve these decision-makers, there has been an increase during the last 20 years in the number of analyses of the health and economic tradeoffs regarding health technologies.^{3,4,5} While these often are referred to generically as “cost-effectiveness” or “cost-benefit” analyses, they are distinct forms of analysis, including the following examples:⁶

- **Cost-minimization analysis (CMA):** least costly among alternatives that produce equivalent outcomes.
- **Cost-effectiveness analysis (CEA):** costs in monetary units, outcomes in quantitative nonmonetary units, e.g., reduced mortality, morbidity, life-years saved.
 - **Cost-consequence analysis (CCA):** a form of CEA, but without aggregating or weighting across costs or outcomes.
 - **Cost-utility analysis:** a form of CEA, with outcomes in terms of utility or quality of life, e.g., quality-adjusted life-years (QALYs).
- **Cost-benefit analysis (CBA):** costs and outcomes in common monetary units.

Throughout this report, we will use the term “cost-effectiveness” or “CE” to refer specifically to this form of economic analysis, and we will make clear by adding other terms (e.g., cost-health tradeoffs) when referring to other forms of economic analysis or evidence that involve some tradeoff or comparison of costs and health outcomes. The extent to which these considerations

² Goodman C. HTA 101. Introduction to health technology assessment. Bethesda, MD: National Library of Medicine, National Information Center on Health Services Research and Health Care Technology, 2004. Accessed August 22, 2005. <http://www.nlm.nih.gov/nichsr/hta101/hta101.pdf>.

³ Neumann PJ. The reluctance to use cost-effectiveness analysis in regulatory decision-making. Safe enough? In: Jones L, ed. Managing risk and regulation. Vancouver, BC: Fraser Institute, 2000:187-94. Accessed August 18, 2005. http://epe.lac-bac.gc.ca/100/200/300/fraser/safe_enough/3-too_safe/10RskNeumann.pdf.

⁴ Elixhauser A, Halpern M, Schmier J, Luce BR. Health care CBA and CEA from 1991 to 1996: an updated bibliography. *Med Care* 1998;36(5 Suppl):MS1-9, MS18-147.

⁵ Elixhauser A, Luce BR, Taylor WR, Reblando J. Health care CBA/CEA: an update on the growth and composition of the literature. *Med Care* 1993;31(7 Suppl):JS1-11, JS18-149.

⁶ Goodman CS. Healthcare technology assessment: methods, framework, and role in policy making. *Am J Manag Care* 1998;4(special issue):SP200-14.

are incorporated into health care stakeholders' decisions to approve, adopt, acquire, reimburse or otherwise use new health technologies varies and is illustrated in the following examples.

- **FDA.** As part of the market approval process, FDA traditionally has evaluated the scientific evidence on the safety and efficacy of investigational pharmaceuticals, biotechnologies and medical devices, though not CE.⁷ The agency is responsible for regulating and ensuring the accuracy of all promotional materials generated by technology manufacturers. While these claims usually pertain only to matters of safety and effectiveness, they can include economic claims for a technology. Although FDA has issued draft guidelines requiring more rigorous standards for making economic claims, debate persists concerning whether FDA should have a role in conducting or using CE or other economic evaluations.⁸
- **CMS.** CMS does not conduct CEAs in the context of national coverage determinations pertaining to health care technologies or services. However, the Centers may consider the potential health and economic impacts on the Medicare program when it sets priorities for which technologies it will examine for national coverage determinations.⁹ CMS also has accepted information supplied by technology sponsors regarding how a technology would replace something more invasive or expensive or save downstream costs to Medicare. In rare cases, it may request such information. For example, after the Balanced Budget Act of 1997 mandated Medicare coverage of colorectal cancer screening tests, CMS requested that AHRQ conduct a health technology assessment (HTA) comparing immunoassay fecal-occult blood test (iFOBT) to the standard of care screening test, including the matter of cost-effectiveness.¹⁰ Some observers contend that matters of cost and value will play a more explicit role in future determinations by CMS.^{11,12}
- **Private third-party payers.** While most private health plans express interest in CE evidence, only a small proportion of third-party payers formally use this in coverage decisions, and payers generally reported that clinical safety and effectiveness data take precedence over economic considerations.¹³ Although most private payers currently reported limited use of CEA, it is likely that CE and other forms of cost-health tradeoff evidence will be considered in coverage and payment level decisions.¹⁴
- **Blue Cross Blue Shield Association (BCBSA) Technology Evaluation Center (TEC).** Coverage decisions by "Blue" plans and other payers often are informed by HTAs conducted by vendors such as BCBSA TEC, ECRI and HAYES, Inc. While costs explicitly are not included in BCBSA TEC criteria, recent economic analyses have been conducted by BCBSA TEC to

⁷ Investigational pharmaceuticals are reviewed as part of the New Drug Application (NDA) process, biotechnologies are reviewed as part of the Biologics License Application (BLA) process, and medical devices are reviewed through either a Premarket Notification, or 510(k), process or through a Premarket Approval process.

⁸ Neumann P, Zimmer D, Paltiel D. The FDA and regulation of cost-effectiveness claims. How should the Food and Drug Administration regulate drug companies claims that their products are cost-effective? *Health Aff* 1996;15(3):54-71.

⁹ McClellan MB, Tunis SR. Medicare coverage of ICDs. *N Engl J Med* 2005;352(3):222-4.

¹⁰ Decision memo for screening immunoassay fecal-occult blood test (CAG-00180N). Baltimore, MD: Centers for Medicare & Medicaid Services, 2003. Accessed August 17, 2005. <http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=87>.

¹¹ Christian M, Martinson M. Getting paid for all your hard work: the basics of reimbursement for healthcare products and services. *Regulatory Affairs Focus* 2002;July:5-10.

¹² Reynolds MR, Josephson ME. MADIT II (Second Multicenter Automated Defibrillator Implantation Trial) debate. Risk stratification, costs, and public policy. *Circulation* 2003;108:1779-83.

¹³ Garber AM. Cost-effectiveness and evidence evaluation as criteria for coverage policy. *Health Aff* 2004;W4-284 (web exclusive).

¹⁴ Ibid.

supplement clinical evidence on technologies such as left-ventricular assist devices and implantable cardioverter-defibrillators (ICDs).^{15,16}

The use of economic evidence in health technology decision-making has been the subject of lively debate. On one hand, economic analyses provide a potentially important tool for decision-makers regarding the health and economic tradeoffs of implementing new technologies, which can be important in allocating scarce resources. On the other hand, uncertainties remain regarding the use of economic analyses in this way, manifesting as concerns that these analyses will be used as a tool for rationing health care without proper consideration of clinical factors. It is apparent from recent examples, such as NAT to ensure the safety of the blood supply, that economic evidence is not always applied in predictable or consistent ways from the perspectives of all stakeholders. In some cases, implicit societal values appear to far outweigh economic considerations.

Notwithstanding ongoing debate regarding the proper role of CEA and other economic analyses in decision-making regarding new health technologies, use of CEA likely is to grow, along with refinements in methodology and applications. The Medicare Modernization Act of 2003 (MMA) included provisions toward greater efficiency and effectiveness of health care delivery that will increase the impetus for economic analyses.^{17,18} In April 2005, CMS issued draft guidance regarding provisions for coverage with evidence development (CED). This guidance outlined a process in which certain Medicare coverage determinations would be linked to ongoing evidence collection, potentially involving aspects of health care utilization and costs, along with various forms of data collection, including claims files, registries and comparative effectiveness trials.¹⁹ Although the collection of cost or resource utilization endpoints was not mentioned as part of the revised guidance issued by CMS in July 2006, CMS acknowledges in this guidance that the data collected as part of CED could be useful for health plans in conducting cost analyses.^{20,21}

Any proposals regarding whether or how an agency or organization should use CEA or other economic analyses must consider how doing so pertains to their respective missions and operations. For example, to the extent that FDA and CMS consider using CE or other economic criteria in their regulatory or payment policies (including for rulemaking or guidance), this may challenge not only their own agency missions and operations, but their roles with respect to each

¹⁵ Special report: cost-effectiveness of left-ventricular assist devices as destination therapy for end-stage heart failure. Chicago, IL: Blue Cross and Blue Shield Association, Technology Evaluation Center, 2004. Accessed August 17, 2005. http://www.bcbs.com/tec/Vol19/19_02.pdf.

¹⁶ Special report: cost-effectiveness of implantable cardioverter-defibrillators in a MADIT-II population. Chicago, IL: Blue Cross and Blue Shield Association, Technology Evaluation Center, 2004. Accessed August 17, 2005. http://www.bcbs.com/tec/Vol19/19_03.pdf.

¹⁷ Medicare Modernization Act. Baltimore, MD: Centers for Medicare & Medicaid Services, 2005. Accessed August 17, 2005. <http://www.cms.hhs.gov/medicarereform/>.

¹⁸ Foote SB, Neumann PJ. The impact of Medicare modernization on coverage policy: recommendations for reform. *Am J Managed Care* 2005;11(3):140-2.

¹⁹ Draft guidance for the public, industry, and CMS staff: factors CMS considers in making a determination of coverage with evidence development. Baltimore, MD: Centers for Medicare & Medicaid Services, Coverage and Analysis Group, 2005. Accessed November 15, 2005. <http://www.cms.hhs.gov/coverage/download/guidancedced.pdf>.

²⁰ Guidance for the public, industry, and CMS staff: national coverage determination with data collection as a condition of coverage with evidence development. Baltimore, MD: Centers for Medicare and Medicaid Services, 2006. Accessed November 30, 2006. http://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=8.

²¹ The July 2006 CED guidance from CMS mentions collection of data regarding utilization of services, but seems to focus on the utilization of the covered technology/service, rather than associated resource utilization per se.

other. Further considerations are broader market factors that might affect health technology innovation, adoption and use.

B. Purpose

The Office of the Assistant Secretary for Planning and Evaluation (ASPE) commissioned The Lewin Group (Lewin) to determine to how and to what extent CE and other economic considerations are incorporated in the approval and adoption of new health technologies and the implications of incorporating, and of not incorporating, such considerations. This report examines the application of CE and other cost-health tradeoff evidence by federal and nonfederal health stakeholders, paying particular attention to the scope of authority, range and/or circumstances of use and responsibilities for regulating cost-effectiveness information by the FDA. The report also considers other public and private health stakeholders who are developers and/or users of this information, particularly as this might be used by or influence decisions of FDA.

Contributing to this report are four case studies that illustrate to what extent and how federal and nonfederal stakeholders used CE data and other forms of economic evidence in decision-making pertaining to particular health technologies. The topics of these case studies were selected in cooperation with ASPE with the goal of achieving a mix of technologies in terms of physical nature (e.g., drug, device), application (e.g., prevention, treatment), condition type (e.g., acute, chronic), indicated population and care setting. Certain findings and other insights derived from these case studies are incorporated throughout this report. The complete case studies appear in Appendix B.

C. Policy Relevance

In the context of debate regarding current and potential means for improving resource allocation in health care, it is helpful to gain an understanding of the ways in which cost-effectiveness and other forms of economic evidence are used in health care decision-making involving new technologies. In addition to describing current uses, this report explains potential barriers to using cost-effectiveness including statutory limitations, political influences and concerns about the appropriateness of including economic factors in health care decision-making. A clearer understanding of this landscape may help to inform policymakers interested in using economic evidence.

Insights regarding current uses of economic evidence also helps to anticipate how shifts in the policies of one group of health care stakeholders might influence others. This is true especially for the federal stakeholders described in this report, which often play critical gatekeeping roles for new health technologies. For example, private payers monitor Medicare coverage decisions and often generate similar coverage policies. A shift in policy regarding the use of economic evidence by a major federal stakeholder such as FDA or CMS could have important consequences for a range of other federal and nonfederal stakeholders. These types of important interrelationships among stakeholders are explored as part of this report.

III. Methodology

Lewin completed two stages of research and analysis culminating in this report. The first was an environmental scan of the current application of economic evidence in decision-making for new health technologies. The second consisted of four case studies conducted to illustrate the

use of this evidence for four technologies: nucleic acid testing; Relenza; drug-eluting stents; and implantable cardioverter-defibrillators.

Relevant literature and experts and/or thought leaders were selected, in order to obtain a representative set of information including the following:

- Conceptual analyses of the main risks and benefits of using CE and other economic information.
- The roles and responsibilities of FDA and other public and private health stakeholders in development and use of CE and other economic evidence.
- Key examples, gaps, challenges, opportunities and trends relevant to use of CE and other cost-health tradeoff data in decision-making by these stakeholders now and in the future.
- The main implications for key health stakeholder organizations flowing from continued or altered (i.e., expanded or contracted) use of CE and other economic information by these stakeholders.
- The main implications for effective and efficient provision of quality health services flowing from continued or altered use of CE and other economic information by these stakeholders.

While having certain elements in common, the methodologies of the environmental scan and the case studies varied, as each task required differing techniques and approaches.

A. Environmental Scan

In order to assess the use of economic evidence in health technology-related decision-making by key federal and nonfederal stakeholders, we used primary and secondary data collection, as described below.

- **Primary data** were collected during 45-60 minute semi-structured discussions with experts representing key federal agencies (AHRQ, CMS, CDC, DoD, FDA, VA, etc.); private payers; manufacturers; and other health stakeholders from the business, academic and policy community (e.g., health economists, staff of technology assessment organizations) that affect innovation, adoption and diffusion of new health technologies. Interviewees were informed that their responses would remain confidential.
- **Secondary data** collection included review of unpublished and published peer-reviewed and other substantive literature that identifies and synthesizes key aspects pertaining to CE and other economic evidence used in decisions to adopt, recommend or cover health technologies by relevant decision-makers. On-line searches were conducted in the MEDLINE/PubMed, The Cochrane Databases, EMBASE, SciSearch, BIOSIS and other relevant databases using combinations of Medical Subject Headings (MeSH) and keywords such as the following:
 - costs and cost analysis, cost-effectiveness, cost-benefit
 - economics, health economics
 - technology assessment, outcome assessment (health care)
 - quality of health care
 - pharmaceutical, device, biotechnology, biomedical technology
 - United States Food and Drug Administration
 - keywords specific to other federal agencies (e.g., AHRQ, CDC, CMS, DoD, VA, OMB)

- keywords specific to areas of health technology use (e.g., blood supply, hospital, health system, managed care organization, health plan)
- keywords specific to aspects of health technology use (e.g., guidance, policy, regulatory, reimbursement)

Lewin used Internet search engines to locate pertinent articles and other relevant information such as regulations or guidance documents pertinent to the CDC, CMS, FDA and other federal agencies. Bibliographies located through on-line searches were a further source for relevant articles. After generating an extensive list of citations from the various search methods, Lewin examined these and identified a relevant subset for inclusion in the environmental scan.

We limited the environmental scan to articles published in English since 1995. Other than a limited search related to the use of CE and other economic analyses outside of the US, we limited the search to the use of these analyses in the US.

B. Case Studies

Primary and secondary data sources were used to examine the extent to which stakeholders used economic evidence in decisions related to drug eluting stents (DES), implantable cardioverter-defibrillators (ICDs), nucleic acid testing (NAT) and the drug Relenza (zanamivir). As described below, we consulted with relevant experts and reviewed pertinent economic studies for each case study.

- **Primary data** were collected during 30-45 minute semi-structured discussions with experts from federal agencies as well as industry, academic and policy-support functions (e.g., health economists, staff of technology assessment organizations). These experts have been involved in activities that affect innovation, adoption and diffusion of new health technologies, including the particular technology in each case study.
- **Secondary data** collection included review of unpublished and published peer-reviewed and other substantive literature describing the findings of economic analyses for the technology or discussing the application of economic evidence in relevant policy decisions. On-line searches were conducted in MEDLINE/PubMed and The Cochrane Databases. Searches included combinations of economic MeSH terms and keywords, as well as case study-specific search terms, as listed below:
 - cost, costs and cost analysis, cost-effectiveness, cost-benefit
 - economics, medical economics
 - nucleic acid testing, NAT, hepatitis C, HCV, HIV (NAT case study)
 - Relenza, zanamivir (Relenza case study)
 - drug eluting stents (DES case study)
 - implantable cardioverter defibrillators, implantable defibrillators (ICD case study)

As with the environmental scan, Lewin used Internet search engines to supplement these searches with other pertinent materials (e.g., regulations, coverage determinations) and used bibliographies to identify additional relevant sources.

IV. Evidence of Cost-health Tradeoffs, Decision-making and New Health Technologies

Key Messages

- There are multiple analytical approaches for assessing the costs and benefits of new health technologies, each suited to answering particular questions.
- The overall level of use of CE or other cost-health tradeoff evidence in decision-making for new health technologies is relatively low in the US, especially compared to certain other countries.
- FDA currently does not consider CE or other economic evidence as part of market approval, postmarket surveillance or guidance development. Some stakeholders interviewed saw potential merit in having the FDA determine the economic impact of guidances.
- AHRQ was the most frequently cited federal agency viewed by stakeholders as being involved in CE and other economic studies. Stakeholders were less certain about the roles of other federal agencies.
- Although economic evidence is being incorporated more explicitly in coverage decisions for pharmaceuticals by private sector payers, other explicit uses of economic evidence by nonfederal organizations is limited.

A. Considerations for Development and Communication of Cost-health Tradeoff Information

The value of a health care technology can be assessed based on the relative benefits (changes in health outcomes, adverse events, quality of life, etc.) and costs associated with using that technology in health care delivery.²² Consideration of the benefit and cost tradeoffs associated with using a technology may range from informal identification of potential clinical and economic implications to systematic economic evaluations that quantify the gains in health outcomes versus the cost/resource allocation required to deliver these gains.

As annual growth in US health spending approaches 8%, now amounting to 16% of GDP, payers, providers, employers and other health stakeholders are exploring less costly approaches to providing high-quality care.^{23,24,25} Given these conditions, many of these stakeholders are interested in more explicit determinations of health and economic implications of technology use. If consumer-driven health care expands, shifting greater payment burden onto individual beneficiaries, there will be greater demand for information about the relative health and economic benefits of alternative health care interventions.²⁶

Despite the acknowledged potential of CEA, the US has been more reluctant than many other wealthy countries (e.g., in Europe, Canada and Australia) to adopt these tools to support policymaking. Health economists have attributed this lesser uptake to methodological considerations (e.g., lack of consistency, potential bias), lack of training among users of CEA information, legal concerns that inhibit dissemination of this information by health care product

²² Draugalis JLR, Stephen JC. Pharmacoeconomic research-facilitating collaboration among academic institutions, managed care organizations, and the pharmaceutical industry: a conference report. *Clin Ther* 1995;17(1):89-107.

²³ Thorpe KE, Florence CS, Joski P. Which medical conditions account for the rise in health care spending? *Health Aff* 2004;W4-437-45.

²⁴ Gabel J, Claxton G, Gil I, et al. Health benefits in 2004: four years of double-digit premium increases take their toll on coverage. *Health Aff* 2004;23(5):200-9.

²⁵ Ginsberg PB, Strunk BC, Banker MI, Cookson JP. Tracking health care costs: continued stability but at high rates in 2005. *Health Affairs* 2006;25:w486-95.

²⁶ Zhang P, Engelgau MM, Norris SL et al. Application of economic analysis to diabetes and diabetes care. *Ann Intern Med* 2004;140(11):972-7.

makers, lack of trust among the producers and users of CEA information and insufficient political will to use such economic information.²⁷

1) Methodological Considerations

Prior to further discussion regarding the environment for CEA and related economic approaches, including their potential role at FDA, it is necessary to distinguish among certain types of economic analyses. While often known generically as “cost-effectiveness analysis” or “cost-benefit analysis,” there are alternative types of analyses that weigh or compare costs and outcomes (benefits or consequences) of health care technology, summarized in Exhibit 2.

**Exhibit 2:
Methods for Assessing Costs and Benefits of New Health Technologies**

Method	Definition	Valuation of Costs	Valuation of Outcomes
Cost-of-illness analysis	Analysis of the total costs incurred by society due to a specific disease	\$	None
Cost-minimization analysis (CMA)	Compares the costs of programs or technologies that achieve the same outcome	\$	Assumes that outcomes are the same
Cost-effectiveness analysis (CEA)	Reports costs in monetary units and outcomes in quantitative nonmonetary units	\$	Natural units (e.g., reduced mortality, morbidity, life years saved)
Cost-consequence analysis (CCA)	A form of CEA, compares the incremental costs and consequences of alternative programs or technologies	\$	Disaggregated consequences of alternate programs or technologies
Cost-utility analysis (CUA)	A form of CEA, with outcomes expressed as patient utility or quality of life	\$	Utilities (e.g., quality-adjusted life years)
Cost-benefit analysis (CBA)	Estimates the net social benefit of a program or intervention as the incremental benefit less the incremental cost	\$	\$
Value of information analysis (VOI)	Characterizes costs associated with obtaining additional information about a program or technology	\$	Additional information vs. what presently is available

Sources: Gold MR, Siegel JE, Russell LB, Weinstein, MC. *Cost-effectiveness in health and medicine*. New York, Bantam, 1995; Zhang P, Engelgau MM, Norris SL, et al. *Application of economic analysis to diabetes and diabetes care*. *Annals of Internal Medicine* 2004;140(11):972-7; Claxton K, Eggington S, Ginnelly L, et al. *A pilot study of value of information analysis to support research recommendations for the National Institute for Clinical Excellence*. CHE Research Paper 4. Centre for Health Economics, University of York, June 2005. Accessed January 4, 2007. <http://www.york.ac.uk/inst/che/pdf/rp4.pdf>.

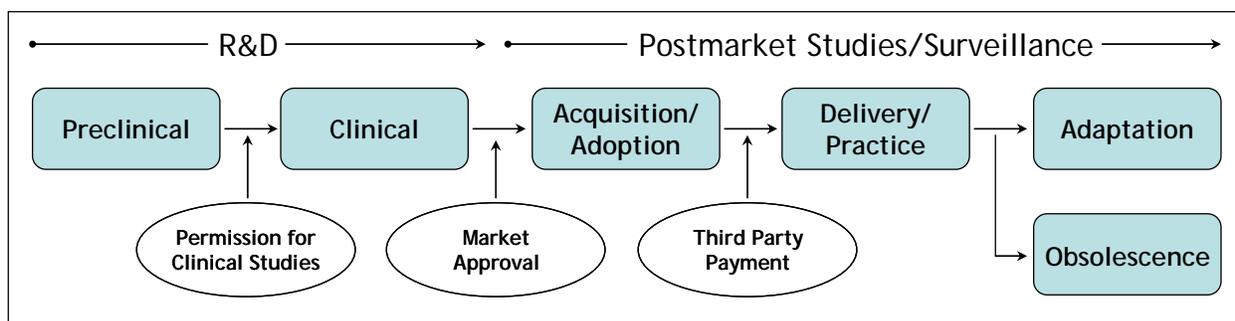
²⁷ Luce BR. What will it take to make cost-effectiveness analysis acceptable in the United States? *Med Care* 2005;43(7):44-8.

As is apparent from their definitions and valuation of costs and outcomes, each of these methods is suited for informing different types of decisions, and health stakeholders may have differing preferences regarding which methods are more robust or useful in certain scenarios. For example, a health plan or managed care organization may prefer the approach of CEA, which enables comparing specific costs and health-related outcomes (e.g., hospital or emergency room admission, length of stay, morbidity and mortality, complications, adverse events) of alternative technologies for a particular patient group or indications. Policymakers concerned with resource allocation across populations or disease areas may desire information generated by cost-utility analysis (CUA), which enables comparing interventions according to their costs and common units of outcomes, e.g., quality-adjusted life years (QALYs), that are not limited to particular types of health-related endpoints. Others may prefer the format of cost-consequence analysis, which presents the full, disaggregated array of costs and outcomes broken out by type rather than in a consolidated ratio, enabling decision-makers to perceive the component costs and outcomes of the alternatives.

2) Conducting CEA and Other Economic Analyses to Inform Decisions Across the Health Technology Lifecycle

CEA and other cost-health tradeoff analyses can inform decision-making at multiple points along the lifecycle of health technology. Two main phases of this lifecycle are research and development (R&D) prior to market approval, followed by a postmarket phase (Exhibit 3). CEAs and other economic evaluations can be conducted during the premarket and postmarket phases, though most are conducted in the postmarket phase to support decisions pertaining to acquisition/adoption of technologies and third-party payment. The health and economic data used in CEAs may be drawn from premarket and postmarket experience.

**Exhibit 3:
Key Phases and Benchmarks of the Health Technology Lifecycle**



Federal and private stakeholders have specific roles throughout the health technology lifecycle, from innovation to diffusion. While NIH primarily is involved in basic biomedical R&D that ultimately leads to advances in pharmaceutical, biotechnologies, medical devices and other technology, it also supports research of technologies already in practice in diverse clinical areas. FDA has roles in premarket and postmarket studies of its regulated technologies. FDA is not charged with evaluating the cost-effectiveness of the products regulated by the agency. In the realm of health services research, AHRQ conducts and supports diverse research and data sources related to evidence-based practice, technology assessment, comparative effectiveness studies and others. Along with CMS, DoD and VA are major health payers whose decisions affect the adoption and diffusion of new technology. CEA or other economic analyses are not used by CMS for making payment decisions for health technology, and other public sector

payers either do not use CEA or do so on a limited basis related to this purpose. DoD and VA also are major providers of health care that make acquisition/ purchasing decisions for health care products and services.

Private payers sometimes use CEA in health care benefits structuring, determining coverage and establishing payment levels. Economic analyses to help inform these decisions may be conducted internally or commissioned to academic experts or vendors. Pharmaceutical and other technology companies also conduct or sponsor versions of CEA to inform their go/no-go decisions for product development, support their case for third-party payment and support marketing of their products.

3) Acceptance and Use of CEA and Other Economic Analyses in the US

Despite the availability of various applications of economic analyses, there are multiple hurdles to their more formal or systematic acceptance and use in the US. Compared to Canada, Europe and Australia, the US has been slower to adopt CEA as part of formal decision-making.²⁸ Some of the frequently cited hurdles to the use of economic evidence in the US include the following:

- ***Concerns about how economic evidence will be used in decision-making.*** Our expert interviewees and others who have addressed this in the literature often express concern that CEA findings will be used as a sole criterion for allocating (rationing) health care, absent other clinical, social and ethical considerations. These stakeholders would consider this form of resource allocation to be an undesirable application of CE evidence. Some experts interviewed for this study indicated that this is of particular concern in the absence of clearly articulated standards for how CE information should be used in decision-making by major health care providers and payers. As observed by one health economist, “rationing under the radar is [sometimes] permitted.”²⁹ Payers may determine that, compared to the standard of care, expensive treatments with small marginal benefits are medically unnecessary. Physicians who work in health care systems that are subject to budget ceilings may make care decisions that reflect the orientation of optimizing the effective use of limited health care resources.
- ***Proper timing to conduct economic analyses.*** Another key challenge of conducting CEAs of new health technologies is the timing of analysis. Early stage analysis may be inconclusive or misleading, due to a lack of sufficient data or because of changes in the technology itself, the indications for which it is used, new data on its safety and effectiveness, changes in costs and other adaptations or developments that render the early findings outdated. DES may be one example of this scenario, given that recent concerns about their safety could shift the risk-benefit tradeoff of these devices and diminish their cost-effectiveness. On the other hand, waiting to conduct a CEA until mature data on costs and outcomes are available may be too late to stem the diffusion of a technology that confers no significant benefit or is simply not worth its costs. There is no ideal time to perform CEA that meets the needs of all stakeholders who can affect the development, adoption and use of technologies. Each stakeholder may choose to develop or assemble available evidence for a CEA to support a particular decision at a given juncture.

²⁸ Luce BR 2005.

²⁹ Neumann P. Using cost-effectiveness analysis to improve health care. Oxford University Press, New York, 2005.

- **Lack of broadly recognized standards.** Many of the experts interviewed for this study noted a lack of broadly recognized standard approaches for conducting rigorous and credible CEAs in the US. For the public sector in particular, the conditions or requirements for conducting CEAs or related economic analyses need to be mandated or otherwise clearly pursuant to an agency's mission. Further, CEAs or other economic analyses that are conducted in support of public sector decisions generally are held to high standards for being systematic, transparent and reproducible.
- **Absence of a systematic process for setting priorities for using CEA.** Public and private sector experts who do conduct or advocate wider use of CEAs concur that they are not required for all technologies. One payer executive stated that the need to conduct CEA rests on factors such as the potential unit and aggregate cost impact of covering the technology. A technology with a high unit cost that offers a substantial marginal health benefit for a small number of beneficiaries is likely to be covered without the need for a CEA. On the other hand, a well conducted CEA would be very useful in informing a coverage decision involving a technology with a lower unit cost that offers a small marginal health benefit and is likely to be used by a large number of beneficiaries. Given the pluralistic nature of health care delivery and payment in the US, there is no systematic national process for setting priorities for or conducting CEA of new health technologies.

As described in the section below, federal agencies are mandated under Executive Order 12866 and other requirements to use CEA, CBA and related forms of economic analysis to assess the impact of new regulations, though typically not to assess particular technologies. Since these mandates apply broadly to all federal agencies, they are described here, rather than in later sections that describe agency-specific applications of economic evidence.

4) Weighing Costs and Benefits of New Federal Regulations

As part of ongoing efforts to reform the regulatory process, the federal government has established certain requirements and provided related guidance for assessing the impact of new regulations. Pertaining to economic analysis in particular is Executive Order (EO) 12866, established in 1993, which requires that a federal agency preparing to publish a new regulation must conduct a regulatory impact analysis that includes consideration of its relative costs and benefits compared to other regulatory alternatives. Released in September 2003, Circular A-4 is the most recent guidance for federal agencies regarding the implementation of EO 12866 from the Office of Management and Budget (OMB). Circular A-4 was intended to clarify for federal agencies the elements of a good regulatory analysis and provide standards for measurement and reporting in regulatory analyses. Other provisions that may involve weighing costs and benefits, or at least accounting for costs, of new regulations are the Regulatory Flexibility Act of 1980 and the Unfunded Mandates Reform Act of 1995. In addition to these provisions, the Institute of Medicine (IOM) published a report in 2006 discussing issues related to CEA in regulatory analysis. This report stemmed, in part, from a 2003 request from OMB for IOM to investigate the current use of CEA in regulatory analysis and provide recommendations to inform future CEA in this context.³⁰

³⁰ Institute of Medicine, Committee to Evaluate Measures of Health Benefits for Environmental, Health and Safety Regulation. Valuing health for regulatory cost-effectiveness analysis. Miller W, Robinson LA, Lawrence RS, eds. Washington, DC: The National Academies Press, 2006.

Executive Order 12866

EO 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits, including potential economic, environmental, public health and safety and other advantages; distributive impacts; and equity.³¹

Under EO 12866, costs and benefits refer to the universe of relevant quantitative and qualitative measures, including measures that are important but may be difficult to quantify. EO 12866 also requires the OMB to review all major rules, except those issued by a military or foreign affairs function and those rules issued by independent agencies such as the Consumer Product Safety Commission (CPSC), Nuclear Regulatory Commission (NRC), Securities and Exchange Commission (SEC) and Federal Communications Commission (FCC).

According to EO 12866, an economic analysis should provide information that will allow decision-makers to determine that:

- There is adequate information indicating the need for and consequences of the proposed action.
- The potential benefits to society justify the potential costs, recognizing that not all benefits and costs can be described in monetary or even in quantitative terms, unless a statute requires another regulatory approach.
- The proposed action will maximize net benefits to society (including potential economic, environmental, public health and safety and other advantages; distributional impacts; and equity), unless a statute requires another regulatory approach.
- Where a statute requires a specific regulatory approach, the proposed action will be the most cost-effective, including reliance on performance objectives to the extent feasible.
- Agency decisions are based on the best reasonably obtainable scientific, technical, economic and other information.

EO 12866 calls for analysis of costs and benefits for a “significant regulatory action,” i.e., likely to result in a rule that may have an annual effect on the economy of \$100 million or more or adversely affect the economy or a sector of it in a material way; create a serious inconsistency or interference with another agency; materially alter the budgetary impact or recipients of entitlements, grants, user fees or loan programs; or raise novel legal or policy issues arising out of legal mandates, the President’s priorities or the principles of EO 12866 itself.³²

³¹ The President: Executive Order 12866-Regulatory Planning and Review. Federal Register Part VIII; October 4, 1993. Washington, DC: Office of Management and Budget. Accessed November 29, 2005. <http://www.whitehouse.gov/omb/inforeg/eo12866.pdf>.

³² Ibid.

Circular A-4

In 2003, OMB published new guidelines for regulatory analysis, known as Circular A-4.³³ These guidelines apply to all agencies of the executive branch of the federal government that issue economically significant proposed or final rules, as defined in EO 12866.³⁴ Circular A-4 became effective for these proposed and final rules on January 1, 2004, and January 1, 2005, respectively.

Although Circular A-4 provides guidance for conducting both CBA and CEA for regulatory impact analyses, Circular A-4 places relatively more emphasis on CEA than previous OMB guidance on this topic.³⁵ Circular A-4 describes the appropriate uses of each method as follows:

“Both benefit-cost analysis (BCA) and cost-effectiveness analysis (CEA) provide a systematic framework for identifying and evaluating the likely outcomes of alternative regulatory choices. A major rulemaking should be supported by both types of analysis wherever possible. Specifically, you should prepare a CEA for all major rulemakings for which the primary benefits are improved public health and safety to the extent that a valid effectiveness measure can be developed to represent expected health and safety outcomes. You should also perform a BCA for major health and safety rulemakings to the extent that valid monetary values can be assigned to the primary expected health and safety outcomes.”

In order to help standardize the way benefits and costs are measured and reported, Circular A-4 also specifies preferred measures and the perspective that should be employed in analyses. For instance, Circular A-4 indicates that all relevant costs *to society* should be included, both public and private, as part of the total costs calculated for a regulation. With regard to measurement of the effectiveness of a regulation as part of CEA, Circular A-4 states that final outcomes (e.g., life-years saved) are preferable to intermediate outcomes (e.g., cases of disease avoided). Circular A-4 categorizes these types of final outcomes as simple measures of effectiveness and describes a set of more comprehensive measures, as described in the excerpt below:

“There are relatively simple measures such as the number of lives saved, cases of cancer reduced, and cases of paraplegia prevented. Sometimes these measures account only for mortality information... There are also more comprehensive, integrated measures of effectiveness such as the number of ‘equivalent lives’ (ELs) saved and the number of ‘quality-adjusted life years’ (QALYs) saved. The main advantage of the integrated measures of effectiveness is that they account for a rule’s impact on morbidity (nonfatal illness, injury, impairment and quality of life) as well as premature death.”

Given these potential effectiveness measures, Circular A-4 states that agencies should try to use at least one of the more comprehensive and integrated measures, where evaluation of morbidity as well as mortality is important to understanding the impact of a new regulation.

³³ Circular A-4. Washington, DC: Office of Management and Budget, 2003. Accessed July 3, 2006. <http://www.whitehouse.gov/OMB/circulars/a004/a-4.pdf>.

³⁴ Memorandum for the President’s Management Council: OMB’s Circular no. A-4, new guidelines for the conduct of regulatory analysis. Washington, DC: Office of Management and Budget, 2004. Accessed July 3, 2006. http://www.whitehouse.gov/omb/inforeg/memo_pmc_a4.pdf.

³⁵ Ibid.

Together, EO 12866 and Circular A-4 encourage more rigorous and standardized approaches to performing CEAs, CBAs and related analyses. Their intended net effect is to lead to more appropriate and beneficial policies.

Other Requirements for Analyses of Federal Regulations

The Regulatory Flexibility Act (RFA) of 1980, as amended (5 USC 601 et seq.), requires federal agencies to review their regulations to ensure that they do not unduly inhibit the ability of small entities to compete. RFA applies when any rule is promulgated that will have a significant economic impact on a substantial number of small entities. If a proposed regulation comes under the Act, an agency must prepare an Initial Regulatory Flexibility Analysis, which it publishes with the proposed rule and sends to the Small Business Administration (SBA). SBA has no OMB-like review function; rather, it monitors agency compliance with the Act. This type of analysis need not involve a CEA or CBA, although it should provide an estimate of the number of small entities on which a rule is expected to have an economic impact.³⁶

Section 202 of the Unfunded Mandates Reform Act of 1995 (UMRA) requires that federal agencies prepare an assessment of anticipated costs and benefits before it finalizes any rule requiring any expenditure by state, local and tribal governments, in the aggregate, or by the private sector of \$100 million (adjusted annually for inflation) in any one year.³⁷

IOM Report on Use of CEA

Released in 2006, the IOM report *Valuing Health for Regulatory Cost-effectiveness Analysis* investigates current federal agency practices for assessing costs and benefits as part of regulatory analysis and examines alternative methods for assessing the health benefits of regulations. This report reviews the relevant legislation and guidance for regulatory analysis (e.g., Circular A-4) and indicates that federal agencies have made strides toward meeting the requirements of Circular A-4 since it was issued in 2003. However, the report also notes that integrated measures of effectiveness (e.g., QALYs) historically have been used less commonly in CEA for regulatory analyses, but these types of measures are beginning to be employed more widely. In order to inform the application of these types of integrated effectiveness measures, the IOM report specifies criteria for selecting measures. For instance, one of the criteria states that the integrated measure selected, “should be applicable to the range of health states and conditions considered in regulatory analysis.”³⁸

The IOM report provides several conclusions and recommendations regarding the use of CEA in regulatory analysis. In brief, the IOM concluded that CEA is feasible to apply in regulatory analyses and provides a useful tool for decision-making, although CEA should not be the sole input into regulatory decisions and that additional research would help improve the application of CEA for this purpose. The IOM report goes on to provide a set of 12 recommendations pertaining to the most appropriate measures of effectiveness, measures of cost-effectiveness that should be reported in every regulatory analysis, future research priorities and related topics.³⁹

³⁶ Regulatory Flexibility Act. Washington, DC: United States Small Business Administration, 1996. Accessed December 20, 2005. <http://www.sba.gov/ADVO/laws/regflex.html>.

³⁷ P.L. 104-4, 2 USC 658-658g, 1501-71.

³⁸ Institute of Medicine, 2006.

³⁹ Ibid.

These recommendations may be useful for federal agencies when conducting regulatory analyses in adherence to EO 12866 and OMB's Circular A-4.

Examples of the application of federal requirements for weighing the costs and benefits of new federal regulations by the FDA are given below in the section on *Use of Cost-effectiveness and Related Economic Analyses by FDA*.

The following section examines current uses of CEA and related economic analyses within health care, including by federal agencies, with an emphasis on FDA's role in regulating the marketing of new health care technologies.

B. FDA Mission and Mandates

The ways in which economic evidence could be generated or used by the federal agencies are influenced by each agency's mission and the scope of its mandates. FDA's mission embraces responsibilities for safeguarding the public health, enhancing innovation and providing useful information to the public:

*"The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health."*⁴⁰

Among health care technologies, FDA's regulatory responsibilities include:

- **Drugs:** product approvals, OTC and prescription drug labeling, drug manufacturing standards.
- **Biologics:** product and manufacturing establishment licensing, safety of the nation's blood supply, research to establish product standards and develop improved testing methods.
- **Medical devices:** premarket approval of new devices, manufacturing and performance standards, tracking reports of device malfunctioning and serious adverse reactions.
- **Radiation-emitting electronic products:** radiation safety performance standards for diagnostic x-ray equipment, laser products, ultrasonic therapy equipment, accrediting and inspecting mammography facilities.

Product approvals and market clearance activities by FDA are managed predominately by three main centers:

- **Center for Drug Evaluation and Research (CDER):** responsible for ensuring the safety and effectiveness of drugs through market approval and surveillance processes.⁴¹

⁴⁰ FDA's mission statement. Rockville, MD: US Food and Drug Administration, 2005. Accessed December 20, 2005. <http://www.fda.gov/opacom/morechoices/mission.html>.

⁴¹ Drug, device, diagnostics approvals & clinical trials glossary. Rockville, MD: US Food and Drug Administration, 2005. Accessed December 21, 2005. <http://www.fda.gov/cber/index.html>.

- **Center for Biologics Evaluation and Research (CBER):** responsible for adequate production, safety and efficacy and oversight of biologics, which include blood and blood products, childhood vaccines, human tissue and tissue derived products and allergenic materials and anti-toxins.
- **Center for Devices and Radiological Health (CDRH):** responsible for ensuring the safety and effectiveness of medical devices and eliminating unnecessary human exposure to man-made radiation from medical, occupational and consumer products. For medical devices, CDRH is charged with reviewing research and marketing requests, surveillance and analysis of adverse events, oversight of good manufacturing practices and performance standards, compliance and providing nonfinancial support for small manufacturers.

The work of the three centers is supported by Office of Surveillance and Biometrics (OSB), Office of Device Evaluation (ODE), Office of Compliance (OC) and Office of Combination Products (OCP). FDA strives to make accurate and timely decisions using state-of-the-art science/technology, develop and frame decisions within a global context, consider total product lifecycles in the decision-making process and work in collaboration and in conjunction with various partners from all sectors to ensure that safe and effective products are available to Americans in a timely manner.⁴²

FDA's overarching activities related to development of new health technologies include:

- Management of the approval process for new health technologies, spanning premarket and postmarket clinical data evaluation via required regulatory submissions and surveillance.
- Development and implementation of regulations that mandate product development requirements.
- Development of guidance documents that serve as information resources to manufacturers.
- Monitoring a broad array of data collection and analysis, manufacturing and communication (e.g., marketing claims made by manufacturers) related to new and existing health technologies.

Other activities responsibilities that may involve, but infrequently focus on, individual technologies include reporting on status of specific regulatory activities and overall performance to Congress, other government agencies (e.g., OMB) and other stakeholders.

Although there are few instances pursuant to its mission that would call for FDA to develop or use CEA or other economic analyses in decision-making regarding new health technologies, the following sections examine aspects of FDA's authority to do so, as well as the implications of changing or expanding this role in the future.

C. Development and Use of CEA and Other Economic Analyses by FDA

All public and private sector experts interviewed for this environmental scan emphasized that FDA's critical role is ensuring that new health technologies are safe, effective and available to consumers in a timely manner. Nearly all interviewees expressed that incorporating CE or other economic considerations into market clearance decisions would be unproductive. Some

⁴² Merrill R. Modernizing the FDA: an incremental revolution. *Health Aff* 1999;18(2):96-111.

expressed that, at worst, it could, at times, compromise or conflict with conducting FDA's primary responsibilities in a timely manner.

There are certain instances in which FDA is called upon to perform CEA or CBA, including pursuant to EO 12866 and other requirements described above. The FDA maintains an economics staff that conducts analyses to fulfill requirements for assessment of regulations, but these focus almost exclusively on broad program or policy impact assessment rather than individual products. For new medical technologies, FDA also is responsible for monitoring labeling and advertising claims under the Food and Drug Administration Modernization Act of 1997 (FDAMA).

Certain economic matters may arise among the responsibilities of the FDA Division of Drug Marketing, Advertising, and Communications (DDMAC).⁴³ The main purpose of DDMAC is to ensure that labeling and advertising claims for drugs comply with section 114 of FDAMA guidelines for dissemination of health economic information. As with clinical evidence on product safety and effectiveness, the main issue for health economics is whether marketed information makes claims that go beyond the FDA-approved labeling for a product. Inappropriate claims are followed by FDA-initiated regulatory warning letters.⁴⁴ DDMAC does not perform or use cost analyses.

The following sections discuss areas of FDA activity where the agency currently is using CEA, areas where there is a potential for future CEA application in decision-making and relevant statutory/mission initiatives in the context of current bounds of authority. This discussion is organized according to FDA's main roles: medical product approval processes; monitoring of manufacturer claims; regulation creation and implementation; and guidance creation.

1) Medical Product Approval Processes

FDA does not consider economic information in its product approval process. The initial premarket approval processes involve regulatory submissions for establishing safety and effectiveness of new drugs, biologics and medical devices. These include Investigational New Drug (IND) applications and New Drug Applications (NDAs) for pharmaceuticals and some biologics; Biologics License Applications (BLAs) for biologics; and Investigational Device Exemptions (IDE), Premarket Approval (PMA) and Premarket Notification [510(k)] applications for devices. Combination products (e.g., drug-device and biologic-device combinations) can involve combinations of these.

Economic data that are useful in CEA can be derived from clinical endpoints used to assess safety and effectiveness in clinical trials of health care technologies. Clinical trials that compare new products to placebo or standard care may involve clinical trial endpoints for adverse events, hospital days and other types of health care utilization that can be translated into costs. While the FDA does not perform CEAs using such data, analysts working with third-party payers, health technology assessment organizations, academic groups and others do draw upon such clinical trial data to perform CEAs.

⁴³ Center for Drug Evaluation and Research. Rockville, MD: US Food and Drug Administration, 2005. Accessed December 21, 2005. <http://www.fda.gov/cder/about/default.htm>.

⁴⁴ Stewart KA, Neumann PJ. FDA actions against misleading or unsubstantiated economics and quality-of-life promotional claims: an analysis of warning letters and notices of violation. *Value Health* 2002;5(5):390-7.

Occasionally, manufacturers will provide FDA with economic data as part of the review process for FDA approval; however, this evidence does not appear to be a significant consideration for approval. For example, according to one industry expert, during the approval process for DES, cost-effectiveness data were provided to the FDA. However, stakeholders interviewed for this case study asserted that the economic evidence provided was not used in any formal way during the approval process or suggested that if it was used at all, it would only have been viewed as supplementary to the clinical evidence.

Findings from the other three case studies support the notion that economic evidence does not play a role in FDA's approval decisions. However, findings from the ICD case study suggest that economic factors may influence the amount of time FDA takes to review and issue approval decisions for new health technologies. In 2003, FDA approved a new lower-cost ICD model after an expedited review period. The device's approval was accompanied by a press release from the FDA's then-commissioner, Mark McClellan, expressing that the, "FDA is committed to helping patients get access to safe and effective new medical technology quickly, at affordable prices."⁴⁵ According to one of the experts we interviewed for the ICD case study, such a press release was unprecedented and may have reflected FDA's cognizance of the costs of medical technologies. It has been suggested that this example illustrates that, while approval does not hinge on economic evidence, such evidence may expedite the process.

FDA oversees various postmarket surveillance and other data collection efforts pertaining to products once they have been cleared or approved for marketing. For devices, postmarket studies are intended to gather safety and effectiveness data, particularly for devices used to support or sustain human life or that present a potential risk to human health. The main purpose of conducting this surveillance is to assess product performance as used in the general population. Most surveillance is conducted and reported by manufacturers, which must submit surveillance protocols for affected devices to FDA for approval. Examples of devices subject to postmarket surveillance are cardiovascular pacemakers and leads, replacement heart valves, coronary vascular stents, implantable infusion pumps and total temporomandibular joint prostheses.⁴⁶ This function has not been used to collect economic data.

For drugs and biologics, postmarket studies can entail adverse event reporting and "phase 4" commitments. FDA's Adverse Event Reporting System (AERS) is a computerized information database that supports postmarket safety surveillance for drugs and therapeutic biologics.⁴⁷ The FDA receives adverse drug reaction reports from manufacturers as required by regulation, while health care professionals and consumers send reports voluntarily through the MedWatch program. These reports are entered into the AERS database. The reports in AERS are evaluated by clinical reviewers in CDER and CBER to detect adverse safety signals and to monitor drug safety. They form the basis for further epidemiological studies, when appropriate. As a result, the FDA may take regulatory actions to improve product safety and protect the public health.

⁴⁵ FDA approves lower cost implantable defibrillator. Rockville, MD: US Food and Drug Administration, 2003. Accessed September 14, 2006. <http://www.fda.gov/bbs/topics/NEWS/2003/NEW00906.html>.

⁴⁶ Postmarket surveillance studies. Rockville, MD: US Food and Drug Administration, FDA Center for Devices and Radiological Health, 2005. Accessed December 20, 2005. <http://www.fda.gov/cdrh/devadvice/352.html>.

⁴⁷ Adverse Event Reporting System (AERS). Rockville, MD: US Food and Drug Administration, Center for Drug Evaluation and Research, 2005. Accessed January 10, 2006. <http://www.fda.gov/cder/aers/default.htm>.

Phase 4 postmarket studies are required of or agreed to by product sponsors that are conducted after FDA has approved a product for marketing (e.g., studies requiring the sponsor to demonstrate clinical benefit of a product following accelerated approval). FDA uses postmarket study commitments to gather additional information about a product's safety, efficacy or optimal use.⁴⁸

In the context of postmarket studies, there only are limited or tangentially related potential avenues for FDA involvement in CE studies of particular products. As part of its process of making national coverage determinations for health care products and services under Medicare, CMS recently initiated a program of coverage with evidence development (CED). This arrangement provides Medicare coverage for medical technologies, including ones that are approved for marketing by FDA, that is linked to certain postmarket data requirements.⁴⁹

In the early draft guidance on CED, CMS made references to the need for and use of data on health care utilization and costs. Among these references, the April 2005 draft guidance made a single reference to cost-effectiveness, in the context of potential data collection in prospective comparative studies that, "can be used to evaluate a broad range of real-world outcomes such as quality of life and cost-effectiveness in addition to monitoring patient safety and benefit and informing decision-making."⁵⁰ These terms and phrases did not appear in the revised guidance CMS released in July 2006, though CMS did acknowledge that data collected via CED could be of use to health plans in conducting cost analyses.⁵¹

Given FDA's prominent role in postmarket surveillance and other postmarket studies, any new or wider CMS activities in postmarket data collection likely are to be coordinated with FDA. However, while CMS' April 2005 draft guidance referred to aligning CED data collection requirements with any clinical study requirements associated with FDA review, and stated that establishing priorities for CED would involve broad stakeholder input including from federal agencies such as FDA, AHRQ, NIH, CDC, DoD and others, interagency cooperation was not addressed in the 2006 revised guidance.

2) Monitoring of Manufacturer Claims Related to Cost-effectiveness

FDA is responsible for monitoring new drug claims and labeling to ensure that advertisements are aligned with and directly relate to approved product indications. Although FDAMA designates this role for FDA, any economic claims that do not relate to the clinical aspects of the approved indication would be subject to oversight by the Federal Trade Commission (FTC). Mislabeling or false statements by companies (such as those not related to off-label use of a product) can result in the issuance of warning letters to cease these promotional practices and in further federal action, should the misleading claims persist after a warning letter is issued.

⁴⁸ Postmarket study commitments: introduction. Rockville, MD: US Food and Drug Administration, Center for Drug Evaluation and Research, 2005. Accessed December 20, 2005. <http://www.fda.gov/cder/pmc/default.htm>.

⁴⁹ Draft guidance for the public, industry, and CMS staff: factors CMS considers in making a determination of coverage with evidence development, 2005.

⁵⁰ Ibid.

⁵¹ Guidance for the public, industry, and CMS staff: national coverage determination with data collection as a condition of coverage with evidence development. Baltimore, MD: Centers for Medicare and Medicaid Services, 2006. Accessed November 30, 2006. http://www.cms.hhs.gov/mcd/ncpc_view_document.asp?id=8.

FDAMA section 114(a) extends and provides the FDA with statutory authority to monitor claims and labeling of drugs and devices in marketing materials for specific audiences, such as managed care organizations and formulary committees.⁵²

For example, AHRQ assisted FDA in reviewing and evaluating the state of the science of CEA and the use of patient-reported outcomes to better enable FDA to use these methods in evaluating new drugs and devices. This helped FDA to draft guidelines for using CEA and patient-centered outcomes as part of the drug approval and promotional claims process.⁵³

Information distributed pursuant to FDAMA is required to fit certain key criteria, as follows:^{54,55,56}

- **Definition of “health care economic information.”** Health economic information for FDAMA is defined as information that pertains to health economics not including clinical information. A problem with this definition is that both health economic and clinical information is included in economic analyses such as CEA or CCA.
- **Definition of “directly related to an approved indication.”** FDAMA requires that marketing claims and labeling information relate directly and only to “an approved indication,” which is intended to limit potential misuse of economic information in product claims. This restriction of clinical scope also limits a manufacturer’s ability to use certain types of cost analyses, because modeling is not allowed to predict long-term trends or extrapolate data from surrogate and intermediate clinical endpoints. As such, any claim has to be, “substantiated by adequate and well-controlled trials.”
- **Definition of “competent and reliable scientific evidence.”** In FDAMA, competent and reliable scientific evidence is representative of the “evidentiary standard” used by the FTC and defined as being, “objective research to yield accurate and reliable results.” According to FTC, evidence for a claim has to be deemed “reasonable” with respect to factors such as the product of interest, type of claim being made and consequence of a false claim. Given this interpretation, FDA allows modeled data for specific instances where substantiating a claim through rigorous clinical trials would be very expensive and the claim can be related directly to an approved indication. For such special cases, FDA also permits the use of observational data, case control or cohort design studies.
- **Dissemination of information to managed care entities.** According to FDAMA Section 114, economic claims can be directed at formulary committees and similar entities that have requisite skills for claims interpretation. In contrast, such dissemination to physicians and patients is not allowed, because of potential lack of comprehension of economic claims.

⁵² Merrill R 1999.

⁵³ Focus on cost-effectiveness analysis at the Agency for Healthcare Research and Quality (AHRQ pub. no. 01-P023). Rockville, MD: Agency for Healthcare Research and Quality, 2001. Accessed November 8, 2005. <http://www.ahrq.gov/research/costeff.htm>.

⁵⁴ Ibid.

⁵⁵ US Congress, Committee report accompanying FDA Reform/Prescription Drug User Fee Act, sec. 114, in International Society for Pharmacoeconomics and Outcomes Research US Legislation Briefing, Health Economics and the FDA Reform Act: Review Discussion, and Potential Impact. Princeton, NJ: ISPOR, 1998.

⁵⁶ Pharmaceutical Research Manufacturers of America comments on Section 114 of FDAMA. Washington, DC: PhRMA, 1998. Accessed November 9, 2005. <http://www.phrma.org/issues/fda/fdama/6-22-98.cfm>.

A health economist whom we interviewed noted that regulation of economic claims under FDAMA may be challenging to the agency, because it may have insufficient staff capacity to do so, particularly given its limited historical authority in this area.

The guidelines used by DDMAC outline the criteria for labeling of effectiveness claims. As noted by one observer, the monitoring of claims and labeling by FDA is not a true evaluation of cost benefit tradeoffs, but just, “a procedural solution to a structural problem.”⁵⁷ Other health economists have suggested that it would be better for FDA to require disclaimers that increase the transparency of underlying assumptions and methodology used to perform economic analyses for drugs and devices. These disclaimers would allow the managed care marketplace and FDA to judge the acceptability of scientific standards for all claims made without the implementation of demanding data requirements. Whereas an error in scientific standards and rigor pertaining to clinical matters may cause physical harm, the potential impact of a miscalculated economic analysis may comprise a suboptimal expenditure.⁵⁸

Permitting health product companies to make unregulated economic claims could provide opportunities for disseminating misleading information in the marketplace, deception and disincentives to conduct methodologically sound health economic research. The possibility of misleading market information may arise from the complexity of CEA and difficulty in interpreting economic analyses. Companies may decide to use modeling to predict long-term CE instead of conducting rigorous clinical trials. The potential for deception can be limited by requiring transparency of methodology, assumptions and inputs used.⁵⁹

FDA’s role in regulating economic claims provides an opportunity for the agency to enable, if not require, conducting higher quality CEAs and other forms of economic analysis. As noted by one health economist, CEA is an underused tool in support of health care decision-making, due to lack of standardization, proper training, trust and political will. To counteract these obstacles, health stakeholders could promote CEA by calling for Congress and FDA to, “recraft FDA policies to foster responsible communications of economic evaluation,” where a possible solution would be, “for FDA to permit companies to promote their products on peer-reviewed cost-effectiveness evidence along with prominent disclaimers.”⁶⁰

3) Economic Impact of New FDA Regulations

As described above, FDA can be required under EO 12866 and other federal requirements to conduct economic analyses, including CEA and/or CBA, as appropriate, pertaining to creation and implementation of regulations.⁶¹ Regulations for which CEA is performed rarely involve specific technologies and usually are related to a process, protocol, set of requirements, etc.

⁵⁷ Evans R. Manufacturing consensus, marketing truth: guidelines for economic evaluation. *Ann Intern Med* 1995;123(1):59-60.

⁵⁸ Luce B, Hillman AL. When is a cost-effectiveness claim valid? How much should the FDA care? *Am J Manag Care* 1997;3(11):1660-6.

⁵⁹ Neumann P, Claxton K, Weinstein MC. The FDA’s regulation of health economic information. *Health Aff* 2000;19(5):129-37.

⁶⁰ Luce BR 2005.

⁶¹ Uniform compliance date for food labeling regulations. *Federal Register*, December 23, 1998;63(246). Rockville, MD: US Food and Drug Administration, 1998. Accessed November 17, 2005. <http://www.fsis.usda.gov/OPPDE/rdad/FRPubs/03-026F.htm>.

A recent example of FDA compliance with these requirements is in connection with the agency's new rule requiring human cell, tissue and cellular tissue-based product (HCT/P) establishments to follow current good tissue practices. The main goal of this regulation is to prevent the introduction, transmission and spread of communicable disease through the handling of HCT/Ps. It established procedures to recover, process, store, label, package and distribute HCT/Ps, along with ways to investigate and report adverse reactions related to communicable diseases following HCT/P handling. As it would for any proposed final rule, FDA needed to determine whether economic impact analysis was required pursuant to EO 12866, RFA and UMRA. In this instance, the HCT/P regulations were found to be a significant regulatory action under EO 12866.

Among other results, FDA analyses showed that the total annualized cost estimates for the final rule would be between \$7.94 million and \$8.11 million per year. The agency also provided cost-effectiveness impact estimates on avoiding the costs of adverse events associated with HCT/P problems such as primary corneal graft failure, bone allograft infection/graft failure and heart valve fungal infections. Regarding RFA, FDA determined that the majority of establishments in the HCT/P industry expected to be affected by this rule were classified as small entities and would incur new costs. Although there was insufficient information to determine what effort would be required to meet the rule, the average annualized costs of the rule per affected small entity was about 0.3-6.0% of average annual revenue. Regarding UMRA, the FDA found that the rule would not result in an economic impact of \$110 million per year (i.e., the original threshold of \$100 million, adjusted for inflation), so no further analysis was required under UMRA.⁶²

Similarly, FDA examined the economic impact of a new requirement for bar codes for drugs and blood products. The purpose of the rule was to help reduce the number of medication errors in hospitals and other health care settings by allowing health care professionals to use bar code scanning equipment to verify that the right drug (in the right dose and right route of administration) is being given to the right patient at the right time. The rule also required the use of machine-readable information on blood and blood component container labels to help reduce medication errors. The regulation was estimated to result in annual benefits of \$5.2 billion and annual costs \$670 million.⁶³

Other recent examples given in a 2004 report from OMB to Congress include FDA estimates of annual benefits and costs of the following:

- ***Trans fat labeling:*** annual benefits - \$230-2,839 million; annual costs - \$9-26 million.
- ***Patent listing requirements and application of 30-month stays of Abbreviated New Drug Applications (i.e., for generic drugs):*** annual benefits - \$226 million; annual costs - \$10 million.

⁶² Current good tissue practice for human cell, tissue, and cellular tissue based products. Federal Register, November 24, 2004;69(226). Rockville, MD: US Food and Drug Administration, 2004. Accessed December 20, 2005. <http://www.fda.gov/cber/rules/gtp.pdf>.

⁶³ Final rule: bar code label requirements for human drug products and biological products. Federal Register, February 26, 2004;69(38). Rockville, MD: US Food and Drug Administration, 2004. Accessed January 14, 2006. <http://www.fda.gov/OHRMS/DOCKETS/98fr/04-4249.htm>.

- **Prohibition on the sale of dietary supplements containing ephedra:** annual benefits – 40-50 fewer illnesses and 7-12 fewer deaths; annual costs – \$7-90 million.⁶⁴

4) Guidance

The FDA issues guidance for various regulated technologies and related processes and procedures. Developed with public input, guidance recommendations are nonbinding to the FDA and the public. They are intended to enable health care stakeholders to understand FDA's current perspectives on a particular subject better. In contrast to regulations, there is no requirement to assess the cost-effectiveness or economic impact of guidance.

Guidance documents can lower market uncertainty and be produced in shorter time periods than regulations. Guidance pertaining to drugs, biologics and devices address matters such as clinical trial design, manufacturing and testing techniques, characterization of production cell lines and other systems and processes issues. As noted in the FDA report on *The Critical Pathway to New Medical Products*, FDA can issue public guidance documents that summarize best practices in a development area and share relevant FDA insights. Medical product sponsors report that guidance documents foster development and innovation in areas of therapeutic need, improve the chances of initial success of a marketing application and shorten the time it takes to get safe and effective treatments to patients. The agency publishes 50-75 draft and final guidances each year. According to FDA, medical devices developed in areas with extant FDA guidance documents are almost twice as likely to be approved after the initial review process and are approved in a third less time according to the FDA.⁶⁵

Guidance on Nucleic Acid Testing

As described in the NAT case study, FDA released a guidance document in 2004 pertaining to the use of HIV and HCV nucleic acid testing (NAT) to ensure the safety of blood donations. Given that approximately 30 million units of blood products are transfused annually, the safety of the blood supply is a significant public health concern for the nation.⁶⁶ The cost of blood product collection, testing, preparation, labeling, storing and transportation has increased in recent years. In 2001, after several years of flat prices, the American Red Cross raised the price of a unit of blood by about 30% to \$170 per unit in 2001.⁶⁷ At that time, the widespread implementation of the process of leukoreduction (removing white blood cells) had made a significant contribution to the cost increase. Newer costly technologies, particularly NAT, which was licensed by FDA in February 2002, further reduces the risk of transmitting human immunodeficiency virus (HIV) and hepatitis C virus (HCV), represented further cost increases.

⁶⁴ Progress in regulatory reform: 2004 report to Congress on the costs and benefits of federal regulations and unfunded mandates on state, local, and tribal entities. Washington, DC: US Office of Management and Budget, Office of Information and Regulatory Affairs, 2004. Accessed January 14, 2006. http://www.whitehouse.gov/omb/inforeg/2004_cb_final.pdf.

⁶⁵ Challenge and opportunity on the critical pathway to new medical products. Rockville, MD: US Food and Drug Administration, 2004. Accessed November 17, 2005. <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html#execsummary>.

⁶⁶ Facts about blood and blood banking. Bethesda, MD: American Association of Blood Banks, 2005. Accessed December 22, 2005. http://www.aabb.org/All_About_Blood/FAQs/aabb_faqs.htm.

⁶⁷ Goodman C 2003.

FDA's NAT guidance makes nonbinding recommendations to blood and plasma providers and testing laboratories on ways to adopt and use NAT for HIV and HCV to test individual and pooled samples of donated human blood and blood components.⁶⁸ Specifically, the guidance makes recommendations specific to product disposition, donor testing and management and serologic testing based on NAT results. The guidance neither includes nor addresses the matter of CEA, although the background documentation accompanying the guidance includes papers and presentations by outside experts that address CEA, including cost per QALY ratios.

As does other FDA guidance, the NAT guidance includes a standard statement:

"This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance."

Some blood industry stakeholders have questioned whether FDA guidance in this area is truly nonbinding. In a comment letter regarding FDA's proposed rule pertaining to guidance (Administrative Practices and Procedures: Good Guidance Practices), a coalition of blood banking organizations noted that the need for an organization to discuss with FDA any alternative approach other than one set forth in a guidance document in order to, "ensure that it complies with the relevant statutes and regulations," means, in effect, that the guidance is binding, whether or not the guidance is identified as being required or recommended. The group suggested that, rather than using the shorter, simpler process of developing guidance in a way that is, effectively, binding, it might be more appropriate for FDA to use the regulatory route.⁶⁹ If such guidance approximates being binding and applies to expensive technologies such as NAT, it could pose a burden on the cost of blood products.

As described in the NAT case study, CEAs of NAT in the literature indicate that it is a relatively costly way to achieve improvements in safety and health outcomes. Indeed, the CE ratios of adding other blood testing technologies in recent years have been high compared to the great majority of health care interventions. A 2002 review article suggested that the cost-utility ratio for blood safety methods introduced and used widely from 1993 to 2000 was on the order of \$500,000 per QALY.⁷⁰ Although there is no official threshold among public or private sector payers in the US, cost-utility ratios of \$50,000-100,000 or more per QALY generally are recognized as high. In the UK the National Institute for Health and Clinical Excellence (NICE), which advises the National Health Service, considers that the likelihood of introducing new technologies into the health service decreases for those whose cost-utility ratios approach and

⁶⁸ Guidance for industry: use of nucleic acid test on pooled and individual samples from donations of whole blood and blood components (including source plasma and source leukocytes) to adequately and approximately reduce the risk of transmission of HIV-1 and HCV. Rockville, MD: US Food and Drug Administration, Center for Biologics Evaluation and Research, 2004. Accessed December 10, 2005. <http://www.fda.gov/cber/gdlns/hivhcvnatbld.htm>.

⁶⁹ Re: docket no. 99N-4783 administrative practices and procedures: good guidance practices. Bethesda, MD: Coalition for Blood Safety, 2000. Accessed November 9, 2005. <http://www.fda.gov/ohrms/dockets/dailys/00/may00/050300/c000009.pdf>.

⁷⁰ Yeh JM, Botteman MF, Pashos CL, et al. Economics of transfusion. *Infusion therapy and transfusion medicine* 2002;29:218-25.

exceed £30,000 per QALY.⁷¹ Although cost-utility ratios for NAT far exceed these thresholds, there has been widespread adoption of the technology since its approval, suggesting the overriding importance of clinical and socio-medical considerations in decision-making regarding the safety of the blood supply.

Notably, some stakeholders interviewed for the NAT case study suggested that FDA may have been more receptive to matters of cost when considering NAT to screen for hepatitis B (HBV), a virus with generally less severe health consequences than HIV or HCV. As described in the case study, HBV NAT was approved by the FDA in 2005, three years after approval for HIV and HCV NAT. Currently, FDA guidance specifies that HBV NAT is optional. Some stakeholders expressed the view that cost considerations did factor into FDA's decision-making regarding HBV NAT. Even so, the agency approved the test, and cost may have been at most an informal factor considered in developing the current guidance on HBV NAT.

Commenting upon the role of NAT for blood safety, our expert interviewees generally noted that FDA should remain focused on ensuring safety and effectiveness of regulated products and not become involved with matters of CE. While some experts agreed that blood product providers and other stakeholders might benefit from such analyses, they suggested that these be performed by entities other than the FDA.

Guidance on Pharmacogenomic Data Submissions

A different example of how guidance might affect or promote cost-effective use of health care technology is the FDA's guidance on pharmacogenomic data submissions. It addresses processes applying to a group of technologies rather than a specific one. As described by FDA, "This guidance is intended to facilitate scientific progress in the field of pharmacogenomics and to facilitate the use of pharmacogenomic data in drug development." The guidance responds, in part, to the reported reluctance of pharmaceutical sponsors to embark on programs of pharmacogenomic testing during drug development, because of uncertainties in how the data will be used by FDA in the drug application review process.

The guidance on pharmacogenomic data submissions provides recommendations to sponsors regarding: 1) when to submit pharmacogenomic data to FDA during product development and review processes; 2) what format and content to provide for submissions; and 3) how and when the data will be used in regulatory decision-making, including when voluntary genomic data submissions would be welcomed by FDA.⁷² The only explicit mention of costs in the guidance is in the context of how FDA feedback to product sponsors on voluntary genomic data submissions might avoid unnecessary time or resources later in the product development process. New pharmacogenomic technologies may enable more targeted and personalized therapies that maximize effectiveness and minimize risk, perhaps resulting in more cost-effective care.

⁷¹ Guide to the methods of technology appraisal. London, England: National Institute for Clinical Excellence, 2004. Accessed November 9, 2005. <http://www.nice.org.uk/page.aspx?o=201973>.

⁷² Guidance for industry: pharmacogenomic data submissions. Rockville, MD: US Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Devices and Radiological Health, 2005. Accessed December 13, 2005. <http://www.fda.gov/cber/gdlns/pharmdtasub.htm>.

As noted above, recommendations in FDA guidance related to new technologies are not legally binding. With respect to guidances, FDA does not have the statutory authority to require or perform any cost-related analyses. However, some stakeholders noted that, while there is no mandate for FDA to consider economic factors in drafting guidance, there is no formal restriction on including this information.

D. Implications of Development and Use of CEA by FDA

Currently, FDA has the authority to perform CEAs and other economic analyses only to determine the impact of regulations. This authority is based primarily on EO 12866, applying methods and standards described in Circular A-4. The Regulatory Flexibility Act and section 202(a) of the Unfunded Mandates Reform Act of 1995 are of tangential relevance to CEAs. When analyzing the cost implications of regulations, the focus of analyses is the impact of the regulation, which may include or affect new health care technologies, but is not focused on the CE or economic impact of particular health care technologies.

FDA does not have statutory authority to perform cost-related analyses in support of guidance. However, as noted above, some stakeholders observed that there is no prohibition against the use of economic evidence by FDA in drafting guidance, suggesting that this currently may be feasible. Formally expanding FDA's authority to incorporate CEAs into such guidance recommendations likely would require a higher level statutory action and, like EO 12866, may have to be a broad statute applying across federal agencies.

Even though some of the experts whom we interviewed suggested that CEA and other economic analyses could be conducted by others and used to inform guidance development, the informal consensus among the interviewees and other experts who have written on this matter is that FDA's focus should remain on ensuring the safety and effectiveness of new health care technologies. Virtually all of our interviewees concurred that incorporating CEA or other cost-related considerations into the market approval process would risk compromising FDA's ability to fulfill its mission. The few interviewees who expressed interest in having FDA consider costs in this way acknowledged that the agency lacks the statutory authority, staff capacity and other resources to do so.

One health economist draws a clear distinction between what the FDA might do and what it should do regarding use of CEA in regulatory decisions:

"A stronger role for the FDA is possible, with the agency given authority to examine the cost effectiveness of prescription drugs before approval. But changing the FDA's approval authority would be a mistake and would embroil the agency in debates about value that are better left to the marketplace."⁷³

The view that FDA should not include cost-effectiveness or other economic considerations in approval decisions was echoed by many stakeholders interviewed for the case study reports.

⁷³ Neumann P. Why don't Americans use cost-effectiveness analysis? Am J Manag Care 2004;10(5):308-12.

E. Use of Cost-effectiveness and Related Analyses by DHHS and Other Relevant Federal Agencies

The federal government has a major role in shaping the health of the nation. DHHS comprises 11 operating divisions, each with unique mandates, missions and priorities. Other federal agencies, such as the Department of Veterans Affairs and the Department of Defense, play critical roles in providing health care for our nation’s veterans and military personnel.

Coupled with an era of growing health care costs due to changing population demographics, rapidly emerging technology and other factors, ensuring efficiency of health care has come to the forefront of many agencies’ agendas. While most agree that health care resource allocation should not be driven by cost-containment efforts using CEA, most health stakeholders acknowledge that CEA and related economic analyses can help federal decision-makers to assess the value of health care technology and the guidelines and regulations that influence the quality and cost of health care.

The federal government has been instrumental in providing methodological guidance and funding for performing CEAs and related economic analyses in health care.⁷⁴ Contributing substantially to the evidence base on CE of health technologies and interventions, the federal government funded health economics studies resulting in more than 500 published articles between 1997 and 2001.⁷⁵ This is one aspect of a growing trend toward consideration of economic measures in health care, and the number of federally funded health economics studies appears to be increasing.⁷⁶ Many parts of the federal government are involved in sponsoring or conducting economic analyses of new health care technologies. Findings from CEA or other economic analyses are used by certain federal agencies to inform a variety of decisions or are made available in the public domain for informing others, including those listed below.

Application of Economic Information	Federal Agency
Research and technical/methodological support	AHRQ, CDC, CMS, NIH, VA
Health technology assessment	AHRQ
Coverage or payment decisions	CMS, DoD, VA
Formulary determination	DoD, VA
Recommendations or clinical practice guidelines	AHRQ (USPSTF), CDC
Regulation of the dissemination of CE information by life sciences manufacturers	FDA
Evaluation of regulations	All federal agencies ⁷⁷

⁷⁴ Gold ML, Siegel JE, Russell LB, Weinstein MC. Cost-effectiveness in health and medicine: the report of the Panel on Cost-Effectiveness in Health and Medicine. New York: Oxford University Press, 1996.

⁷⁵ Siegel JE, Byron SC, Lawrence WF. Federal sponsorship of cost-effectiveness and related research in health care: 1997-2001. Value Health 2005;8(3):223-36.

⁷⁶ Ibid.

⁷⁷ Pursuant to Executive Order 12866 and Circular A-4, any federal agency releasing a regulation is required to conduct a regulatory impact analysis, including consideration of relative costs and benefits compared to other regulatory alternatives. These analyses primarily gauge the impact of an entire regulation and rarely, if ever, focus on particular health technologies.

Current involvement with economic information is described in greater depth for each of six federal departments and agencies, including CMS, AHRQ, CDC, NIH, VA and DoD. While this report is not intended to provide detailed analysis of the uses of CEA and related analyses in these departments and agencies, it does characterize the primary uses and implications of the use of economic information to the activities of the FDA. In addition, we examine the value of expanding the role of cost-health tradeoff evidence in these federal agencies. Through understanding the current federal pathways for developing and using economic information, we identify potential opportunities for collaboration with regard to generating and using information from economic analyses.

1) Centers for Medicare & Medicaid Services

Agency Overview and Mission

CMS is the branch of DHHS that administers Medicare and sponsors state-run Medicaid and State Children's Health Insurance Programs (SCHIP). Approximately 42 million Americans, including those aged 65 and over, people with disabilities (including some under age 65) and those with end-stage renal disease (ESRD), receive health insurance coverage under Medicare. According to CMS, Medicare expenditures in 2005 were projected to be \$335.5 billion, or 17.8% of national health care expenditures, and projected to rise substantially in 2006 to \$420.1 billion, or 20.7% of national health expenditures, in part reflecting full implementation of the new Medicare prescription drug benefit.⁷⁸ Medicare is the largest US health care payer, with great influence extending even beyond its beneficiary populations.⁷⁹

Overview of Medicare and Medicaid and Influence on Adoption and Diffusion

Medicare is administered at the national level by CMS and, at the local and regional levels, CMS contracts with three types of nongovernmental entities to make local and regional coverage determinations and administer payment of Medicare claims.⁸⁰ Medicare coverage and payment determinations often have broad impacts on patient access to, as well as provider adoption and use of, new health technologies, as these decisions are monitored closely by other public and private payers. Although nearly 90% of all coverage decisions are made at the local or regional level, when coverage issues cannot be resolved locally, are subject to wide variations in local coverage policy or are otherwise considered to be of national importance, they can be raised to the national level for a coverage determination.⁸¹ Once coverage is established, Medicare uses various payment systems to determine how much the program will pay for covered services, procedures and technologies in certain health care settings.⁸²

⁷⁸ National health care expenditures projections: 2005-2015. Baltimore, MD: Centers for Medicare & Medicaid Services, Office of the Actuary, 2003. Accessed July 31, 2006. <http://www.cms.hhs.gov/NationalHealthExpendData/downloads/proj2005.pdf>.

⁷⁹ Fact sheet: Medicare at a glance. Menlo Park, CA: The Henry J. Kaiser Family Foundation, 2004. Accessed November 2, 2004. <http://kff.org/medicare/loader.cfm?url=/commonspot/security/getfile.cfm&PageID=33319>.

⁸⁰ These three types of contractors used to administer the Medicare program locally and regionally include fiscal intermediaries, carriers and durable medical equipment regional carriers (DMERCs).

⁸¹ The Lewin Group. Outlook for medical technology innovation: will patients get the care they need? Report 2: Medicare payment process and patient access to technology. Washington, DC: AdvaMed, 2000.

⁸² Two predominant payment systems under Medicare are retrospective fee schedules and prospective payment systems. For the majority of services, provider type or site of service determines which payment system is used.

Administered jointly by the federal and state governments, Medicaid provides coverage for individuals earning less than a specified income level and for those with certain disabilities. While the federal government is responsible for setting the minimum level of benefits to be covered under Medicaid, states have the ability to expand the scope of covered services and eligibility for the program.⁸³ With regard to payment for Medicaid services, Medicare payment rates often serve as an important benchmark affecting Medicaid payment levels.

Statutory Considerations in Medicare Coverage Determinations

Medicare's coverage determinations are governed by statutory limits that indicate that the program may cover only those items and services considered, "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."⁸⁴ Over the past two decades, CMS has attempted, at certain points, to define criteria used to determine if an item or service is "reasonable and necessary," intended to be helpful in implementing its coverage policies. In 2003, Congress requested that CMS publicize factors used in making national coverage determinations.⁸⁵ Despite these attempts at increased transparency and clarity of important factors, debate persists regarding the true meaning and interpretation of the "reasonable and necessary" limitation. With regard to CE and related economic considerations, some experts contend that cost-related factors may fall under the "reasonable" part of the clause, citing undue economic burden to health systems, payers, providers and consumers if CE evidence is wholly disregarded. It remains unclear whether, or to what extent, economic evidence will be incorporated into Medicare policy decisions, but statutory interpretations will be relevant.

Current Involvement with Economic Information

At certain points throughout the Centers' history, CMS has considered using CE information as part of decision-making for coverage of new medical technologies.⁸⁶ In 1989, CMS issued a proposal in the *Federal Register* to include CE as a factor in coverage determinations.^{87,88} However, this proposal encountered many of the common concerns about the use of CE information, including mistrust of CE analytic methods, political pressure from various interest groups, concerns about harming the physician-patient relationship and other cultural and social factors.^{89,90,91} Ultimately, this proposal was not adopted. At present, CMS formally does not consider CE or other evidence pertaining to costs in making coverage determinations.^{92,93}

⁸³ The Medicaid program at a glance. Menlo Park, CA: The Henry J. Kaiser Family Foundation, 2004. Accessed November 8, 2004. <http://www.kff.org/medicaid/2004-04.cfm>.

⁸⁴ 42 USC § 1395.

⁸⁵ Bagley GP, Maxwell R. Linking Medicare coverage to research participation: reasonable and necessary? Washington, DC: Washington Legal Foundation, 2005. Accessed December 19, 2005. http://www.medicarerguide.com/MDRG/2005/200506_BagleyWLPwhitepaper.pdf.

⁸⁶ Neumann PJ. Using cost-effectiveness analysis to improve health care. Oxford, England: Oxford University Press, 2005.

⁸⁷ Neumann PJ, Rosen AB, Weinstein MC. Medicare and cost-effectiveness analysis. *N Engl J Med* 2005;353(14):1516-22.

⁸⁸ Medicare program: criteria and procedures for making medical services coverage decisions that relate to health care technology. *Federal Register* 1989;54(30):4302-18.

⁸⁹ Neumann PJ 2005.

⁹⁰ Stanton MS. Implantable cardioverter defibrillators: an excellent case study. *Health Affairs* 2005;24(1):52-4.

⁹¹ Neumann PJ 2005.

⁹² Neumann PJ, Rosen AB 2005.

However, cost or CE information, along with information about disease burden and other clinical or epidemiological aspects, may be one factor in CMS decisions regarding whether to review certain new technologies as part of a national coverage determination (NCD). For example, in reference to implantable cardioverter-defibrillators, which are costly devices used to restore normal heart rhythms in people with certain cardiac conditions, the Director of the CMS Coverage and Analysis Group, Steve Phurrough, stated:

“If an [implantable cardiac defibrillator] were a buck and a quarter, would we have gone through this entire process of reviewing the evidence at all? Maybe not. But, because it’s a bit more than a buck and a quarter we wanted to make sure the evidence was clear and that it was a benefit. We don’t use cost to decide the evidence issue, but we do use cost to decide if this is important enough to address.”⁹⁴

As described in the ICD case study, the role of economic considerations in restrictions placed on Medicare coverage of ICDs has been a subject of heated discussion. While CMS officials maintained that the restricted coverage was based on clinical evidence, other stakeholders, including some from the medical device industry and professional associations, held the view that the restrictions were intended to restrict the use of a costly device. In response to these arguments, former CMS Chief Medical Officer Sean Tunis explained that the matter of Medicare coverage of ICDs was “about the money” and that the Medicare budget allowed very little wiggle room to accommodate the cost of ICDs without under-compensating for other types of health care.

Apart from matters of coverage, CMS has indicated that CE evidence could be used in setting payment levels, especially where expensive new technologies offer only marginally improved or equivalent benefits compared to existing alternatives.⁹⁵ There are recent examples of CMS considering the use of CE information in setting payment levels for new medical technologies, though CMS has yet to incorporate CE evidence formally into payment decisions. In the case of immunoassay fecal-occult blood testing (iFOBT), CMS considered using CE evidence, but eventually decided against using it to inform payment level determinations. Stakeholders reported that cost analyses were provided to decision-makers at CMS during the process of determining coding and payment for the new technology. The extent to which this evidence was considered for new coding and payment is unclear.

CMS does not use economic evidence in decision-making for state Medicaid programs, which are administered by the states. Attempts to use this type of evidence historically have been met with resistance. The most frequently cited example of this is from the Oregon Medicaid program, which experimented in the late 1980s and early 1990s with using cost information to inform coverage decisions for an expanded population of Medicaid recipients.⁹⁶

Despite limited use of CE evidence in policymaking, CMS funds CE research relevant to the Medicare population for certain emerging health technologies. During 2003 coverage deliberations for iFOBT, CMS commissioned AHRQ to conduct a study of the clinical impacts

⁹³ Garber AM 2004.

⁹⁴ Neumann PJ 2005.

⁹⁵ Ibid.

⁹⁶ Ibid.

and CE of alternative modes of colorectal cancer screening.^{97,98} In the case of lung volume reduction surgery (LVRS), CMS cosponsored with NIH a CE study conducted in parallel to a clinical trial.⁹⁹ Similar types of CE research are ongoing and planned at CMS, though there is no indication that the resulting CE information has affected CMS policies.¹⁰⁰

Contemporary Policy Developments

In recent years, certain key policy developments have come to the forefront, which may influence CMS's use of CE information. Selected developments are detailed below:

- **Medicare Prescription Drug, Improvement and Modernization Act of 2003.** While CE considerations are not a focus of MMA, experts have noted certain potential implications for the use of CEA.¹⁰¹ First, through competition of regional prescription drug plans, some experts predict that CE evidence increasingly will shape formulary determinations for Medicare beneficiaries. Many private plans currently use CE evidence in developing formulary guidelines; this trend may affect Medicare beneficiaries as well.

Pertaining to certain drugs and biologics, MMA limits CMS from using the reference pricing technique known as "functional equivalence." When considering payment levels for two technologies within the same therapeutic class, functional equivalence would set the payment level for technologies of similar efficacy at the lowest payment level within the therapeutic class. As summarized by one health economist, "a standard of functional equivalence applies a CE principle: assuming that alternative interventions are equivalent, one should not pay more for one of them."¹⁰² Because it often is extremely difficult to establish that two technologies are equally efficacious, many argue that pricing based on functional equivalence can be flawed.¹⁰³

Section 1013 of the MMA provides a mechanism by which AHRQ may conduct comparative effectiveness research for selected health care interventions, technologies and drugs as relevant to the Medicare population. Section 1013 focuses exclusively on comparative clinical outcomes, efficiency and effectiveness, without reference to CE.¹⁰⁴ Industry experts have suggested that, while CE may have been reasonable to include in the scope of comparative effectiveness research under Section 1013, studies of CE may have been

⁹⁷ Decision memo for screening immunoassay fecal-occult blood test (CAG-00180N). Baltimore, MD: Centers for Medicare & Medicaid Services, 2003. Accessed August 17, 2005. <http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=87>.

⁹⁸ Van Ballegooijen M, Habbema JDF, Boer R, Zauber AG, Brown ML. Report to the Agency for Healthcare Research and Quality. Comparison of the cost-effectiveness of fecal occult blood tests with different test characteristics in the context of annual screening in the Medicare population. Rotterdam, Netherlands: Erasmus University; New York, NY: Memorial Sloan-Kettering Institute Cancer Center; Bethesda, MD: National Cancer Institute, 2003. Accessed August 17, 2005. <http://www.cms.hhs.gov/coverage/download/id87.zip>.

⁹⁹ Ramsey SD, Sullivan SD. Evidence, economics, and emphysema: Medicare's long journey with lung volume reduction surgery. *Health Aff* 2005;24(1):55-66.

¹⁰⁰ One current cost-effectiveness study co-funded by CMS and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is focused on daily hemodialysis.

¹⁰¹ Neumann PJ, Rosen AB 2005.

¹⁰² Ibid.

¹⁰³ Ibid.

¹⁰⁴ Medicare Prescription Drug, Improvement, and Modernization Act of 2003. Public Law 108-173, 108th Congress. Baltimore, MD: Centers for Medicare & Medicaid Services, 2003. Accessed December 12, 2005. <http://www.medicare.gov/medicarerreform/108s1013.pdf>.

excluded from Section 1013 due to political concerns regarding how such information might be used.¹⁰⁵ Of note is that, although MMA Section 1013 does not address economic evidence, it does refer to the use of comparative effectiveness information for certain coverage purposes, “CMS may not use data obtained through this provision to withhold coverage of a prescription drug.”¹⁰⁶

MMA also prescribes certain demonstration projects for the Medicare population. For instance, as part of the Medicare Replacement Drug Demonstration, Medicare pays for drugs or biologic agents replacing those covered under Medicare Part B. Congress requires CMS to evaluate all demonstration projects with regard to patient access, patient outcomes and CE. In the case of the Medicare Replacement Drug Demonstration, Medicare will compare selected health care costs of those beneficiaries enrolled in the demonstration (i.e., receiving replacement drugs) to the same costs in a control group of beneficiaries receiving the drugs currently covered under Medicare Part B.¹⁰⁷

- **Coverage with Evidence Development.** In April 2005, CMS issued a draft guidance outlining its considerations in extending national coverage with the condition of prospective data collection.¹⁰⁸ This draft guidance stated that a lack of evidence about costs and utilization associated with a new health technology may result in the use of coverage with evidence development (CED). This original draft guidance suggested that technologies covered with the requirement of evidence development may be required to collect data on costs and utilization. In turn, these types of endpoints potentially could be used to develop estimates of CE. Despite the mention of cost-related endpoints in the original draft guidance, a revised guidance issued by CMS in July 2006 did not address the collection of cost or resource utilization data as part of CED.¹⁰⁹ However, this guidance did suggest that clinical data collected via CED could be useful for cost analyses conducted by health plans.
- **Executive Order 12866.** As a result of EO 12866, which was created in 1993, and Circular A-4, any federal agency issuing an economically significant (i.e., annual effect on the economy of \$100 million or more) proposed or final rule regulation is required to conduct a regulatory impact analysis, including CEA. These analyses are intended to help agencies assess new regulations in comparison to the costs and benefits of regulatory alternatives.¹¹⁰ To date, agencies such as the Environmental Protection Agency (EPA), which issue numerous regulations, have been more affected by these mandates. Agencies like CMS, which are not involved in the same type of regulatory activities, are not affected to the same extent. In any case, these analyses primarily gauge the impact of an entire regulation and rarely, if ever, focus on particular health technologies.

¹⁰⁵ Neumann PJ, Rosen AB 2005.

¹⁰⁶ MMA 2003.

¹⁰⁷ Overview of the evaluation of the Section 641 demonstration. Baltimore, MD: Centers for Medicare & Medicaid Services, 2005. Accessed December 6, 2005. http://www.cms.hhs.gov/researchers/demos/641Eval_Brief1a.pdf.

¹⁰⁸ Draft guidance for the public, industry and CMS staff: factors CMS considers in making a determination of coverage with evidence development, 2005.

¹⁰⁹ Guidance for the public, industry, and CMS staff: national coverage determination with data collection as a condition of coverage with evidence development, 2006.

¹¹⁰ For more information about Executive Order 12866, Circular A-4 or other legislative mandates related to cost-effectiveness and regulations, see Section IV: Cost-effectiveness Evidence, Decision Making & New Health Technologies.

Due in part to some of these policy developments and in part to increasing pressure to contain health care costs, some experts anticipate that CMS' use of CE information in policymaking likely is to increase or become more explicit. There are early signs of a shift in this direction, as experts indicate that current discussions regarding certain technologies (e.g., left ventricular assist devices) address CE among other components. In addition, experts indicate that CMS currently is conducting an internal study to examine the feasibility of considering CE evidence in defining substantial clinical improvement for outpatient technologies for additional payment.

CMS also may experience pressure from independent federal advisory groups such as the Medicare Payment Advisory Commission (MedPAC) to incorporate CE into coverage and payment decisions.¹¹¹ For example, in its June 2005 report to Congress, MedPAC examined the current and potential future uses for CE in the Medicare program.¹¹² MedPAC suggested that Medicare could take on a role in standardizing CEA methods, gathering CE evidence from manufacturers during coverage deliberations, sponsoring CE research, disseminating CE information to beneficiaries and health professionals and applying CE evidence to prioritize pay-for-performance and disease management efforts. A June 2006 report completed for MedPAC by the Institute for Clinical Research and Health Policy Studies at the New England Medical Center included an analysis of published CEAs pertaining to colorectal cancer screening and implantable cardioverter defibrillators. This review offered the following concluding observations:¹¹³

"Our review indicates that for high profile and potentially high-cost Medicare-reimbursed services, such as ICDs and CRC screening, there are numerous cost-effectiveness analyses in the medical literature. Many of the studies measure outcomes in terms of costs per life year or QALY gained, hence providing a convenient basis for comparison.... To the extent that policy makers are interested in evaluating specific interventions and understanding the implications of different assumptions on cost-effectiveness ratios, they may wish to conduct or contract for additional analyses of the published estimates."

In its June 2006 report to Congress, entitled *Increasing the Value of Medicare*, MedPAC included a chapter addressing Medicare's use of clinical and cost-effectiveness evidence and discussed findings from the above analysis.¹¹⁴ As part of this report, MedPAC indicated planned investigations into the infrastructure that could be developed for Medicare to consider CE as well as clinical evidence. MedPAC also stated that it will continue to consider issues regarding funding and prioritization of CE research, especially with regard to a potential role for Medicare and suggested that there may be other ways for Medicare to use CE evidence. For instance, MedPAC indicated interest in exploring the provision of CE information to

¹¹¹ MedPAC is an independent federal body that advises the Medicare program on access to care and quality of care issues and reports to Congress on payment issues for Medicare's managed care program (Medicare Advantage) and providers under the fee-for-service system.

¹¹² Report to the Congress: issues in a modernized Medicare program. Chapter 8: Using clinical and cost effectiveness in Medicare. Washington, DC: Medicare Payment Advisory Commission, 2005. Accessed January 25, 2006. http://www.medpac.gov/publications/congressional_reports/June05_Entire_report.pdf.

¹¹³ Alhun E, Cohen J, Neumann P. Review and analysis of cost-effectiveness analyses for two Medicare-covered services. Washington, DC: Medicare Payment Advisory Commission, 2006. Accessed July 13, 2006. http://www.medpac.gov/publications/contractor_reports/Jun06_Cost_Effectiveness.pdf.

¹¹⁴ Report to the Congress: increasing the value of Medicare. Chapter 10: Medicare's use of clinical and cost-effectiveness information. Washington, DC: Medicare Payment Advisory Commission, 2006. Accessed July 13, 2006. http://www.medpac.gov/publications/congressional_reports/Jun06_EntireReport.pdf.

beneficiaries and health professionals and including CE evidence in pay-for-performance, screening, disease management and rate-setting activities.

If CMS were to incorporate CE evidence more explicitly in coverage and payment policymaking, it may face such challenges as the lack of a well-defined process and infrastructure to assess CE evidence and translate findings into policy. Experts also indicate that, while CMS employs staff with very strong credentials in economic evaluation, it may have insufficient expertise in CEA for health care technology and services to take on a significant role in this area, although additional relevant federal expertise exists at AHRQ and other HHS agencies.

2) Agency for Healthcare Research and Quality

Agency Overview and Mission

AHRQ is the main health services research branch of DHHS charged with facilitating improvement of health care quality, safety, efficiency and effectiveness.¹¹⁵ Research supported by AHRQ spans a range of topics, including quality improvement, health care costs, technology assessment and health care outcomes and effectiveness research.¹¹⁶ Some major programs and initiatives funded by AHRQ include the National Guidelines Clearinghouse, Evidence-based Practice Centers (EPCs), Consumer Assessment of Healthcare Providers and Systems and the Healthcare Cost and Utilization Project.¹¹⁷ In addition, AHRQ convenes and provides technical assistance to the US Preventive Services Task Force (USPSTF), an independent panel of experts that generates evidence-based recommendations about a range of preventive services.

The intended audience for AHRQ-sponsored research is broad, including clinical, health system and public policy decision-makers, who use research findings to make informed health care decisions. For instance, with regard to health care policy, technology assessments conducted by AHRQ have helped to inform recent CMS coverage determinations related to technologies such as positron emission tomography (PET) for patients with breast cancer.¹¹⁸

Current Involvement with Economic Information

As part of a larger body of AHRQ-funded research, AHRQ is recognized as a leader in conducting or sponsoring CEAs and facilitating the consideration of CE evidence by other federal agencies.¹¹⁹ A study reviewing federally-sponsored CE research over the five-year period 1997-2001 revealed that AHRQ is one of the largest federal funders of CE research. This study also found that, compared to other federal funders of CEAs, AHRQ funds research across

¹¹⁵ Mission and budget. Rockville, MD: Agency for Healthcare Research and Quality, 2005. Accessed December 13, 2005. <http://www.ahrq.gov/about/budgtix.htm>.

¹¹⁶ What is AHRQ? (AHRQ Publication No. 02-0011). Rockville, MD: Agency for Healthcare Research and Quality, 2002. Accessed December 13, 2005. <http://www.ahrq.gov/about/whatis.htm>.

¹¹⁷ AHRQ profile: advancing excellence in health care. (AHRQ Publication No. 00-P005). Rockville, MD: Agency for Healthcare Research and Quality, 2001. Accessed December 13, 2005. <http://www.ahrq.gov/about/profile.htm>.

¹¹⁸ AHRQ annual report on research and financial management, FY2002. Rockville, MD: Agency for Healthcare Research and Quality, 2002. Accessed December 13, 2005. <http://www.ahrq.gov/about/annrpt02/annrpt02b.htm>.

¹¹⁹ Fact sheet: focus on cost-effectiveness analysis at the Agency for Healthcare Research and Quality, 2001.

a broad range of health interventions and health conditions, with infectious diseases and cardiovascular disease leading the list of most frequently studied conditions.¹²⁰

Much of the CE research supported by AHRQ is overseen by its Research Initiative in Clinical Economics (RICE) and is developed and reviewed through multiple pathways within the agency, as described below.^{121,122}

- **Development of CE Evidence.** AHRQ is involved in many activities for generating new knowledge with regard to CE of health services and technologies. Extramural research grants awarded to investigators are one of the key ways this information is generated. According to the agency, since 1985, approximately 1 in 10 of these externally-conducted, investigator-initiated studies have included CEA.¹²³ For certain technologies, AHRQ also has sponsored CEAs in conjunction with clinical trials. As requested by CMS, AHRQ often is commissioned to conduct evidence reviews and technology assessments of selected technologies, a small number of which include CEAs. For example, CMS commissioned AHRQ to conduct a comparative clinical and CE study regarding screening iFOBT for a coverage review in 2003.^{124,125} AHRQ also collaborated with CMS and the National Heart, Lung and Blood Institute to support CEA of lung-volume-reduction surgery conducted in parallel to a large clinical trial using prospective Medicare claims data.¹²⁶
- **Synthesis and Review of Existing Economic Evidence.** Although AHRQ is not a policymaking agency, much of the research it generates is used by other federal and nonfederal health care stakeholders to inform their policymaking, which, in turn, can affect adoption and diffusion of new health technologies. Established by AHRQ in 1997, the Evidence-based Practice Centers (EPCs) are under contract with AHRQ to review and analyze the state of existing clinical and economic evidence. In establishing the EPCs, AHRQ included centers with expertise in CEA.¹²⁷ Within the EPC process, topics are selected for review by the EPCs through a nomination process in which potential partner organizations propose topics and relevant questions of interest.¹²⁸ While the majority of topics relate to clinical evidence regarding a particular technology or intervention, some topics reviewed by EPCs relate to CE or other economic or cost-health tradeoff evidence. For example, a 2004 EPC report considered the CE, in addition to safety and efficacy, of

¹²⁰ Siegel JE, Byron SC 2005.

¹²¹ Research Initiative in Clinical Economics. Rockville, MD: Agency for Healthcare Research and Quality, 2005. Accessed December 14, 2005. <http://www.ahrq.gov/rice/>.

¹²² Siegel JE 2005. Federal sponsorship of cost-effectiveness and related research in health care: 1997-2001.

¹²³ Synthesis of "statistical innovations for cost-effectiveness analysis." Rockville, MD: Agency for Healthcare Research and Quality, 2005. Accessed November 8, 2005. <http://www.ahrq.gov/rice/gardsum.htm>.

¹²⁴ Decision memo for screening immunoassay fecal-occult blood test (CAG-00180N), 2003.

¹²⁵ Van Ballegooijen M 2003.

¹²⁶ National Emphysema Treatment Trial Research Group. Cost-effectiveness of lung-volume-reduction surgery for patients with severe emphysema. *N Engl J Med* 2003;348(21):2092-102.

¹²⁷ Helfand M. Incorporating information about cost-effectiveness into evidence-based decision-making. The Evidence-Based Practice Center (EPC) model. *Med Care* 2005;43(7):II33-43.

¹²⁸ Evidence-based Practice Centers partner's guide. Rockville, MD: Agency for Healthcare Research and Quality, 2005. Accessed November 8, 2005. <http://www.ahrq.gov/clinic/epcpartner/epcpartner.pdf>.

cardiac resynchronization therapy for patients with symptomatic congestive heart failure. Results of this particular review revealed uncertainty about the CE of the therapy.¹²⁹

Sponsored by AHRQ, the USPSTF reviews evidence regarding clinical preventive services and issues recommendations about which preventive services should be incorporated into primary care.¹³⁰ The USPSTF is acknowledged widely as employing high standards of evidence and typically provides recommendations to use only those technologies or interventions with well-established evidence. As a result of this rigorous review process and the role of the USPSTF as an independent panel administered by AHRQ, its recommendations are cited widely by health professional associations, quality assurance groups, health plans and others.

In addition to reviewing clinical evidence, the USPSTF reviews economic evidence about preventive health services. For selected interventions, the USPSTF completes systematic reviews of published CEAs to complement reviews of clinical evidence.¹³¹ The USPSTF also uses CE and other cost-health tradeoff information synthesized during evidence reviews by the EPCs in making recommendations.¹³² The USPSTF communicates its findings via *The Guide to Clinical Preventive Services* and ongoing updates on the AHRQ USPSTF website, including those drawing on CE evidence, e.g., colorectal and cervical cancer screening.¹³³

Contemporary Policy Developments

MMA Section 1013 added to the relationship between CMS and AHRQ.¹³⁴ In fulfilling the MMA mandate to conduct comparative effectiveness research relevant to CMS programs (i.e., Medicare, Medicaid and SCHIP), AHRQ created the Effective Health Care Program in 2005 with the goals of synthesizing, generating and translating evidence related to the comparative effectiveness of health services.¹³⁵ As part of this program, the EPCs (described above) address the goal of synthesizing available evidence and the Clinical Decisions and Communications Science Center has a key role in translating findings into meaningful and understandable information for decision-makers.

¹²⁹ McAlister F, Ezekowitz J, Wiebe N, et al. Cardiac resynchronization therapy for congestive heart failure. Evidence Report/Technology Assessment No. 106. (Prepared by the University of Alberta Evidence-based Practice Center under Contract No. 290-02-0023.) AHRQ Publication No. 05-E001-2. Rockville, MD: Agency for Healthcare Research and Quality, 2004. Accessed December 13, 2005. <http://www.ahrq.gov/downloads/pub/evidence/pdf/resynchf/resynchf.pdf>.

¹³⁰ About USPSTF. Rockville, MD: Agency for Healthcare Research and Quality, US Preventive Services Task Force, 2005. Accessed November 8, 2005. <http://www.ahrq.gov/clinic/uspstfab.htm>.

¹³¹ Saha S, Hoerger TJ, Pignone MP, et al. The art and science of incorporating cost-effectiveness into evidence-based recommendations for clinical preventive services. *Am J Prev Med* 2001;20(3S):36-43.

¹³² Meenan RT, Fleming C, Whitlock EP, et al. Cost-effectiveness analyses of population-based screening for abdominal aortic aneurysm. Evidence synthesis. (AHRQ Publication No. 05-0569-C). Rockville, MD: Agency for Healthcare Research and Quality, 2005. Accessed December 13, 2005. <http://www.ahrq.gov/clinic/uspstf05/aaascr/aaacost.htm>.

¹³³ The Guide to Clinical Preventive Services 2005. Recommendations of the US Preventive Services Task Force. Rockville, MD: Agency for Healthcare Research and Quality, 2005. Accessed November 9, 2005. <http://www.ahrq.gov/clinic/pocketgd.pdf>.

¹³⁴ MMA 2003.

¹³⁵ Frequently asked questions: Effective Health Care and the Medicare Modernization Act Section 1013. Rockville, MD: Agency for Healthcare Research and Quality, 2005. Accessed November 8, 2005. <http://effectivehealthcare.ahrq.gov/aboutUs/faq.cfm>.

In order to address the goal of generating new comparative effectiveness evidence, AHRQ established the Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network, consisting of 13 different research centers.^{136,137} Equipped with electronic medical data, members of the newly created DEcIDE Network immediately began working on 15 studies of the comparative clinical effectiveness of various health technologies and services. Among the topics included in these initial DEcIDE Network projects are outcomes of chronic obstructive pulmonary disease management, comparative effectiveness and safety of new glucose control therapies for diabetic patients and treatment outcomes for older adults taking antipsychotic medications.^{138,139,140}

CEA is not considered formally in DEcIDE Network projects. However, some current projects include endpoints to assess resource utilization and health care costs associated with particular health services or interventions, which could be used for CEA or related economic analyses. For example, the current project evaluating new glucose control therapies for diabetic patients incorporates clinical outcomes (e.g., medication-related adverse events) and resource utilization measures (e.g., rates of hospitalization and related costs).¹⁴¹ At present, it is unclear whether CEA will have any formal role in DEcIDE Network projects.

3) Centers for Disease Control and Prevention

Agency Overview and Mission

Focused on protecting public health through prevention and disease control initiatives, the CDC is a major sponsor of US prevention-oriented research and funder of prevention and control programs. Adopting a public health perspective in all its activities, the CDC recently began a paradigm shift toward a more holistic orientation to prevention and health protection. This new approach incorporates a greater emphasis on protecting health in all stages of life and forming productive partnerships with health systems and stakeholders.¹⁴² Key activities in fulfilling the mission of the CDC include monitoring and researching health and threats to health; conducting research on and implementing prevention and health promotion initiatives; and serving as a source of training, leadership and public health policy.¹⁴³

¹³⁶ DEcIDE Network. Rockville, MD: Agency for Healthcare Research and Quality, 2005. Accessed December 13, 2005. <http://effectivehealthcare.ahrq.gov/decide/index.cfm>.

¹³⁷ AHRQ launches new "Effective Health Care Program" to compare medical treatments and help put proven treatments into practice. Rockville, MD: Agency for Healthcare Research and Quality, 2005. Accessed December 13, 2005. <http://www.ahrq.gov/news/press/pr2005/effectivepr.htm>.

¹³⁸ Outcomes of COPD management. Rockville, MD: Agency for Healthcare Research and Quality, 2005. Accessed December 13, 2005. <http://effectivehealthcare.ahrq.gov/decide/decide.cfm?topic=5>.

¹³⁹ Comparative effectiveness and safety of new therapies for glucose control in diabetes mellitus. Rockville, MD: Agency for Healthcare Research and Quality, 2005. Accessed December 13, 2005. <http://effectivehealthcare.ahrq.gov/decide/decide.cfm?topic=8>.

¹⁴⁰ Health outcomes of antipsychotic treatment in older adults. Rockville, MD: Agency for Healthcare Research and Quality, 2005. Accessed December 13, 2005. <http://effectivehealthcare.ahrq.gov/decide/decide.cfm?topic=7>.

¹⁴¹ Comparative effectiveness and safety of new therapies for glucose control in diabetes mellitus, 2005.

¹⁴² State of CDC. Atlanta, GA: Centers for Disease Control and Prevention, 2005. Accessed December 14, 2005. <http://www.cdc.gov/cdc.pdf>.

¹⁴³ Vision, mission, core values and pledge. Atlanta, GA: Centers for Disease Control and Prevention, 2005. Accessed December 14, 2005. <http://www.cdc.gov/about/mission.htm>.

Current Involvement with Economic Information

Over the last decade, CDC's capacity for conducting economic analyses and its tendency to use CE evidence has increased. This is due, in part, to CDC's implementation in 1992 of a fellowship program attracting economists to CDC to learn about the intersections of economics and public health. Approximately 50 economists now work at CDC as a result of this program, and each year 5-10 additional economists enter new fellowships. This base of economic expertise allows CDC to conduct cost-related research projects and issue guidelines incorporating economic evidence where available and relevant for use by other health care stakeholders and CDC grantees. According to a review of federally sponsored CE research during 1997-2001, CDC is on par with AHRQ in funding the largest number of CE and related studies among DHHS agencies.¹⁴⁴

CDC's economic-related work focuses on interventions with the potential to influence population health. The Center's economic work often is aligned with programmatic needs in prevention and health protection. A recent analysis found that CDC funds more than twice as many cost-related studies for preventive interventions as any other federal agency.¹⁴⁵ More than half of federally-funded CE studies related to vaccinations were attributed to CDC funding. CDC funding of CE research focuses primarily on infectious diseases, HIV/AIDS and injuries. As preventive interventions are emphasized less often by industry, CDC's economic research on these topics may help to fill important knowledge gaps. Examples of CDC's involvement with CE research and recommendations are described below.

- **Research.** A prominent example of CE research supported by CDC is the work conducted by its Diabetes Cost-effectiveness Group. As new diabetes-related interventions emerge, this group works to generate CE evidence and present clinical and cost-related findings in a meaningful and understandable format to inform decisions of policymakers, public health and health care system stakeholders, providers and others. Studies conducted by this group often employ mathematical models to simulate longer-term effects of an intervention on clinical, quality of life and economic endpoints, which enables estimating long-term CE.

According to key staff at CDC, there is great demand for CE expertise at the local level, and this demand varies with the amount of economic research CDC has conducted in a community. For instance, CDC conducted an economic analysis following the events of 9/11 that stimulated interest in economic research in those areas. Currently, demand for economic fellows exceeds CDC's capacity to provide them to all interested communities.

- **Recommendations.** Along with other public and private stakeholders, CDC supports the work of the Task Force on Community Preventive Services, an independent, nonfederal entity with a central role in assessing and delivering recommendations for community, population and health system preventive health care services.¹⁴⁶ Recommendations of the Task Force are organized into *The Guide to Community Preventive Services (Community Guide)*, which was first released in 2005.¹⁴⁷ The *Community Guide* synthesizes findings for a range of

¹⁴⁴ Siegel JE, Byron SC 2005.

¹⁴⁵ Ibid.

¹⁴⁶ Community Guide. About us. Atlanta, GA: Centers for Disease Control and Prevention, 2005. Accessed December 14, 2005. <http://www.thecommunityguide.org/about/default.htm>.

¹⁴⁷ The Community Guide. Atlanta, GA: Centers for Disease Control and Prevention, Task Force on Community Preventive Services, 2005. Accessed December 14, 2005. <http://www.thecommunityguide.org/>.

preventive interventions focused on health behaviors (e.g., physical activity); environmental health considerations (e.g., exposure to tobacco smoke); and a series of diseases, conditions and causes of injuries (e.g., cancer, diabetes, motor vehicle-related injuries). For each of these health topics, the Task Force conducts systematic reviews of the effectiveness of selected interventions and provides either a recommendation for use or a conclusion that insufficient evidence exists to recommend implementation.¹⁴⁸

For those interventions that are “strongly recommended” or “recommended” in the *Community Guide*, systematic reviews of published economic evidence are conducted as a second phase. CEAs are one of four types of economic analysis included in the Task Force’s review. The Task Force intends that findings about economic efficiency of selected preventive services will help inform decisions of health care stakeholders regarding resource allocation and other needs.¹⁴⁹

CDC issues recommendations and advisories on various other public health topics. For example, CDC has issued several advisories regarding influenza antivirals. As confirmed by interviews for this case study, these advisories make no reference to economic data and appear to be based solely on clinical and epidemiological considerations.

4) *National Institutes of Health*

Overview and Mission

As the medical and behavioral research arm of DHHS, NIH generates scientific knowledge for use in enhancing the nation’s health.¹⁵⁰ Each year, NIH invests more than \$27 billion in funding medical research, the majority (80%) of which occurs via competitively awarded grants to universities, medical schools and research institutions.¹⁵¹ A smaller proportion (10%) of NIH research is conducted intramurally by the 27 Institutes and Centers, which have their own research priorities organized by health-related activities, health conditions, organ systems or other administrative functions.¹⁵²

Current Involvement with Economic Information

Given its research-oriented role, NIH involvement with economic information focuses on the development, rather than the use, of economic evidence. On a limited basis, CEAs may be performed as part of clinical trials funded by NIH or as separate studies involving modeling or other methods. NIH staff also are asked to assist with technology assessments, sometimes including CEAs, which are requested of AHRQ by CMS during coverage or payment deliberations. NIH staff assisted with the 2003 deliberations for screening iFOBT.

¹⁴⁸ The Guide to Community Preventive Services. At a glance. Atlanta, GA: Centers for Disease Control and Prevention, 2005. Accessed December 14, 2005. <http://www.thecommunityguide.org/overview/at-a-glance.pdf>.

¹⁴⁹ The Guide to Community Preventive Services. Chapter 11: Understanding and using the economic evidence. Atlanta, GA: Centers for Disease Control and Prevention, Task Force on Community Preventive Services, 2005. Accessed December 14, 2005. <http://www.thecommunityguide.org/econ/Economics.pdf>.

¹⁵⁰ About NIH. Bethesda, MD: National Institutes of Health, 2005. Accessed December 14, 2005. <http://www.nih.gov/about/>.

¹⁵¹ NIH budget. Bethesda, MD: National Institutes of Health, 2005. Accessed December 14, 2005. <http://www.nih.gov/about/budget.htm>.

¹⁵² Institutes, centers and offices. Bethesda, MD: National Institutes of Health, 2005. Accessed December 14, 2005. <http://www.nih.gov/icd/>.

A 2005 review of federally-sponsored CE research found that NIH funds approximately 70% of all federally-funded health economic studies and 84% of all studies funded by agencies within DHHS.¹⁵³ Within NIH, there are interesting variations with regard to sponsorship of CEAs and related economic analyses. Among the NIH Institutes and Centers, the National Cancer Institute (NCI), the National Institute of Mental Health (NIMH) and the National Institute on Drug Abuse (NIDA) fund the greatest number of these types of studies.¹⁵⁴ Among these top three funders, health topics addressed in CE research vary according to the focus of each Institute. Among the 49 CE and related studies funded by NCI during 1997-2001, 88% focus on cancer. For NIDA, the majority of CE studies focus on substance abuse (71%). While 44% of NIMH-funded studies address mental health and 58% address HIV/AIDS, the majority of the mental health-related projects were funded by NIMH only, and the HIV/AIDS-related projects typically were jointly funded. For NIMH and NIDA, the majority of CE projects focus on pharmaceutical or health education interventions, while the majority of NCI's CE studies involved screening interventions.

5) Department of Veterans Affairs and Department of Defense

The Department of Veterans Affairs (VA) and the Department of Defense (DoD), through TRICARE, are involved in health care delivery and payment for approximately 7.6 million veterans and more than 8 million military personnel and their families.^{155,156} Aside from CMS, the VA and DoD represent two of the largest sources of public health care in the US.

Department of Veterans Affairs

Overview and Mission

The mission of the VA, the second largest federal department, is to serve and advocate for the medical care, benefits and recognition of veterans and their families. Within the VA, the Veterans Health Administration (VHA) is charged with managing the largest integrated US health care system, which helps veterans cope with disabilities, adjust to civilian life and handle other medical and social challenges.¹⁵⁷ The VA maintains a national network of 157 hospitals, 869 outpatient clinics, 134 nursing homes, 42 domiciliaries, 206 readjustment counseling centers and 57 veterans benefits regional offices.¹⁵⁸

Current Involvement with Economic Information

The VA generates and uses health economic evidence to guide certain program policies, as described below.

¹⁵³ Siegel JE, Byron SC 2005.

¹⁵⁴ Ibid.

¹⁵⁵ Veterans Health Administration key staff. Washington, DC: Veterans Health Administration, 2005. Accessed December 19, 2005. <http://www1.va.gov/directory/guide/manager.asp?pnun=30233>.

¹⁵⁶ Growth in medical spending by the Department of Defense. Washington, DC: Congressional Budget Office, 2003. Accessed December 19, 2005. <http://www.cbo.gov/ftpdocs/45xx/doc4520/09-09-DoDMedical.pdf>.

¹⁵⁷ Aspinall SL, Good CB, Glassman PA, Valentino MA. The evolving use of cost-effectiveness analysis in formulary management within the Department of Veterans Affairs. *Med Care* 2005;43(7):II-20-6.

¹⁵⁸ Department of Veterans Affairs organizational briefing book. Washington, DC: Department of Veterans Affairs, 2005. Accessed December 14, 2005. <http://www.va.gov/ofcadmin/orgbrfbook.pdf>.

- **Research.** During the five-year period 1997-2001, the VA sponsored 68 CE or other health economics studies, representing 13% of all federally-sponsored CE research. Compared to other departments and agencies, the VA sponsored more of these studies than all but two DHHS agencies (AHRQ and CMS) and supported the most studies of any non-DHHS federal entity.¹⁵⁹ Most studies sponsored by VA focused on cardiovascular disease and stroke, substance abuse and infectious diseases (excluding HIV/AIDS). The three leading types of interventions studied were pharmaceuticals, screening and diagnostics.

Within the VA, the Health Economics Resource Center (HERC) conducts CEAs and is an important resource for guidance in conducting CEAs.¹⁶⁰ CE research emerging from or guided by the HERC often addresses key topics for the VA health system, supporting decision-makers in the system. For instance, a 2003 HERC study used decision modeling to analyze the CE of various management strategies (e.g., PET using 18-fluorodeoxyglucose) for patients with solitary pulmonary nodules.¹⁶¹

- **Use of CE and Other Economic Information.** Given resource allocation challenges inherent to operating a health care delivery system within a fixed budget, CE and related economic considerations generally are acknowledged as an implicit part of VHA decision-making. CE and other economic evidence are considered explicitly in certain aspects of VHA health care. Specifically, as part of formulary determinations, the VHA is making more explicit use of CEA and other economic analyses.¹⁶² In order to respond most effectively to the needs of its beneficiaries, the VHA maintains both national and regional formularies, and the Pharmacy Benefits Management (PBM) Strategic Healthcare Group maintains the current listing of drugs on the national formulary.

Clinical pharmacists within the PBM consider each new drug to come to market. As part of this review, cost analyses were included in drug monographs and drug class reviews starting in 2003 and, in 2004, the VHA began to request formal CEAs from manufacturers of certain drugs. There is some evidence that VHA may consider CE evidence more often for new or expensive drugs. VHA also may use clinical and quality of life outcomes data from manufacturers to complete their own economic analyses of new drugs.¹⁶³ During the review process, the VHA also welcomes pharmaceutical companies to present CE models, fostering public-private interaction. The VHA anticipates increasing the role of CEA in the drug review process and to inform drug use criteria and disease state guidelines.

¹⁵⁹ Siegel JE, Byron SC 2005.

¹⁶⁰ Mission statement. Menlo Park, CA: Health Economics Resource Center. Accessed November 8, 2005. http://www.herc.research.med.va.gov/about/mission_statement.asp.

¹⁶¹ Gould MK, Sanders GD, Barnett PG, et al. Cost-effectiveness of alternative management strategies for patients with solitary pulmonary nodules. *Ann Intern Med* 2003;138(9):724-35.

¹⁶² Aspinall SL 2005.

¹⁶³ Ibid.

Department of Defense

Overview and Mission

DoD administers TRICARE, a managed health care program covering more than 8 million active duty and retired military personnel and their families.^{164,165} TRICARE is available to personnel and their families in the Army, Navy, Marine Corps, Air Force, Coast Guard, Public Health Service and National Oceanic and Atmospheric Administration. Three basic health plan options are offered under TRICARE, including TRICARE Prime (health maintenance organization), TRICARE Extra (preferred provider organization) and TRICARE Standard (fee-for-service plan), each with varying levels of cost sharing.¹⁶⁶ Retired military personnel who also are eligible for Medicare are covered under an expanded program called TRICARE for Life, which offers payment secondary to Medicare and requires no monthly premiums.

Current Involvement with Economic Information

Not unlike the VHA, the TRICARE program operates within budgetary constraints while striving to provide high quality health care to its beneficiaries. Given Congressional Budget Office (CBO) estimates that DoD health care spending nearly doubled from 1988 to 2003, the program may be under increased pressure to contain costs. Currently, CE evidence for pharmaceuticals is evaluated by TRICARE as part of the formulary determination process. Statute requires the DoD Pharmacy and Therapeutics (P&T) Committee to evaluate both clinical attributes and CE of pharmaceuticals compared to drugs in the same therapeutic class to guide designation of drugs for inclusion on the DoD Uniform Formulary, comprising the Basic Core Formulary and the Extended Core Formulary.¹⁶⁷

The DoD Pharmacoeconomic Center (PEC) conducts economic analyses in support of the formulary review process, in addition to monitoring other cost-related trends and providing information to inform clinical practice guidelines.¹⁶⁸ TRICARE plans to adopt e-prescribing and electronic health record systems, helping to reduce adverse drug reactions and improving the CE of pharmaceutical use.

F. Use of Cost-effectiveness and Related Analyses by Nonfederal Stakeholders

Outside of the federal government, a range of other stakeholders play important roles in the US health care system. These stakeholders are involved in research and development, market approval, evaluation, coverage and payment, purchasing, adoption and use of health services as described below. The roles of relevant stakeholders in these phases are described briefly below,

¹⁶⁴ Growth in medical spending by the Department of Defense, 2003.

¹⁶⁵ TRICARE handbook. Falls Church, VA: Office of the Assistant Secretary of Defense (Health Affairs) and the TRICARE Management Activity, 2004. Accessed December 19, 2005. http://www.tricare.osd.mil/TricareHandbook/Show_all.cfm.

¹⁶⁶ Growth in medical spending by the Department of Defense, 2003.

¹⁶⁷ Uniform Formulary Blanket Purchase Agreement Information. Falls Church, VA: Office of the Assistant Secretary of Defense (Health Affairs) and the TRICARE Management Activity, 2005. Accessed October 27, 2005. http://www.tricare.osd.mil/ufbpa/UFBPA_Info.cfm.

¹⁶⁸ Department of Defense Pharmacoeconomic Center. San Antonio, TX: Pharmacoeconomic Center, 2005. Accessed January 12, 2006. <http://www.pec.ha.osd.mil/mission.htm>.

followed by discussion regarding their involvement with CEA and other economic considerations in health care.

1) Innovation, Research and Development

Manufacturers and other sectors of industry are involved actively in devising, testing and producing new health technologies. Their investment in R&D results in new or improved pharmaceuticals, diagnostics, medical devices and other products. Health technology companies increasingly are aware of evidence required for regulatory and reimbursement decisions in the US and abroad.

Faced with decisions about which technologies to develop, medical technology companies may consider the potential cost or CE implications of bringing a particular technology to market. A 2003 survey of AdvaMed member companies revealed that both consumer and payer demand for CE information about new medical technologies were among the top 10 factors influencing companies' product development priorities.¹⁶⁹ Currently, CEAs and related economic analyses are used by manufacturers at various points during R&D and marketing. Results of these analyses routinely are submitted to agencies in other national health systems such as the National Institute for Health and Clinical Excellence (NICE) in the UK, where economic evidence more commonly is required and more explicitly considered than in the US. Within the US, manufacturers may choose to share relevant CE information with private payers and CMS to inform their coverage and payment determinations. According to stakeholder interviews, this happened during the coding and payment determination process at CMS for DES, as described in the case study for this technology.

Although industry can share economic evidence, manufacturers are concerned about how this evidence may be used in policymaking. First, many health care stakeholders perceive that CE and other economic evidence is used as a tool for cost-containment or to justify limiting access to particular technologies. For instance, drug manufacturers have expressed opposition to the VHA's use of CE information in making formulary decisions, due to concerns about access.¹⁷⁰ Industry stakeholders also expressed concerns about actual or potential use of CE information by CMS. Citing the financial investment required to develop CE evidence, industry stakeholders expressed frustration over submitting such evidence when its use and impact is perceived as unpredictable.

Initial suggestions from industry stakeholders for improving confidence in the process for reviewing CE evidence included: 1) clarifying and publicizing preferred assumptions for manufacturers to use in conducting CEAs; 2) involving industry representatives in developing guidelines related to CEAs and discussions about the process for incorporating this evidence into policymaking; and 3) providing incentives for manufacturers to collect economic evidence by building rewards into the system when a technology offers demonstrated value.

¹⁶⁹ The medical technology industry at a glance. Washington, DC: Advanced Medical Technology Association (AdvaMed), 2004. Accessed December 28, 2005. <http://www.advamed.org/newsroom/chartbook.pdf>.

¹⁷⁰ Aspinall SL 2005.

2) FDA Regulation of Marketing New Technology

Market clearance by FDA is critical to the success of the technologies regulated by the agency. During the submission and review process, manufacturers often interact with the FDA, and sometimes other agencies such as CMS, in an attempt to anticipate and respond to evidence requirements of those agencies. Given requests from private and public payers for CE evidence, manufacturers may anticipate demand for this information when designing clinical trials for a new technology. To the extent that manufacturers include economic endpoints in clinical trials being conducted to demonstrate technology safety and efficacy for FDA, this evidence may be available for use by payers or other decision-makers. As described in our case studies, manufacturers frequently collect economic and cost-effectiveness data and sometimes provide these data to FDA during the approval process. However, there is no evidence to suggest that such data have influenced FDA's approval decisions.

3) Health Technology Assessment

Public and private sector payers, providers and other health care stakeholders often rely on health technology assessments (HTAs) to inform their technology coverage or acquisition decisions. Higher profile breakthrough technologies tend to be subject to HTA, particularly if they have a large potential direct or indirect health or economic impact. One influential HTA program is the joint Technology Evaluation Center (TEC) of the Blue Cross Blue Shield Association (BCBSA) and Kaiser Permanente.^{171,172} Assessments from BCBSA TEC often rise to national visibility and serve as an important source of information for Blue Cross and Blue Shield plans and other payers.¹⁷³ A medical advisory panel comprising independent, nationally recognized experts in HTA, clinical research and medical specialties, has scientific accountability for all TEC assessments.

Among the BCBSA TEC reports, a limited number contain CEAs. In 2004, BCBSA TEC completed two with CEAs, including for implantable cardioverter-defibrillators (ICDs) and left-ventricular assist devices (LVADs).^{174,175} Another report with a CEA, focusing on coronary computed tomography angiography (CTA) for symptomatic patients, is in progress.¹⁷⁶ In addition to its HTAs, BCBSA TEC also has been involved in evaluating CE and other economic evidence under its contract with AHRQ as an Evidence-based Practice Center (EPC). In this

¹⁷¹ The Blue Cross and Blue Shield Association Technology Evaluation Center has been in place since 1985. Its collaborative relationship with Kaiser Permanente began in 1993.

¹⁷² In addition such groups as BCBSA TEC, many large health plans and networks, e.g., Aetna, CIGNA and United Healthcare, have extensive internal technology assessment capabilities and they supplement internal expertise with assessments purchased from HTA vendors such as Hayes, Inc., ECRI or others.

¹⁷³ Technology Evaluation Center. Chicago, IL: Blue Cross Blue Shield Association, 2004. Accessed December 30, 2005. <http://www.bcbs.com/tec/>.

¹⁷⁴ Special report: cost-effectiveness of implantable cardioverter-defibrillators in a MADIT-II population, 2004.

¹⁷⁵ Special report: cost-effectiveness of left-ventricular assist devices as destination therapy for end-stage heart failure, 2004.

¹⁷⁶ TEC assessments. Chicago, IL: Blue Cross Blue Shield Association, Technology Evaluation Center, 2005. Accessed December 28, 2005. <http://www.bcbs.com/tec/tecassessments.html#progress>.

role, BCBSA TEC has completed one report examining the relative clinical attributes and CE of androgen suppression to treat prostate cancer.^{177,178}

While BCBSA's TEC reports can be influential among government and private payers, it is less clear that this is the case for the TEC reports focused on cost-effectiveness. During interviews for the ICD case study, stakeholders suggested that the TEC report for ICDs, which focused on the cost-effectiveness of the technology, was not as influential as other, more clinically-oriented TEC reports. However, the importance of the TEC ICD report could be more subtle, as it may serve as a model for the integration and synthesis of economic data from many large RCTs.

4) Coverage and Payment

Private payers often consider a variety of sources of information in determining coverage and payment for new health technologies. Often, private payers are influenced by CMS coverage decisions and certain of the larger private health plans. In addition, they also consider reviews of clinical evidence from HTA vendors such as BCBSA TEC and may conduct their own internal HTAs to inform coverage decisions.

In formulating coverage policies, health plans and other private payers first consider clinical evidence. In most instances, CE and other economic evidence is not considered explicitly in making coverage decisions. However, cost-related considerations are not entirely absent from decision-making processes. A survey of medical directors of 228 managed care plans found that only 40% reported using formal CEA for decision-making, while 90% indicated that cost is one factor in their decision-making.^{179,180} Even in cases in which medical directors cite CE as a factor in decision-making, CE generally is not cited among explicit coverage criteria.¹⁸¹ While CE considerations may be used in private payer coverage determinations, matters of CE are not included among formal coverage criteria. Some reasons why private payers and plans have not adopted CE criteria into coverage and payment to a greater extent relate to methodological concerns, such as lack of consensus about threshold values for determining CE and difficulty in representing uncertainty in CEAs.¹⁸²

Although payers generally do not consider CE explicitly in coverage determinations, there is evidence to suggest that costs play a larger role in determining benefits structure and setting payment levels for new health technologies. Payers routinely consider costs in adjusting benefits structure in accordance with the potential economic impact of covering the technology. For instance, a private payer may require increased cost-sharing or prior authorization for costly technologies that likely are to be used by many beneficiaries. In some cases, payers and managed care plans address CE in their definitions of medical necessity.¹⁸³ In order to evaluate

¹⁷⁷ AHRQ Evidence-based Practice Center. Chicago, IL: Blue Cross Blue Shield Association, Technology Evaluation Center, 2005. Accessed December 28, 2005. <http://www.bcbs.com/tec/ahrqepc.html>.

¹⁷⁸ Relative effectiveness and cost-effectiveness of androgen suppression in the treatment of prostatic cancer. Rockville, MD: Agency for Healthcare Research and Quality, 1999. Accessed December 28, 2005. <http://www.ahrq.gov/clinic/epcsums/prosumm.htm>.

¹⁷⁹ Neumann PJ 2005.

¹⁸⁰ Garber AM 2004.

¹⁸¹ Neumann PJ 2005.

¹⁸² Garber AM 2004.

¹⁸³ Neumann PJ 2005.

CE for these types of purposes, many payers are open to receiving economic models or other forms of CE information from manufacturers.

Coverage of pharmaceuticals, often as part of formularies, is one area within coverage policy in which economic evidence has begun to be incorporated more explicitly by private payers and plans. In 1998, Regence BlueShield health plan was the first of its kind to require drug manufacturers to supply economic evidence, in addition to clinical evidence, as part of the formulary review process.¹⁸⁴ Since their release in 2000, many health plans and pharmacy benefit managers began to use formulary guidelines from the Academy of Managed Care Pharmacy (AMCP), which call for evidence of a drug's relative economic value to be included with clinical evidence in dossiers submitted for review of new drugs. As of early 2004, more than 50 health plans, pharmacy benefit management organizations, hospitals and Medicaid programs began using the AMCP format or a similar format. While the AMCP format and other similar processes were widely adopted for pharmacy benefits management, this movement also ushered in new concerns. These include the increased burden on manufacturers to develop, analyze and submit economic value information and that health plans may not have the required expertise to evaluate submitted economic information.¹⁸⁵

Although pharmacy benefit management is acknowledged as an area in which the explicit use of economic evidence has grown, this did not arise in the case study on Relenza. This may suggest that economic evidence was not used in formulary management with regard to Relenza, but it also may simply reflect that private payers are not required to make their decision-making processes transparent to the public, making it difficult to determine which factors are weighed in decisions.

5) Purchasing and Use

New health technologies reach consumers through a variety of pathways, depending on the type of technology. For instance, some products (e.g., home blood glucose monitors) are intended for use directly by consumers without direct involvement by health care professionals. Many other health technologies, including certain pharmaceuticals, medical devices and diagnostics, are used or prescribed in clinical settings. Depending on the pathway through which a consumer's health care is influenced by a particular medical technology, a range of stakeholders are involved in the purchase and use of new health technologies, including employers, group purchasing organizations (GPOs), providers, provider associations, policymakers and consumers.

Employers and Group Purchasing Organizations

Many Americans covered under private health plans receive health care as part of employer-sponsored health benefit plans. Often, premiums and other health care expenses are reduced for employees who choose employer-sponsored rather than individual coverage, because employers are able to negotiate more competitive rates with plans. Employers use a range of strategies to achieve a desirable complement of benefits at a low rate for employees

¹⁸⁴ Neumann PJ 2005.

¹⁸⁵ Neumann PJ. Evidence-based and value-based formulary guidelines. *Health Aff* 2004;23(1):124-34.

including strategic purchasing alliances.¹⁸⁶ Operating under similar logic for the benefit of a different group of stakeholders, GPOs use purchasing volume to achieve lower negotiated health care costs for a range of health care providers. For both groups, value-based purchasing has become a central goal in recent years, focusing on purchasing health services based on measures of quality care. While CE may be an implicit consideration in health care quality, there is less evidence that employers and GPOs are using CEA to inform decisions than there is to suggest that purchasing decisions increasingly are made with regard to overall value and quality of care. In fact, certain groups, such as the National Business Group on Health, have been working to convey CEA as a tool for employers.¹⁸⁷ As health care costs continue to increase, it is possible that the use of economic evidence may expand. However, the future role of economic evidence for employers, GPOs and other large purchasing entities remains unclear.

Clinicians and Other Health Care Providers

While operating within health plan benefit limits, providers and provider organizations have great influence on adoption of new technologies into practice. There is little evidence that providers generally conduct formal considerations of CE when determining what health interventions to deliver. However, providers often are aware of economic issues surrounding new medical technologies, and they must keep informed about coverage and payment policies of major public and private payers. In addition, providers often refer to guidelines when determining a course of treatment. These guidelines may be issued by health professional organizations, public entities (e.g., USPSTF) or other organizations.

Consumers

Given increasingly prevalent cost-sharing arrangements inherent to many of today's health plans, consumers are experiencing more financial impact of costly health services. Indeed, these cost-sharing arrangements are intended to make consumers more aware of the costs of the health care they receive.¹⁸⁸ Consumer-driven health plans (CDHPs), which entrust consumers with the responsibility of selecting efficient health care options given appropriate decision-making tools and incentives, are one development that may prompt increased demand from consumers for CE and other cost-health tradeoff information. However, as reflected in the NAT case study, consumers, health care providers and other stakeholders may emphasize minimizing health risk, including statistically remote chances of contracting a serious disease, regardless of cost to third-party payers.

Other Nonfederal Health Stakeholders

Health care providers have options of using certain costly technologies in providing care. NAT to screen the blood supply is one example of these types of technologies. As illustrated in the case study for NAT, there was variation among blood banks in the US with regard to the use of economic evidence to determine whether to implement NAT for detecting certain infectious diseases. Stakeholders from some blood banks indicated that they did not consider economic evidence at all, instead viewing the use of NAT as a societal and ethical obligation.

¹⁸⁶ Reference guide. Purchasing coverage: purchasing strategies. Oakland, CA: California HealthCare Foundation, 2005. Accessed December 28, 2005.

<http://www.healthcoverageguide.org/referenceguide/index.cfm?itemID=21410>.

¹⁸⁷ Cost-effectiveness analysis: an employer decision support tool. Washington, DC: National Business Group on Health, 2004. Accessed December 28, 2005. <http://www.businessgrouphealth.org/pdfs/ceaissuebrief.pdf>.

¹⁸⁸ Neumann PJ 2004. Why don't Americans use cost-effectiveness analysis?

Stakeholders from other blood banks, however, explained that CEA was used at least to some extent to determine whether to implement NAT to screen the blood supply.

G. Use of Cost-effectiveness and Related Analyses Outside of the US

While models vary among countries, CE and other economic evidence generally plays a larger role in health care policy decisions in other industrialized nations than it does in the US.¹⁸⁹ In most of Western Europe, Australia and Canada, the use of CE evidence in policy decisions is increasing and, in certain of these countries, CE evidence has been part of the decision-making process for a decade or more.^{190,191} In countries that explicitly consider health economic factors, CEAs are conducted as part of HTAs and other analyses to inform decisions regarding coverage and payment, acquisition, public health interventions and others.¹⁹²

Differences between the US and other countries in the use of CE evidence are attributed to a range of cultural and social differences and to differing views on the role of government in health care. One health economist studying these differences identified five types of barriers that may impede the use of CE evidence in the US, including those that are methodological, training, legal, trust and political. This economist found that certain of these barriers are lower for other western countries (e.g., lack of expertise), but concluded that, “the ‘will’ to make it happen,” is the primary ingredient necessary to achieve US adoption of CE evidence. In contrast to the US, decision-makers in other countries tend to have more common acceptance of CE as a method of resource allocation toward maximizing value of health care resources.¹⁹³

US and international health systems differ in important ways. For instance, many other western countries employ national health care systems with regulatory and reimbursement systems that are aligned more closely than in the US. Acknowledging the significant cultural, social and health system differences between the US and other countries, some of our interviewees cited certain programs of incorporating CE evidence in other countries that may serve as useful models for the US. More than half of stakeholders interviewed cited as an instructive model the system used by the UK’s NICE. The NICE model and other approaches adopted by Australia and Canada, which also are useful for the US discussion, are described below.

1) NICE and the UK Approach

Launched in the spring of 1999 as a Special Health Authority in the Department of Health, NICE was envisioned as an independent source of guidance for the National Health Service (NHS) in the UK.^{194,195,196,197} Three categories of guidance are issued by NICE, including public

¹⁸⁹ Siegel JE. Cost-effectiveness analysis in US healthcare decision-making. Where is it going? *Med Care* 2005;43(7):II-1-4.

¹⁹⁰ Luce BR 2005.

¹⁹¹ Maynard A, Bloor K. Dilemmas in regulation of the market for pharmaceuticals. *Health Aff* 2003;22(3):31-41.

¹⁹² Neumann PJ 2004. Why don’t Americans use cost-effectiveness analysis?

¹⁹³ Luce BR 2005.

¹⁹⁴ In April 2005, NICE merged with the Health Development Agency and took the name of National Institute for Health and Clinical Excellence.

¹⁹⁵ NICE guidance does not apply to the entire United Kingdom. Guidance relating to health technologies and clinical practice applies to the NHS in England and Wales; guidance on interventional procedures applies to the NHS in England, Wales and Scotland; and guidance on public health applies only to England’s NHS. See <http://www.nice.org.uk/> for additional information

health, health technologies and clinical practice guidance. Topics for guidance are nominated by a range of stakeholders, including health professionals, patients, members of the Department of Health and others. Guidance developed by NICE does not represent a mandate to the NHS to implement or deny provision of any particular health technology. However, NICE guidance is used by the NHS in setting policy and is referenced by a range of other stakeholders in providing health care and making policy decisions.¹⁹⁸

From its inception, economic considerations have been a part of NICE's role. In addition to other key priorities, NICE guidance is intended to help the NHS make resource allocation decisions in order to achieve the greatest possible value for its health care expenditures.¹⁹⁹ Economic evidence is reviewed as part of NICE's guidance regarding new and existing pharmaceuticals, treatments, devices, diagnostics and health promotion strategies. For example, a 2003 technology appraisal guidance on the use of coronary artery stents assessed the CE of percutaneous coronary interventions (e.g., angioplasty), considering the CE of different procedures (e.g., coronary artery bypass grafting) and angioplasty with and without bare metal and drug-eluting stents.²⁰⁰

One of the case studies examined the NICE appraisal of Relenza. In its first ever evaluation (1999), NICE concluded that clinical trial data did not demonstrate sufficiently Relenza's efficacy to justify the costs of the drug and the strain it would place on the nation's health system.²⁰¹ While the NHS heeded NICE's guidance, many patient groups, politicians and members of the pharmaceutical industry criticized it, claiming that it constituted rationing. In late 2000 (and again in 2003), NICE issued revised guidance regarding Relenza, authorizing prescription of the drug to patients who meet various criteria designed to ensure that the flu is diagnosed early and accurately. NICE asserted that these revisions showed its commitment to evidence-based medicine, while others claimed that no new compelling evidence existed and that the committee's reversal was just a response to earlier criticisms.

2) Australian and Canadian Approaches

Australia and Canada have been early adopters in requiring economic evidence from pharmaceutical companies and incorporating that evidence into pharmaceutical reimbursement decisions. In 1993, Australia initiated its Pharmaceutical Benefit Scheme (PBS), which requires pharmaceutical companies to submit evidence on the CE of new drugs. As part of this system, companies submit economic evidence for review by the Pharmaceutical Benefits Advisory Committee (PBAC), along with other clinical and implementation factors.^{202,203}

¹⁹⁶ Secretary of States speech. London, England: National Institute for Clinical Excellence, 1999. Accessed December 21, 2005. http://www.nice.org.uk/emcat.aspx?page=oldsite/back/frank_dobson.htm.

¹⁹⁷ Neumann PJ 2005.

¹⁹⁸ Information about the work of NICE. London, England: National Institute for Health and Clinical Excellence, 2005. Accessed October 21, 2005. <http://www.nice.org.uk/page.aspx?o=249084>.

¹⁹⁹ Secretary of States speech, 1999.

²⁰⁰ Guidance on the use of coronary artery stents. Technology appraisal 71. London, England: National Institute for Clinical Excellence, 2003. Accessed December 21, 2005. http://www.nice.org.uk/pdf/TA71_coronaryarterystents_fullguidance.pdf.

²⁰¹ Relenza: a drug too far? British Broadcasting Corporation, October 26, 2000. Accessed September 1, 2006. <http://news.bbc.co.uk/2/hi/health/990232.stm>.

²⁰² Maynard A 2003.

The Canadian province of Ontario adopted a similar process one year later. In order to be added to the formulary of the Ontario Drug Benefit Plan, pharmaceutical companies are required to submit economic evaluations to the Drug Quality and Therapeutics Committee (DQTC), which makes recommendations to the Ontario cabinet. Similar to the NICE process, DQTC recommendations are not binding on the Ontario government, however DQTC recommendations about which drugs should be reimbursed are almost always adopted.²⁰⁴ While the Australian PBS system is considered by some to be the “gold standard” (or most stringent) for such processes, some have noted the closed nature of the process and called for greater transparency in PBAC’s deliberations and criteria.^{205,206,207}

V. Potential Implications for the Food and Drug Administration

Key Messages

- The limited use of economic evidence among federal agencies is attributed to lack of agency authority, uncertainty about appropriate ways to conduct and apply CEAs and public and policymaker concerns about using cost analyses to limit access to care.
- To the extent that CMS, other public and private sector payers, or health care providers become involved in using CE information in ways that increase market pressure for more cost-effective health care, this would further diminish any rationale for FDA to use CE information in regulating health technologies.
- Despite potential benefits of coordinated activities among federal agencies (e.g., more predictable regulatory and payment processes for new technology manufacturers), obstacles remain to communication of economic data among the relevant agencies.
- Many stakeholders acknowledge the value of federal involvement in developing, sharing and using economic evidence; AHRQ often is cited as an agency that could serve in a coordinating or expert advisory capacity for these efforts.
- Aspects of international models for incorporating economic evidence into decision-making are relevant for public and private sector efforts in the US

As described above, multiple federal agencies are involved to varying extents in generating and using CE and other cost-health tradeoff evidence. Although interest in this area is growing, the actual use of economic evidence in federal health decision-making remains limited. Among the reasons cited by interviewees for this study and in the literature for the limited use of economic evidence are:

- Perceived lack of authority to use economic evidence within the mission of an agency (e.g., FDA).
- Lack of political will to change current laws to incorporate economic evidence into decision-making.
- Political and social unease with using CE criteria to inform health policymaking.
- Concerns from health technology manufacturers about how CE or other economic evidence submitted to regulators or payers might affect the market success of a technology.

²⁰³ Taylor RS, Drummond MF, Salkeld G, Sullivan SD. Inclusion of cost effectiveness in licensing requirements of new drugs: the fourth hurdle. *Br Med J* 2004;329:972-5.

²⁰⁴ Laupacis A. Incorporating economic evaluations into decision-making. The Ontario experience. *Medical Care* 2005;43(7):11-15-19.

²⁰⁵ Outtersson MK. Free trade in pharmaceuticals. *Med J Aust* 2004;181(5):260-1.

²⁰⁶ Lu CY, Ritchie J, Williams KM, Day RO. Recent developments in targeting access to high cost medicines in Australia. *Aust New Zealand Health Policy* 2005;2(1):28 [Epub ahead of print].

²⁰⁷ Taylor RS 2004.

- Continuing debate about the appropriate ways to conduct and apply CEAs (e.g., proper thresholds for determining CE).

As described above, FDA currently does not use CE or other economic evidence, mainly because these considerations are not specified in its mandate to review safety and effectiveness of regulated products. However, other federal activities regarding economic analyses may have implications for the current mission of the FDA. The CMS guidance on coverage with evidence development (CED) is a policy development that could have potential impact for the FDA. The 2006 revised CED guidance does not mention the collection of any cost or resource utilization measures as part of CED. Still, clinical data that is collected for CED for technologies that are regulated by FDA could supplement postmarket surveillance efforts of FDA.

If FDA were to consider economic evidence as part of its premarket review, postmarket surveillance or other regulatory activities, it likely would encounter some of the challenges listed above. To the extent that CMS, other public and private sector payers or health care providers become involved in using CE information in reimbursement, acquisition or other health care delivery decisions, this could increase market pressure for more cost-effective health care. This also might diminish any rationale for FDA to use CE or related economic analyses in regulating health technologies.

A. Collaboration between FDA and Other Stakeholders

1) Federal Stakeholders

Few collaborative models exist among the federal stakeholders to facilitate incorporation of economic analyses in health care decision-making. Rather, cost-related activities in each federal agency tend to operate largely independently. There are a few exceptions to this finding, which involve collaboration between AHRQ and other federal entities to foster development of CE or other economic evidence, as follows.

- **AHRQ and FDA (and other federal agencies).** With certain other federal agencies, including FDA, AHRQ has facilitated the use or review of CE information.²⁰⁸ In the late 1990s, AHRQ assisted FDA staff in reviewing and evaluating the state of the science of CEA and the use of patient-reported outcomes to help the FDA understand opportunities to use these methods in evaluating new drugs and devices better. According to AHRQ, as a result of this collaboration, the FDA was to have addressed the use of CEA and patient-centered outcomes as part of guidance for product claims in labeling and advertising.^{209,210} However, these guidelines do not appear to include a CE component.
- **AHRQ and CMS.** CMS commissions AHRQ to conduct technology assessments for selected technologies that occasionally incorporate CE or other economic analyses. At times, other federal agencies may be part of the effort AHRQ initiates to fulfill these requests. In the case of the iFOBT technology assessment, a representative from NCI was involved in the

²⁰⁸ Fact sheet: focus on cost-effectiveness analysis at the Agency for Healthcare Research and Quality, 2001.

²⁰⁹ Draft guidance for industry: providing clinical evidence of effectiveness for human drug and biologic products. Rockville, MD: US Food and Drug Administration, 1997.

²¹⁰ Guidance for the use of HRQL to support medical product claims in labeling and advertising (under development). Rockville, MD: US Food and Drug Administration, 1999.

assessment.²¹¹ In other cases, AHRQ and CMS work in parallel to generate evidence on clinical attributes and CE or cost-health tradeoffs of a new technology. For instance, in the case of lung-volume-reduction surgery, CMS and the National Heart, Lung and Blood Institute co-sponsored a large, multi-center clinical trial, and AHRQ provided funding for a parallel CE study using claims and reimbursement records provided by CMS.²¹²

- **CMS and FDA.** Although not specific to cost, there are recent examples of FDA and CMS communicating prior to market approval of a new technology, which may facilitate more timely, and potentially concurrent, decisions regarding FDA market approval and Medicare coverage of a new technology. During clinical trials, technology manufacturers may draft a Letter of Authorization allowing communication between FDA and CMS related to review of a particular technology. In the case of DES, coordination between CMS and the FDA (facilitated by company representatives) occurred, allowing for parallel creation of new Medicare reimbursement codes and market approval of the technology. This near simultaneity, however, was not motivated by economic evidence. Indeed, to date, this avenue has not been used to enable transfer of cost-related information, and there is no indication to date that FDA or CMS would seek such information through this type of agreement. Nevertheless, as exemplified in the unusual instance of DES, communication between industry and key federal agencies leading to parallel review processes by FDA and CMS can improve market conditions for launching a new health technology.

2 Nonfederal Organizations

In principle, interaction between federal and private sector groups could occur at nearly every point along the health care continuum. In practice, interaction varies depending on the type of private sector stakeholder and priorities of the federal agency. Typical interactions are described below, with emphasis on contact between private stakeholders and FDA.

- **Health technology manufacturers** tend to have more contact with FDA during the product approval and postmarket phases. These interactions focus largely on matters of safety and effectiveness, along with such aspects as good manufacturing practices and other regulatory compliance, but not on economics. Industry stakeholders report that they occasionally share economic information with CMS, mainly as part of payment level determinations following coverage. Industry members facilitated communication between CMS and the FDA shortly before DES were approved and received new Medicare reimbursement codes.
- **HTA vendors** such as BCBSA TEC, ECRI and HAYES, Inc., can interact with federal agencies concerning CE and other economic considerations. For example, while BCBSA TEC has minimal interaction with federal agencies as part of producing its technology evaluation reports, it interacts with AHRQ in its role as an EPC, producing systematic evidence reviews for that agency. As HTA groups often assess new and emerging technologies, they sometimes are asked by federal agencies to report findings on topics of interest. This was the case in 1997, when BCBSA TEC presented findings of its report on the CE of

²¹¹ Technology assessments for screening immunoassay fecal-occult blood test (CAG-00180N). Baltimore, MD: Centers for Medicare & Medicaid Services, 2003. Accessed January 3, 2006. <http://www.cms.hhs.gov/mcd/viewtechassess.asp?id=87>.

²¹² Ramsey SD, Sullivan SD. Evidence, economics, and emphysema: Medicare's long journey with lung volume reduction surgery. *Health Aff* 2005;24(1):55-66.

computer-assisted Pap smear technology to an interagency task force. Although interaction may not be formalized, materials produced by health HTA vendors often are used by federal and nonfederal health care stakeholders.

- **Private payers and health benefit managers** generally do not have formal interaction with federal health agencies with regard to development or use of CE or other economic information. Payers typically do not cover technologies regulated by the FDA until the agency clears or approves them for market. Private payers often acknowledge that they observe and are influenced by CMS payment policies. Most payers have special provisions to pay for certain costs associated with the use of investigational technologies (e.g., cancer chemotherapies) in the context of clinical trials meeting certain conditions (e.g., being conducted under NIH protocols).
- **Providers and provider associations** may interact with FDA during product approval and postmarket phases. This might occur, for instance, if a specialty provider group is involved in advocating the approval of a new diagnostic test or related medical technology based on grounds of safety and efficacy. These groups also may interact with CMS as part of agency development of coverage or payment policies, e.g., establishing a new code or payment level for a new diagnostic or treatment procedure.
- **Consumers** currently have little interaction with federal agencies regarding CE or other cost-health tradeoff evidence. As health care costs continue to rise and cost-sharing and consumer-driven health decisions become more prevalent, consumers may seek to exert pressure on government, as well as health care providers and manufacturers, to generate and make available more information about health and economic trade-offs of technologies and services. Advocacy from the growing population of Medicare beneficiaries could affect CMS's current use of economic evidence. For example, Medicare beneficiaries might seek cost information as part of plan selection for Part D prescription drug coverage.

B. Obstacles to Transfer of Economic Knowledge Among Federal Agencies and Potential Implications

Certain obstacles impede communication of economic data among federal agencies. The primary obstacles generally relate to a lack of knowledge about CEAs and other economic activities within and among federal agencies, as follows.

- **Within federal agencies, especially larger ones, it often is not feasible for staff to maintain an understanding of all current cost-related work underway across their agencies.** Often, economic studies are conducted by more than one part of an agency. For instance, one unit of a large agency may be working on CEAs pertaining to a particular disease or technology, while another unit is working on an unrelated economic study. Without a central or shared reference of cost-related studies sponsored by the agency, staff are not always aware of the investigators involved if they receive a request for information from outside of the agency.
- **Federal agency stakeholders often identify certain agencies (typically AHRQ) as being involved in CE studies, but are uncertain about the development or use of CE or other economic information in other agencies.** To the extent that stakeholders in the federal government are unaware of activities in other agencies, they may be less aware of opportunities for interagency collaboration or information exchange. For instance, while

CMS explicitly does not consider CE pertaining to new health technology, some stakeholders in the field believe that CE evidence does play a role, if only an implicit one.

- ***Within the federal government, the availability of internal CE expertise may not support broader CEA efforts.*** According to some of our interviewees, due to staff turnover, many federal agencies have lost staff with CEA expertise and have not replaced this expertise. Therefore, even within federal agencies, key staff may not be in place to help translate economic evidence into meaningful findings and facilitate communication with other federal stakeholders.

In addition to these obstacles, communication may be limited by agency mandates and missions. As noted elsewhere in this report, the FDA is mandated to review safety and effectiveness data, but not economic factors.

Given that efforts to generate and use CE and other cost-health tradeoff evidence are underway in multiple federal health agencies, increased collaboration, communication and transfer of economic knowledge may allow federal agencies to:

- Avoid duplicative efforts
- Maximize value of investing in health economic research if the findings are applicable or useful to a range of agencies
- Develop a means for broader priority setting of CEAs and related economic analyses
- Translate CEA and related economic findings into practice more efficiently
- Achieve greater system-wide efficiency and potential cost savings

C. Value of Expanding the Role of Cost-effectiveness and Other Economic Evidence and Potential Implications for the FDA

Many interviewees perceived value in enhancing federal involvement in generating and using CE and other economic evidence for policymaking. In raising opportunities for expanding federal involvement, interviewees often cited AHRQ as the best-positioned federal facilitator. Some stakeholders have suggested that AHRQ's existing framework for evaluating clinical evidence, particularly in the EPC program, could be adapted effectively for economic evidence.²¹³ Indeed, some EPC reviews have focused on CE or related economic issues. Consistent with the current EPC framework, AHRQ could implement a system in which priorities are set for CE topics in an open and transparent process. Using this type of approach could help address stakeholder concerns about lack of prioritization in CE research, as well as help make economic information more accessible to health care decision-makers.²¹⁴

Building upon current efforts, stakeholders suggest that AHRQ may have a continued role as a source of expertise on CEA. For instance, if Congress were to endorse a public-private partnership to consider CE evidence in health care, AHRQ could serve in a coordinating or expert advisory capacity. If this type of arrangement were adopted, it could help to formalize

²¹³ Helfand M 2005.

²¹⁴ Ibid.

the development and use of CE evidence in decision-making, perhaps paving the way for other federal agencies, including the FDA if appropriate, to consider economic evidence explicitly.

As FDA's mandate pertaining to health care products does not address economic matters, the use of cost-related information by private sector stakeholders currently has little or no impact on the agency. If FDA were to expand its mission to include cost considerations, some of the cost-related work conducted in the private sector would become relevant to agency decisions. In particular, manufacturers would be more likely to collect cost data as part of clinical trials in support of market approval of new products. It is more likely, however, that FDA will not undertake cost or CE as a consideration in market approval of regulated products, but that FDA will confer with CMS, AHRQ, NIH, DoD, VHA or other federal agencies about anticipating emerging technologies subject to their respective missions. To the extent that these missions include matters pertaining to costs or to health and economic tradeoffs of technologies, these agencies might share information or try to align their evidence requirements accordingly.

Various health economists and other experts also suggest that a new or existing organization could be designated for conducting CEAs on new health technologies, for example:

"A strong, independent organization to conduct or evaluate CEAs would also be beneficial. Public organizations, such as the USPSTF, have made some progress. Government agencies, such as the Agency for Healthcare Research and Quality and the National Institutes of Health sponsor selected CEAs. However, a clearly articulated policy for coordinating CEA research across [HHS] agencies has never existed.

"A new agency within the US Department of Health and Human Services could be established, but political forces would conspire against it. A better idea is to create a quasi-public entity like the Institute of Medicine to judge the cost effectiveness of new therapies, though it too would be hard-pressed to weather the political storms. In the end, the best hope may be a decentralized reform like the emerging Academy of Managed Care Pharmacy formulary guidelines. Such reform could permit explicit considerations of value without the fallout of centralized government assessments."²¹⁵

D. Relevant Lessons for the FDA and Other US Stakeholders from International Use of CE and Related Analyses

Given that the FDA is responsible for reviewing regulated technologies for market approval and not to make reimbursement decisions, the Australian and Canadian processes for incorporating economic evidence into reimbursement policy are not particularly relevant for the FDA, though they may be for payers. Also, through approaches such as the Academy of Managed Care Pharmacy (AMCP) format for formulary submission and others, certain US stakeholders already have begun to review economic evidence for pharmaceutical policymaking. Elements of the Australian and Canadian systems may have relevance for these and other stakeholders in strengthening the use of CE information for reimbursement of pharmaceuticals or instituting a system to consider economic data. Given contemporary uncertainties regarding the way that CE and other economic evidence is used in policymaking,

²¹⁵ Neumann PJ 2004. Why don't Americans use cost-effectiveness analysis?

a system such as Australia's, which is less transparent and amenable to stakeholder input, likely would not help to foster the use of economic evidence in US policymaking.

While the NICE process for technology appraisals and similar reviews is not analogous to FDA processes for evaluating safety and effectiveness of its regulated health care technologies, the NICE model may be of interest regarding introducing CE and other cost-health tradeoff considerations into the US system in a more formal and standardized way. As noted above, more than half of the interviewees referenced NICE, and many implied that a NICE-like system may be useful in the US. Some attributes of the NICE process that interviewees regarded as being attractive for the US include the following:

- ***NICE employs an open approach, including input from multiple stakeholders.***²¹⁶ Transparency, openness and general consistency of the NICE process of receiving feedback and evidence from a range of stakeholders, including industry, ensures that NHS adopts an inclusive view of a particular health care issue and engenders a sense of collaboration and trust in the larger community.
- ***Guidance issued by NICE is not mandatory or binding on the NHS.*** This has symmetry to certain existing systems in the US, including the FDA advisory committees in approval decisions and Medicare Coverage Advisory Committee (MCAC) recommendations for coverage to CMS.
- ***NICE is a Special Health Authority in the NHS.*** As such, NICE regards itself as an independent source of guidance, helping to diminish concerns about inherent bias or conflict of interest it could have in advising NHS.
- ***The NICE model brings together staff with expertise to evaluate the quality of economic evidence and marshals supplementary external experts, as needed.*** Given concerns about the use of CEA in health care, having appropriate institutional expertise is critical to producing well-respected and useful assessments.

These attributes could be considered in establishing any function in a federal agency for conducting CEs and other economic analyses for informing new health technology decisions. Any such efforts should involve an open and transparent process for review, which would lend greater authority to and acceptance of policy recommendations.

VI. Summary of Key Findings and Policy Implications

A. Summary of Key Findings

Citing an environment of rising health care costs and insufficient access to care for many Americans, nearly all stakeholders interviewed recognized some potential value of using CE or other cost-health tradeoff evidence in decision-making pertaining to new health technology. While recognizing this potential value, interviewees also expressed caution regarding how economic evidence is and could be incorporated into policymaking. Many interviewees stressed that economic evidence should not be applied for cost control alone or rationing of safe and effective interventions, and that any considerations of CE or other cost-health tradeoffs should be inputs to a broader set of important factors mediating the introduction and use of

²¹⁶ Neumann PJ 2005.

new health care technology. Further, interviewees acknowledged tension in relationships among certain stakeholder groups concerning matters such as transparency, openness and clarity of the process for incorporating economic evidence. Responses about the development, current use and potential use of economic evidence tended to differ by the type of stakeholder interviewed. Among federal stakeholders, perspectives about the role of FDA were influenced by the extent of interaction between the interviewee's agency and FDA. Broad findings regarding the use of CE and other cost-health tradeoff evidence in health care, as well as findings specific to the FDA, are provided below.

1) Broad Findings Regarding Current Use of Economic Evidence in Health Care

In general, formal use of CE evidence in the US is less common than in certain other nations, including Australia, Canada and the United Kingdom. There are many potential explanations for the differential uptake of CE evidence in the US and abroad. The literature in this area cites potential obstacles such as methodological concerns, insufficient training, legal concerns, insufficient trust and social acceptance and health system and political barriers. Stakeholders suggested that trust, social acceptance and political will may be among the most important of these factors.

Currently in the US, a number of key federal agencies are involved in developing CE or other cost-health tradeoff evidence and applying this evidence to decision-making. For each agency, the extent of and authority for development and use of economic evidence is prescribed largely by the agency's legislated mission and any applicable regulations. Five agencies were identified as having a role in development of CE or other cost-health tradeoff evidence, including AHRQ, CDC, CMS, NIH and the VA. In diverse ways, federal agencies sometimes also consider, review or use CE or other economic evidence to inform certain decisions (e.g., payment level, benefit structure, program impact). These agencies include AHRQ (USPSTF), CDC, CMS, DoD, FDA and the VA. While interviewees generally were familiar with the use of CEA in one or more of these federal agencies, the one most frequently cited was AHRQ.

Although these agencies have some role in the development or use of economic evidence, the overall level of use of economic evidence in decision-making for new health technologies is relatively low. Across the four case studies, none of these agencies explicitly incorporated economic considerations into their decision-making processes for the selected technologies. When economic factors were involved, they were more tangential to the process, e.g., informing CMS about which technologies to evaluate for coverage rather than whether to cover a particular technology.

Health economists and other stakeholders suggested that CE and other economic evidence can serve as an important input to inform more effective and efficient health decision-making in the US. Especially given rising health care costs and system constraints, many of our interviewees expressed that greater and more explicit adoption of CEA by CMS, other federal entities and private sector payers would inform more credible resource allocation decisions and contribute to better value in health care. There was not consensus among stakeholders interviewed regarding the most appropriate point in the technology lifecycle for use of CE or other cost-health tradeoff evidence. However, stakeholders also were careful to note that patient health considerations are of greatest importance, and that economic factors can be among multiple considerations in health policy or clinical decisions.

Stakeholders suggested that one of the system constraints that may impede increased use of CE evidence is the current lack of standard criteria for determining when economic factors are relevant and how they are to be used in decision-making. Technology manufacturers expressed that, when they submit economic data to federal agencies like CMS, they are uncertain how the information will be used and how it will affect adoption and payment of their technology. Specifically, industry stakeholders expressed concerns that economic evidence may be weighted too high relative to other important factors, thereby diminishing matters of clinical utility and patient access. As highlighted in the ICD case study, industry and professional association stakeholders may perceive that economic factors are at the root of decisions, while decision-makers maintain that clinical evidence drives decision-making. These and other concerns contribute to industry's perception that current applications of CE and other economic evidence in health care delivery and policy decisions are lacking in transparency and resulting in somewhat unpredictable outcomes.

Both manufacturers and payers articulated issues that may arise because there currently is not a uniformly accepted standard for information included in CEAs. Manufacturers expressed that payers provide little or no guidance regarding what should be included in CEAs to support payment decisions. As a result, manufacturers use varying assumptions and endpoints in these analyses and then, when they submit these analyses to payers, the payers find that the CEAs did not employ desired endpoints or assumptions. From the standpoint of public and private payers, CE models submitted by manufacturers often are insufficiently relevant to decision-making. For instance, payers indicated that manufacturers are not always explicit about assumptions used in CE models, and that these models often are not designed for interactive use by payers.

In addition to concerns about how CE and other cost-health tradeoff evidence will be used and how economic analyses should be designed, many stakeholders also indicated that there is currently no national, standardized process for setting priorities among health issues that may merit economic analysis. Many federal and nonfederal stakeholders emphasized that the US lacks a systematic approach to determining priorities for economic research applying to interventions across a range of health conditions. As a result, current allocations of economic research may not address the most pressing health topics and reviews of economic evidence may not account systematically for variations in the quality of this evidence.

2) Findings Related to FDA and Economic Evidence

Currently, the role of FDA in development or use of economic evidence is very limited. This is due, in large part, to the fact that consideration of CE or other economic evidence is not pursuant to FDA's mission to review evidence of safety and effectiveness during market approval and postmarket surveillance. FDA does have the responsibility to regulate claims of CE made by manufacturers about particular technologies. Many interviewees believed that FDA's regulation of such claims may unnecessarily stifle the availability of useful CE evidence for new health technologies. In addition to regulation of economic claims, FDA also may become involved in assessing CE if it issues a regulation related to a new health technology. If FDA (or any other federal agency) issues new regulations meeting certain criteria, then it is required to conduct a regulatory impact analysis, including of the CE of such regulations, as mandated by EO 12866 and Circular A-4. However, these analyses primarily gauge the impact of an entire regulation and rarely, if ever, pertain to particular health technologies that may be subject to these regulations.

In contrast to the impact analysis pertaining to new regulations, FDA has no statutory authority or mechanism for evaluating the economic impact of guidances. Periodically, FDA issues guidance documents to address clinical trial design, good manufacturing practices (GMPs) or use of new technologies within the blood industry. A 2005 FDA guidance on the use of a particular type of NAT to screen the blood supply received attention from some economists and other stakeholders. Despite the considerable additional cost of NAT and its only incrementally improved effectiveness, FDA formally did not consider the economic impact of this guidance since it has no means in place to evaluate these factors. As described elsewhere in this report, stakeholders interviewed for the NAT case study and the broader environmental scan perceived some merit in developing a mechanism for review of guidance documents. Stakeholders indicated that, if such a mechanism were developed, the reviewing agency would have to establish criteria for evaluating CE or economic impact, determine which stakeholders should be involved and identify an appropriate source of funding. In addition, some stakeholders commented that, while FDA has no formal statutory authority to perform economic impact analyses of guidances, there are no apparent prohibitions for FDA to consider economic evidence when drafting guidance. Therefore, some have suggested that it may be possible for FDA to incorporate economic evidence in this capacity.

FDA, CMS and other stakeholders (including manufacturers) are communicating more often during the review phase for new health technologies. During internal reviews and as a result of this type of communication, FDA may consider resource utilization or other potentially cost-related endpoints (e.g., average length of stay in hospitals) if these endpoints relate directly to safety and effectiveness (e.g., associated with elevated risk of developing secondary/nosocomial infections). Despite increased communication among FDA and these parties, and some greater interest on the part of payers and some other stakeholders in CE and other cost-health tradeoff evidence, this does not appear to be broadening the scope of FDA's focus beyond matters of safety and effectiveness.

Virtually all interviewees expressed that consideration of CE or other economic evidence during market approval or postmarket surveillance could compromise or distract from the FDA's core mission of ensuring safety and effectiveness of regulated health care technology. Many stakeholders emphasized how resource intensive FDA's responsibilities are regarding ensuring safety and effectiveness of health care technology, and that FDA currently lacks the internal capacity and statutory authority to incorporate economic evidence into its decisions. Some stakeholders expressed concerns that weighing economic evidence at the approval phase for a new technology might result in withholding or delaying market entry of beneficial technologies. These sentiments regarding the appropriateness of including economic factors in approval and postmarket surveillance were echoed by many stakeholders interviewed for the case studies.

B. Summary of Stakeholder Suggestions

Stakeholders interviewed were forthcoming about contemporary development and use of CE and other economic evidence, as well as perceived limitations to potentially beneficial applications of such evidence. Some interviewees suggested ways of remedying these limitations. Themes and individual suggestions for using economic evidence for new technologies are compiled here. Stakeholder suggestions are divided into two broad headings: 1) process and implementation considerations; and 2) considerations specific to the FDA.

1) *Process and Implementation Considerations*

The great majority of interviewee suggestions relate to modifying the current system to better incorporate economic evidence into open and transparent policymaking processes. Overarching questions inherent to implementing such provisions address which entities might coordinate the process and potential sources of funding.

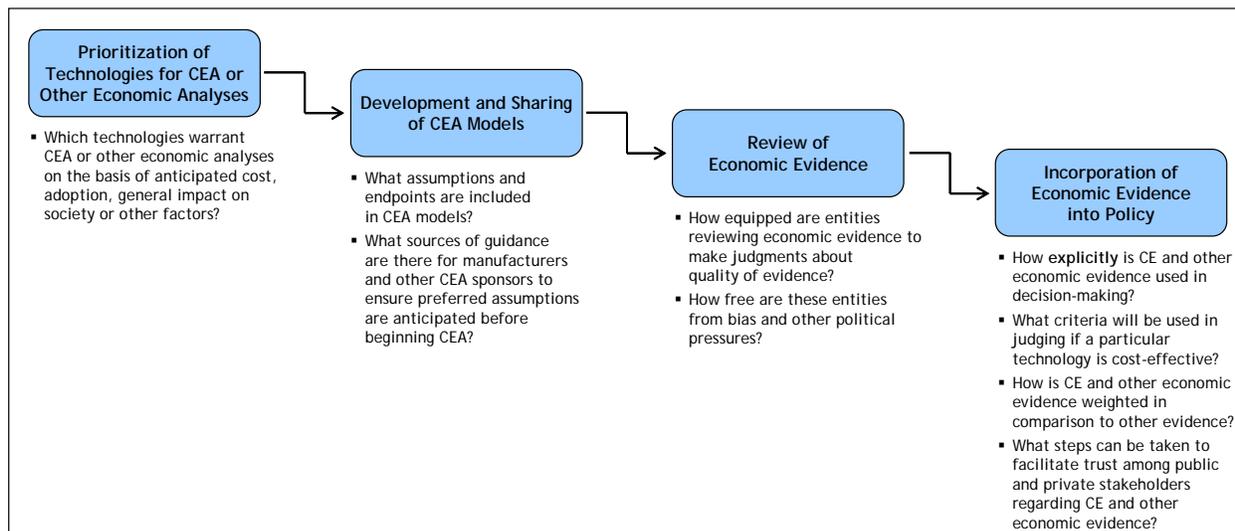
Several options emerged from stakeholder suggestions about the proper entities to coordinate a system for review and use of economic evidence. Among the federal agencies, stakeholders were most likely to identify AHRQ as the most appropriate and best equipped agency to take on this role. Many stakeholders emphasized that AHRQ currently is acting as a facilitator of CE evidence development and use and, hence, would be a natural choice. However, some other stakeholders suggested that any federal entity coordinating such a process would be susceptible to political pressures that might introduce bias into activities.

As such, stakeholders also suggested creating a new entity to fill this role, including either an independent entity within government or a fully independent body. Many stakeholders proposed establishing in the US a body with a role similar to that of NICE in the UK, which acts independently as a Special Health Authority to the National Health Service, providing guidance informed by clinical and economic evidence. Some stakeholders also referenced the Federal Reserve (the central bank of the US) as a similar arrangement that could serve as a potential model. Other stakeholders favored establishing an entity that would act independently of government or industry. Among options discussed was an organization with a status similar to that of the Institute of Medicine, which would be responsible for coordinating the steps involved in setting priorities for and conducting or sponsoring CEAs. Other independent models were offered, including the Pharmacoeconomic Research Institutes (PERIs) model that has been suggested by Princeton economist Uwe Reinhardt. PERIs would be funded to conduct economic research on drugs using funding from a small surcharge on the pharmaceutical industry.

Aside from the PERIs strategy, few suggestions emerged from this environmental scan related to funding new systems for incorporating CE or other economic evidence into policymaking. Nevertheless, stakeholders emphasized that responsibility for funding should be shared by public and private stakeholders, ideally in some form of partnership.

Stakeholder suggestions about individual steps in the process of incorporating CE or other economic evidence into decision-making fall roughly into four main categories, as depicted in **Exhibit 4**, along with relevant questions at each step. Suggestions are summarized according to these four categories.

**Exhibit 4:
Key Considerations for Integrating CE and Other Economic Evidence into Policy**



Setting Priorities Among Technologies for CEA or Other Economic Analyses

Stakeholders emphasized the importance of instituting means to set priorities for determining which technologies warrant CEA or other forms of economic analysis. In suggesting approaches, some stakeholders noted that AHRQ already has instituted a process for identifying topics for clinical evidence assessments as part of its Evidence-based Practice Centers (EPC) program. Similar to the process used by NICE in the UK, the EPC program selects from among topics nominated for systematic evidence review by professional associations, payers, patient groups and other organizations. Some stakeholders suggested that this portion of the EPC process might be expanded to provide a systematic priority setting process for implementing economic studies.

Development and Sharing of CEA Models

Manufacturers often conduct or sponsor CEAs for internal purposes and to share with decision-makers, including payers, providers and others. Stakeholders reported that manufacturers often submit CEA models only to learn from payers that the models do not incorporate assumptions or endpoints preferred by the payers. From their standpoint, payers often find that models submitted by manufacturers are not interactive and that assumptions used in the models are not readily apparent. As such, stakeholders suggested the need for an objective entity or entities to help set standards about assumptions to be used in CEAs and guidelines for manufacturers to help increase transparency of models submitted to payers. Increased clarity may help to guide CEAs conducted or sponsored by technology manufacturers, so that they may be aligned better with payer expectations. This may mitigate manufacturer risk and improve timeliness of decisions regarding market approval and payment.

Review of CE and Other Cost-health Tradeoff Evidence

In addition to establishing guidelines for developing and sharing CEA models, stakeholders suggested that an objective entity might have a role in reviewing CE and other cost-health tradeoff evidence. Some stakeholders proposed that an agency such as AHRQ could have a role in coordinating economic analyses, including evaluating the quality of available evidence and

synthesizing findings from existing literature, in the current manner of EPCs. Well-recognized technology assessment groups such as BCBSA TEC, ECRI or HAYES may have similar roles.

Incorporation of CE and Other Economic Evidence into Policy

To improve the clarity and transparency of current CEA efforts, stakeholders suggested that the private and public sector payers could facilitate greater trust among industry stakeholders by clearly establishing how economic evidence will be used (e.g., for what types of decisions) and its role relative to other technology attributes or criteria. Some stakeholders suggested that establishing a public-private partnership to develop a standard framework for use of CE and other economic evidence may enhance transparency and strengthen trust in these processes.

2) Considerations Specific to FDA

The resounding view of the stakeholders whom we interviewed for both the environmental scan and case studies was that FDA should not consider CE or other economic factors in market approval or postmarket surveillance. As such, no stakeholder raised suggestions for using these processes at FDA. However, stakeholders did offer suggestions pertaining to other ways in which FDA might affect CE or other economic evidence directly or indirectly.

For instance, some stakeholders proposed ways to respond to concerns that FDA's regulation of economic claims made by manufacturers may inhibit availability of CE evidence for new health technologies. One health economist suggested that FDA consider adding disclaimers about assumptions used in CEAs to products advertised using CE claims.²¹⁷ For instance, one proposed disclaimer could read, "This claim of cost-effectiveness is based on assumptions and simulations that may not meet the FDA criteria for claims of efficacy and safety."²¹⁸ As described previously, certain stakeholders raised the potential importance of granting FDA the authority to evaluate economic impact of its guidance documents.

The few stakeholder suggestions pertaining to use of CEA or other economic analyses by the FDA reflected their general concurrence that CEA is beyond the realm of FDA's responsibilities pertaining to marketing and postmarket surveillance of regulated health care technologies. Stakeholders emphasized that expanding the purview of the agency to include matters of CE or other economic evidence, even given a new legislative mandate, would compromise the importance of the agency's core mission pertaining to the regulated technologies.

C. Conclusions and Policy Implications

In an era of rapidly rising health care costs that account for an increasing portion of the GDP, many health care stakeholders call for more effective methods of allocating resources. Cost-effectiveness analysis and other forms of economic analysis that weigh health benefits and costs among alternatives are potential tools to inform decision-making. Today, the use of economic evidence in health care decision-making pertaining to new health technologies is relatively low. There are important potential implications of using, and not using, this evidence.

²¹⁷ Luce BR 2005.

²¹⁸ Ibid.

If cost-effectiveness or other economic evidence is incorporated to a greater extent in decision-making for new health technologies, the following considerations may be relevant:

- ***Greater use by one party could stimulate broader use of economic evidence.*** If certain stakeholders, especially key federal stakeholders such as FDA or CMS, incorporate economic considerations to a greater extent, this could encourage more use among other stakeholders. For instance, if FDA were to adopt economic criteria as part of the approval process, which appears unlikely and is not supported by the vast majority of stakeholders interviewed, it could help clear the path for CMS to introduce similar criteria in coverage or payment decisions. Alternatively, should CMS explicitly adopt economic considerations as part of coverage decisions, private payers may more actively use such evidence or do so indirectly if their coverage decisions are informed by those of CMS. If AHRQ were to take on a larger role with regard to producing or otherwise supporting the generation or use of economic evidence, it potentially could enhance efforts of other stakeholders. Hence, increased use of economic evidence by one stakeholder could amplify use in general.
- ***If certain stakeholders adopt economic evidence into decision-making, this could encourage further economic studies to be conducted.*** If FDA or CMS were to begin to consider explicitly such evidence, manufacturers of drugs, devices and other health technologies may be more inclined to sponsor or conduct CEAs or other economic studies as part of clinical data collection. However, if the results of such studies were not favorable, manufacturers also may have incentives to withhold such evidence. If more economic research were stimulated as a result of increased use of economic evidence, it may be necessary to set priorities among technologies that may merit economic analysis in order to use available research funds efficiently.
- ***To address concerns regarding the use of economic factors in decision-making, stakeholders may need to consider how to ensure that economic evidence is used appropriately and accounts for societal values.*** This could include formalizing ways of using economic evidence and ensuring transparency in relevant decision-making processes.

If the use of economic evidence in health care decision-making is not altered substantially, another set of implications could arise:

- ***Stakeholders, including the public, may have an opportunity to become more familiar with and interested in incorporating economic factors into health care decision-making.*** Currently, there are concerns regarding the use of economic evidence in this context. These concerns can be addressed, at least in part, to the extent that stakeholders continue to standardize the methodology for incorporating this evidence in a transparent way.
- ***If CEA or other economic analyses are not adopted into health technology decision-making, the need for some means of informing health care resource allocation will remain.*** As rising health care costs account for a larger portion of the GDP, the cost of health care technology, particularly new “high-ticket” technologies, will draw stakeholder and public attention.
- ***Aside from resource allocation, not using economic evidence could place financial burden upon certain stakeholders.*** For example, stakeholders interviewed expressed the view that, while FDA guidance documents technically are not binding, they often are perceived that way. If economic factors are not considered during the guideline development process (e.g., costs for various stakeholders of implementing a particular technology), those

responsible for implementing the technology may have trouble managing additional expenses.

VII. Description of Study and Data Limitations

This study used primary and secondary data collection. As part of the environmental scan and case studies, primary data collection involved semi-structured interviews with selected health care stakeholders. Those interviewed for the environmental scan were selected to represent public and private sector perspectives on the use of economic evidence in new health care technology decision-making. In addition, when observations were noted from one stakeholder, we attempted, where possible and appropriate, to verify these observations during other interviews. Although we sought a broad sample of expert interviewees, this was not systematically representative of the relevant health care community. Therefore, broad findings should not be interpreted as representative of all relevant health care stakeholders or particular sectors. These qualifications regarding the interpretation of findings also apply to information gathered in interviews for the case study reports.

Secondary data collection for the environmental scan and case studies involved structured literature searches in databases such as MEDLINE/PubMed and supplementary web-based searches. While we sought to update the content of the report as new policy developments or clinical findings emerged, very recent developments may not be fully explored as part of this report. Given the lag time between completion of a study and publication, it is unavoidable that the published literature (clinical or economic) for new health technologies may be somewhat outdated. For technologies like drug-eluting stents, for which new clinical evidence has recently emerged, published economic analyses have yet to incorporate the latest findings.

A final limitation of this study pertains to insufficient transparency and some uncertainty among many stakeholders regarding how economic evidence is used in decision-making. Although this report highlights certain instances in which the matter of whether economic evidence was used is clear, the answer is not so straightforward in many cases. For instance, descriptions of the use of economic evidence by private payers are limited because private payers often do not publicize their coverage criteria or rationale for particular decisions.

Despite these limitations, this report provides an extensive overview of the ways in which economic evidence currently is and is not used in decision-making regarding new health technologies. This may be useful in informing future policy or other initiatives in this area.

Appendix A: Environmental Scan Protocol

Guiding Research Questions

The guiding questions for the environmental scan included, for example, the following:

Use of Cost-effectiveness and Economic Analyses by FDA

- 1) How and to what extent can FDA use cost-related analyses to inform decision-making? This will include, but not be limited to the following key questions:
 - a) What are the circumstances under which FDA can request and use cost-related analyses in decision-making, guidance development, regulatory policy or for other purposes? What are the sources and boundaries of this authority?
 - b) What gaps currently are present in the development and use of cost-related analyses/information by FDA? What challenges might these pose to fulfillment of FDA's mission?
- 2) How and to what extent has FDA used cost-related analyses to inform decisions historically?
- 3) What are the implications of using or not using cost-related analyses, including examples (e.g., specification of a particular technology for NAT testing)?
- 4) What is the value of extending/altering FDA's authority to request and use cost-related analysis? What relevant criteria might be used to inform circumstances of use? What implications would this have for the FDA? What implications would this have for other health stakeholders?

Use of Cost-effectiveness and Economic Analyses by DHHS and other Relevant Federal Agencies

- 1) How do DHHS (e.g., CMS, CDC) and other federal agencies with health-related responsibilities (e.g., VA, DoD) use cost-related analyses in their decision-making?
- 2) Do these uses of cost-related information have implications for fulfilling the mission of the FDA now or in the future (e.g., monitoring of safety)?
- 3) How and to what extent do FDA, DHHS and other federal agencies work together to facilitate and incorporate use cost-related analyses in decision-making? What are some of the best examples of collaborative/cooperative models to date?
- 4) What obstacles or gaps currently inhibit the transfer of economic data/knowledge among health stakeholders? What are the implications, risks and benefits of communicating or not communicating this information?
- 5) What is the value of expanding the development, communication and use of cost-related information on new health technologies among health-related federal agencies? What implications would this have for the FDA? What implications would this have for other health stakeholders?

Use of Cost-effectiveness and Economic Analyses by Nonfederal Stakeholders

- 1) How and to what extent do private health stakeholders (i.e., private payers, managed care organizations, group purchasing organizations, health technology manufacturers) use cost-related analyses in their decision-making?
- 2) How and to what extent do private health stakeholders interact with FDA, DHHS and other federal agencies regarding development and use cost-related analyses? What are some of the best examples of collaborative/cooperative models to date?
- 3) Do these uses of cost-related information have implications for fulfilling the mission of the FDA now or in the future (e.g., monitoring of safety)?

Use of Cost-effectiveness and Economic Analyses Outside of the US

- 1) Are there best practices examples (relevant to the US health system) of how other nations (e.g., the United Kingdom, Canada, Australia) have applied and/or shared cost-related data to enhance health decision-making?
- 2) Is integration of these best practices feasible in the US health system? What are the implications of adoption for FDA, DHHS and other health stakeholders?

Considerations for Development and Communication of Health Economic Information

- 1) Are some types of cost-related analyses better for answering certain questions than others? Is there a standard framework or criteria for selecting and using a certain method based on the question? Is there a particular type of analysis that is more interpretable and/or useful to the public, policy and health decision-makers?
- 2) What data sources are available for certain types of cost or cost-effectiveness analyses? What gaps/obstacles in collecting and analyzing cost-related data relevant to FDA and other stakeholder decision-making exist (e.g., insufficient data, inconsistent data, data collection issues, bias in collection and analyses)? What are feasible options for overcoming these obstacles?

Implementation Considerations

- 1) If FDA or other federal health stakeholders were to expand requirements for cost-related analyses, who should be responsible for conducting and funding these studies (e.g., industry, FDA, a third party organization)?
- 2) Under what circumstances should an agency or organization be required to perform cost-related analyses (e.g., criteria that indicate merit or priority for cost-related analysis)?
- 3) What agencies or organizations are best equipped to provide cost-related analyses (e.g., FDA, ASPE, AHRQ, other third party organizations, life sciences manufacturers)?
- 4) What are the primary implementation considerations for FDA, other agencies of DHHS and other health stakeholders? What are the potential actions or next steps? What are the implications of these actions/next steps?

Appendix B: Case Study Reports

CASE STUDY I: NUCLEIC ACID TESTING

A. Magnitude and Importance

Blood is a highly valued and vital health care resource that is required in a large proportion of medical procedures. In 2001, the most recent year for which data are available, institutions in the US collected more than 15 million units of whole blood and red blood cells, approximately 14 million units of which were transfused to 4.9 million patients.²¹⁹ The volume of blood transfused in the US is estimated to be increasing by approximately 6% each year.²²⁰

The accessibility of safe blood is vital for millions of people in the US, including accident victims, transplant recipients, cancer patients, patients undergoing a wide range of surgeries, and others.²²¹ For this reason, the blood supply is rigorously screened and tested throughout the collection and transfusion process, to ensure its safety. Biological and technological advancements have led to consistent improvements in blood supply safety.²²²

Human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) are the three transfusion-transmitted viruses of greatest concern to health. In particular, concern about the risks of transfusion-transmitted HIV and HCV has led to major advances in blood screening tests.²²³ Blood donations have been tested for the presence of HIV-1 infection (the strain of HIV most commonly found in the US) since 1992 and for the presence of HCV since 1990. Until 1999, testing for HIV-1 and HCV relied on the detection of antibodies or antigens in blood. Detection of antibodies requires that the donor's immune system already has mounted a response against the virus. Detection of antigens necessitates that a certain threshold amount of virus (i.e., viral load) is present in the body. Antibodies and antigens, therefore, are not immediately detectable following infection, creating a "window period" or a time during which a donor can be infected with a virus and still test negative on screening tests.²²⁴

The window period for detecting viral antibodies and antigens using tests developed in the 1990s was 22 days for HIV-1 and 82 days for HCV.²²⁵ An antigen test developed in 1996 reduced the window period for HIV from 22 to 16 days. Together, antibody and antigen tests (collectively known as serologic tests) lowered the risk of HIV infection from a single blood transfusion to approximately 1 in 676,000. Serologic tests to detect HCV reduced the risk of

²¹⁹ How many units of blood are collected each year? Bethesda, MD: National Blood Data Resource Center, 2006. Accessed August 9, 2006. http://www.aabb.org/Documents/Programs_and_Services/NBDRC/faqs.htm.

²²⁰ Ibid.

²²¹ Blood facts. Charlotte, NC: American Red Cross, Carolinas Blood Services Region, 2006. Accessed August 9, 2006. <http://www.redcrossblood.org/facts.htm>.

²²² The Lewin Group. A special report: ensuring blood safety and availability in the US. Washington, DC: Advanced Medical Technology Association, 2002.

²²³ Custer B. Economic analyses of blood safety and transfusion medicine interventions: a systematic review. *Transfusion Medicine Reviews* 2004;18(2):127-43.

²²⁴ FDA approves first nucleic acid test (NAT) system to screen whole blood donors for infections with Human Immunodeficiency Virus (HIV) and hepatitis C virus (HCV). Rockville, MD: US Food and Drug Administration, 2002. Accessed August 9, 2006. <http://www.fda.gov/bbs/topics/ANSWERS/2002/ANS01140.html>.

²²⁵ Ibid.

receiving HCV from a unit of blood to less than 1 per 100,000 screened units of blood.²²⁶ Thus, though the risk is very small, infected blood still may be missed using serologic testing.²²⁷

B. Overview of the Technology

A key technology used to ensure the safety of the blood supply is nucleic acid testing (NAT), which can detect the presence of viral genes in blood.²²⁸ NAT, also known as nucleic acid amplification technology, relies on polymerase chain reaction techniques to achieve billion-fold amplification of the target gene.²²⁹ Tests can be conducted on “minipools” of 16-24 plasma samples (MPNAT) or on individual donations of blood (IDNAT).²³⁰ NAT can be used to detect viral contamination in whole-blood donations and in donated blood components, such as plasma, red blood cells and platelets. Because it does not rely on the immune system to develop antibodies or the viral load in the body to exceed a certain level, NAT further minimizes the window period during which a virus is undetectable. NAT reduces the window period for detection of HIV-1 by approximately 50%, from an average of 22 days to 12 days. The window period for HCV is reduced from 82 days to 25 days, a decrease of 70%.^{231,232}

Under the regulatory mechanism of an FDA Investigational New Drug (IND) approval, blood banks in the US have used NAT to screen blood donations for both HIV-1 and HCV since 1999.²³³ At that time, it was estimated that the cost of using NAT would add an additional \$5 to \$7 to each blood donation.²³⁴ NAT received full FDA approval in 2002.²³⁵ In 2004, the FDA licensed NAT to screen blood for HIV-1 and HCV and issued guidance recommending that all blood donations that were non-reactive to antibody testing be screened using NAT. Because both antigen testing and NAT test for direct markers of HIV, the FDA’s 2004 guidance stated that HIV antigen testing is unnecessary when HIV-1 NAT is used.²³⁶

Between April 1999 and December 2004, approximately 50.3 million units of blood were tested for HIV using NAT in the US, and approximately 53.3 million units of blood were tested for HCV. Of the blood tested, 18 units tested positive for HIV that had tested negative using

²²⁶ The Lewin Group, 2002.

²²⁷ FDA approves first nucleic acid test (NAT) system to screen whole blood donors for infections with Human Immunodeficiency Virus (HIV) and hepatitis C virus (HCV), 2002.

²²⁸ Ibid.

²²⁹ The Lewin Group, 2002.

²³⁰ Busch MP, Dodd, RY. Nucleic acid amplification testing and blood safety: what is the paradigm? *Transfusion* 2000;40:1157-60.

²³¹ FDA approves first nucleic acid test (NAT) system to screen whole blood donors for infections with Human Immunodeficiency Virus (HIV) and hepatitis C virus (HCV), 2002.

²³² Ibid.

²³³ Stramer SL, Glynn SA, Kleinman SH, et al. Detection of HIV-1 and HCV infections among antibody-negative blood donors by nucleic acid-amplification testing. *New England Journal of Medicine* 2004;351(8):760-8.

²³⁴ New, faster blood test may make blood supply safer. *AIDS Alert* 1999;14(11):130-1.

²³⁵ Nucleic acid-amplification testing further safeguards nation’s blood supply, NHLBI study shows. Bethesda, MD: National Heart, Lung and Blood Institute, 2004. Accessed August 21, 2006. <http://www.nhlbi.nih.gov/new/press/04-08-18.htm>.

²³⁶ Guidance for industry: use of nucleic acid tests on pooled and individual samples from donors of whole blood and blood components (including source plasma and source leukocytes) to adequately and appropriately reduce the risk of transmission of HIV-1 and HCV. Rockville, MD: US Food and Drug Administration, 2004. Accessed August 9, 2006. <http://www.fda.gov/Cber/gdlns/hivhcvnatbld.pdf>.

antibody testing, and 230 units that tested negative for HCV using antibody testing tested positive for HCV using NAT.²³⁷ A 2004 study estimated that NAT helped to prevent the transmission of 5 HIV-1 infections and 56 HCV infections between 1999 and 2002.²³⁸ This study also estimated that NAT has reduced the risk of transfusion-transmitted HIV-1 and HCV to about 1 in 2 million blood units.

International prevalence of nucleic acid testing varies. In 2005, NAT was being used to test blood donations in France, Germany, Italy, Spain, Switzerland and the UK.²³⁹ The Australian Red Cross Blood Service began screening all blood donations using NAT in 2000.²⁴⁰ Canadian Blood Services began NAT screening of blood donations for HCV in 1999 and, in 2001, it began using NAT to screen all blood donations for HIV-1.²⁴¹ Between 2001 and 2003, 6.14 million blood donations were screened using NAT in France.²⁴²

Despite the prevalence of HIV and HCV NAT and its ability to minimize the window period for viral detection relative to other blood safety technologies, the cost-effectiveness of NAT is under debate, both in the US and internationally. The cost-effectiveness of NAT has been the subject of several published analyses, as described below.

C. Economic Value of the Technology

Our search for economic studies regarding HIV and HCV NAT returned a total of 4 relevant studies, including 3 primary data studies and 1 secondary/synthesis study. All 3 of the primary data studies used decision-analytic economic models to assess the cost-effectiveness of NAT relative to pre-existing serologic screenings for HIV, HCV or HBV. Of the 4 relevant studies, 2 were written by researchers in the US and 2 were authored by researchers based in other countries. Studies conducted in the US are described separately in this case study from those conducted in other countries.

The terms “cost-effectiveness” and “cost-utility” are used interchangeably in the literature. Formally, cost-utility is recognized as a specific form of cost-effectiveness, where the outcomes of interest are units that reflect patient utility for different levels of health status or quality of life. A common unit used in cost-utility analyses is the quality-adjusted life year (QALY). The literature about these types of economic analyses of blood safety technologies uses both terms.

²³⁷ Busch MP. Window periods, errors and transfusion risks in the era of NAT. Presentation at FDA Workshop on Donor Deferrals in Era of NAT. Rockville, MD: US Food and Drug Administration, 2006. Accessed August 20, 2006. <http://www.fda.gov/cber/summaries/nat030806mb.pdf>.

²³⁸ Stramer SL 2004.

²³⁹ Laperche S. Blood safety and nucleic acid testing in Europe. *Euro Surveill* 2005;10(2):3-4.

²⁴⁰ Effectiveness of blood screening procedures prior to transfusion and organ or tissue screening before transplantation. Copenhagen, Denmark: World Health Organization, Regional Office for Europe, 2006. Accessed August 9, 2006. http://www.euro.who.int/HEN/Syntheses/hepatitisC/20050411_3.

²⁴¹ Nucleic acid testing. Ottawa, Ontario: Canadian Blood Services, 2006. Accessed August 9, 2006. http://www.blood.ca/CentreApps/Internet/UW_V502_MainEngine.nsf/9749ca80b75a038585256aa20060d703/8dfe21e7e9a6322f85256ab100687de2?OpenDocument.

²⁴² Pillonel J, Laperche S. Trends in risk of transfusion-transmitted viral infections (HIV, HCV, HBV) in France between 1992 and 2003 and impact of nucleic acid testing (NAT). *Euro Surveill* 2005;10(2):5-8.

Both primary data studies conducted in the US assessed the cost-effectiveness of NAT from the perspective of the health care system. As described below, one study found the cost-effectiveness of NAT to be uniformly poor (i.e., highly costly per unit of health outcome), with MPNAT for HIV and HCV and the elimination of HIV antigen testing achieving the greatest cost-effectiveness.²⁴³ The other economic analysis conducted in the US concluded that, although the cost-effectiveness of NAT is outside the range of that for most medical and health care interventions, it is not outside the range of accepted cost-effectiveness ratios for established blood safety measurements in the US, such as HIV antigen testing for blood donations and other blood-related interventions such as autologous (for oneself) blood donation prior to undergoing certain surgical procedures.²⁴⁴ The economic analysis conducted in Spain concluded that adding HCV NAT to serological testing would not be cost-effective.²⁴⁵ The systematic review conducted in The Netherlands of cost-effectiveness analyses of blood safety technologies concluded that NAT is not cost-effective.²⁴⁶

1. Research Conducted in the United States

One of the US economic analyses, published in 2003, examined the marginal cost-effectiveness of using NAT for HIV, HCV and HBV in whole-blood donations using 2001 disease incidence data from the American Red Cross.²⁴⁷ The cost-effectiveness of using IDNAT versus MPNAT and the cost-effectiveness of testing for HIV, HCV with or without testing for HBV were all analyzed. This study estimated that the addition of MPNAT to HIV antigen testing would add a total of 62 quality-adjusted life years (QALYs) per year in the US, while the addition of IDNAT would add a total of 90 QALYs per year. The cost per QALY gained for adding IDNAT in addition to HIV antigen testing ranged from \$8.4 million to \$9.1 million, depending on whether HBV testing was included. Adding MPNAT to HIV antigen testing would result in a cost per QALY gained ranging from \$5.8 million to \$7.6 million, depending on whether or not a test for HBV was included. The study found that eliminating HIV antigen testing and using only NAT would reduce costs, but cost per QALY gained would remain above \$4 million. On the basis of these calculations, the authors concluded that the cost-effectiveness of adding NAT to serologic testing is poor. They also concluded that the most cost-effective strategy is to use HIV and HCV MPNAT and to eliminate antigen testing for HIV.

A US study published in 2004 examined the cost-effectiveness of adding either IDNAT or MPNAT to pre-existing serologic testing protocols for HIV, HCV and HBV, both including and excluding HIV antigen testing for blood donated in the US.²⁴⁸ Compared with serologic testing alone, MPNAT was found to save a total of 102 additional QALYs and IDNAT was found to save an additional 115 QALYs. Serologic testing (excluding HIV antigen testing) coupled with MPNAT

²⁴³ Jackson BR, Busch MP, Stramer SL, AuBuchon JP. The cost-effectiveness of NAT for HIV, HCV, and HBV in whole-blood donations. *Transfusion* 2003;43(6):721-9.

²⁴⁴ Marshall DA, Kleinman SH, Wong JB, et al. Cost-effectiveness of nucleic acid test screening of volunteer blood donations for hepatitis B, hepatitis C and human immunodeficiency virus in the United States. *Vox Sanguinis* 2004;86(1):28-40.

²⁴⁵ Pereira A, Sanz C. A model of the health and economic impact of posttransfusion hepatitis C: application to cost-effectiveness analysis of further expansion of HCV screening protocols. *Transfusion* 2000;40(10):1182-91.

²⁴⁶ van Hulst M, de Wolf JT, Staginuss U, et al. Pharmaco-economics of blood transfusion safety: review of the available evidence. *Vox Sanguinis* 2002;83(2):146-55.

²⁴⁷ Jackson BR 2003.

²⁴⁸ Marshall DA 2004.

resulted in an incremental cost-effectiveness ratio (ICER) of \$1.5 million per QALY gained. While including or excluding HIV antigen testing resulted in the same benefit, excluding HIV antigen testing resulted in lower costs. Serologic testing (excluding HIV antigen testing) in conjunction with IDNAT was found to be associated with an ICER of \$7.3 million per QALY gained.

This study confirmed that the cost-effectiveness of adding NAT to current serological testing far exceeds the traditionally recognized, though informal in the US, threshold of \$50,000 to \$100,000 per QALY gained.²⁴⁹ Yet, the authors concluded that the cost per QALY of adding NAT is not outside the range of accepted costs for measures ensuring blood safety.^{250,251} The authors published cost-effectiveness determinations of changes to the blood screening protocol in the US for which cost per QALY ratios far exceeded traditionally recognized thresholds. Despite an estimated cost of \$2.3 million per QALY gained for adding HIV-1 p24 antigen testing (vs. HIV antibody testing only) and an estimated cost of \$2.0 million per QALY gained for the addition of HIV RNA polymerase chain reaction testing (vs. HIV antibody testing only) for screening donated blood, both tests have been implemented.

2. Research Conducted in Other Countries

The US findings are very similar to those reported by international researchers. A 2000 analysis published by researchers in Spain used a decision analytic model to assess the health and economic impact of post-transfusion hepatitis C and to calculate the cost-effectiveness ratio of adding HCV NAT. The study found a cost-effectiveness ratio of \$1.8 million per QALY gained and concluded that, while antibody testing for HCV results in net-savings for the health care system, the addition of HCV NAT results in little gain and comes at a very high cost.²⁵²

A 2002 systematic review conducted by researchers in The Netherlands reviewed 15 cost-effectiveness analyses of blood product safety.²⁵³ The review found antibody testing for HIV and HCV to be cost saving, with a cost-effectiveness of \$3,600 per QALY gained. However, the cost-effectiveness ratio of HIV NAT or HCV NAT was found to be greater than \$1.5 million per QALY gained. The review concluded that, while ratios above \$2 million per QALY gained for blood product safety are accepted in the US, allocation of money to less cost-effective strategies neglects more cost-effective ones with greater health benefits if health budgets are fixed.

3. Study Limitations

At the time of publication of both US economic analyses, the cost of purchasing IDNAT technology was not known, and the cost of MPNAT was fluctuating. Both Jackson et al. and Marshall et al. stated that their conclusions are highly dependent on their predictions of the

²⁴⁹ Although commonly used as a rough threshold for what might be considered a cost-effective intervention, this can vary and is not empirically based.

²⁵⁰ Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *Canadian Medical Association Journal* 1992;146(4):473-81.

²⁵¹ Marshall DA 2004.

²⁵² Pereira A 2000.

²⁵³ van Hulst M 2002.

costs of IDNAT and MPNAT.^{254,255} For this reason, Jackson et al. stated that it cannot be inferred from their study results that one form of NAT is more cost-effective than the other.²⁵⁶

Jackson et al. acknowledged that, because the number of blood samples testing negative with serologic tests and positive with NAT is lower than predicted by window-period modeling, the cost-effectiveness of NAT might be poorer than they reported.²⁵⁷ The systematic review conducted in The Netherlands was criticized by other researchers for including studies from several different geographic regions, which could have confounded comparability of the evidence.²⁵⁸

A systematic review of economic analyses of blood safety and transfusion medicine interventions conducted in the US between 1982 and 2003 identified a total of 19 studies. Among these, 6 were classified as being of high quality, 10 as fair quality and 3 as poor quality. The review highlighted the shortcomings of economic analyses of blood safety in general and specifically called for researchers to describe more explicitly the cost parameters used in their studies and to adopt an analysis perspective that is relevant and useful to decision-makers.²⁵⁹

D. Critical Appraisal of Relevant Decisions

In order to fully understand the role of economic evidence in decision-making regarding HIV and HCV NAT in the US, we consulted with four experts, including one member of academia and three members of industry. We also reviewed guidance documents issued by governmental and private organizations to assess the role of economic evidence in HIV and HCV NAT decision-making.

1. Use of Economic Evidence in HIV and HCV NAT Decision-making

Economic evidence regarding implementation of HIV and HCV NAT is used differently by government and industry. Use of economic evidence relating to HIV and HCV NAT also varies among blood banks in the US.

Decision-making at the FDA

Economic evidence and cost-effectiveness analyses appear to have played no role in the FDA's decision to designate HIV and HCV NAT as INDs or as formally approved tests. The appropriateness of the FDA to not apply economic analyses in this decision was echoed universally by members of the blood banking industry and by academic researchers. Guidance documents issued by the FDA regarding HIV and HCV NAT make no mention of cost-effectiveness or other economic analyses.²⁶⁰ Two experts interviewed for this case study

²⁵⁴ Jackson BR 2003.

²⁵⁵ Marshall DA 2004.

²⁵⁶ Jackson BR 2003.

²⁵⁷ Ibid.

²⁵⁸ Custer B 2004.

²⁵⁹ Ibid.

²⁶⁰ Guidance for industry: use of nucleic acid tests on pooled and individual samples from donors of whole blood and blood components (including source plasma and source leukocytes) to adequately and appropriately reduce the risk of transmission of HIV-1 and HCV, 2004.

expressed the view that, if any economic evidence did play a role in decision-making regarding HIV and HCV NAT, it was not used or discussed transparently.

One expert did describe a presentation given by a leading blood safety authority on the cost-effectiveness of HIV and HCV NAT to FDA's Blood Products Advisory Committee (BPAC) during this decision-making process. BPAC meets four times a year and advises the FDA's Commissioner of Food and Drugs on matters related to biologic and medical devices. According to this expert, the cost-effectiveness analysis was received with some interest, but economic evidence regarding HIV and HCV NAT was not considered by the committee to be relevant to decision-making.²⁶¹

Although it does not pertain directly to HIV and HCV NAT, a 2000 meeting of the HHS Advisory Committee on Blood Safety and Availability, which makes recommendations to the Secretary and whose members include representatives from the FDA, HHS, industry and academia, included discussion of the role that cost-effectiveness analyses could have in decisions regarding blood safety.²⁶² In the minutes of the August 2000 meeting, many members of the committee explicitly acknowledged the limited resources available to devote to health care and specifically to blood safety. The applicability of cost-effectiveness analyses to decision-making regarding blood safety technologies also was noted by many committee members. A leading academic researcher described society's demand for inexpensive, risk-free blood, concluding that, "this committee is the perfect forum for considering options and opportunities." While it does not appear that any Advisory Committee on Blood Safety and Availability meetings included discussions specifically focused on the cost-effectiveness of HIV and HCV NAT, this transcript indicates that cost-effectiveness analyses and their role in decision-making regarding blood safety technologies were discussed in forums that included FDA representatives.

Decision-making at US Blood Banks

Although some sources reported frustration on the part of industry regarding the 2004 non-binding FDA guidance on implementation of HIV and HCV NAT technologies, the general sentiment among members of industry consulted for this case study was that the guidance was expected and that most blood banks were preparing to or had already implemented NAT when the guidance was released. However, some members of industry described the difficulty they faced implementing HIV and HCV NAT as quickly as was recommended.

Use of economic evidence in HIV and HCV NAT decision-making appears to vary across blood banks in the US. At some blood banks, the decision to implement NAT was seen as a societal and ethical obligation, and economic analyses did not play a role in the decision to begin using the technology. Experts at these blood banks expressed the view that any life-saving technology should be implemented, regardless of cost. However, experts at other blood banks said that cost-effectiveness analyses are used in deciding what tests to use and that

²⁶¹ Blood Products Advisory Committee charter. Rockville, MD: Center for Biologics Research and Evaluation, US Food and Drug Administration, 2006. Accessed September 8, 2006. <http://www.fda.gov/cber/advisory/bp/bpchart.htm>.

²⁶² The role of various considerations in decision making related to new and existing blood safety measures. Washington, DC: US Department of Health and Human Services, Advisory Committee on Blood Safety and Availability, 2000. Accessed September 8, 2006. <http://www.hhs.gov/bloodsafety/transcripts/20000824.html>.

cost-effectiveness did play a role in deciding how to implement HIV and HCV NAT. Cost-effectiveness considerations appear to be more relevant for blood banks that test blood that has been collected by other clients.

Blood bank experts universally acknowledged the extremely high cost per QALY gained associated with NAT and the general economic strain it places on blood banks. These experts also described the high cost of purchasing NAT assays and indicated that blood banks are in constant price negotiations with the companies that supply the tests. All experts discussed the growing pressure on blood banks to reduce the cost of blood while adding new tests and improving the safety of the blood supply. Blood banking experts agreed that, while the use of NAT has contributed, in part, to the recent increase in the cost of blood, this increase is owed more to the implementation of other blood safety measures, particularly leukoreduction, which is currently being used by several major US blood banks. Interestingly, several members of industry indicated that they would like to see the FDA take into account cost and cost-effectiveness when issuing guidance regarding blood safety because of the expense associated with the technologies and the economic strain these decisions place on blood banks.

2. Barriers to Use of Economic Evidence in HIV and HCV NAT Decision-making

A variety of barriers to the use of economic evidence in decision-making regarding HIV and HCV NAT were cited during our interviews with stakeholders, including the FDA's mandate to protect public health and the high premium Americans place on a safe blood supply.

Decision-making at the FDA

The FDA is mandated to protect the health of the public by assuring safety, effectiveness and security of drugs and other biological products.²⁶³ According to interviews conducted with FDA staff, it is not mandated to consider cost in individual product appraisal. That the FDA's mandate is to ensure safety and effectiveness of regulated health care products, not cost-effectiveness, was strongly emphasized by all expert interviewees as a reason why economic evidence was not used in HIV and HCV NAT decision-making.

The premium placed on a safe blood supply is further evidenced by the actions of the US Congress, which intervened in favor of increased testing during the FDA's consideration of whether to require HIV antigen testing in 1995.²⁶⁴ One expert interviewed for this case study described a letter written by a member of Congress in 1997 to BPAC expressing what he believed to be the inappropriate influence of cost-effectiveness analyses on decision-making regarding HIV antigen testing and instructing the FDA not to consider cost-effectiveness at all in regard to blood safety. According to this expert, the effect of this letter and other congressional intervention has been long-lasting and continues to influence the role of economic evidence in FDA decision-making regarding blood safety. While fear of the risk of HIV may have been more widespread during the 1990s than it is today, this type of experience

²⁶³ FDA's mission statement. Rockville, MD: US Food and Drug Administration, 2006. Accessed August 30, 2006. <http://www.fda.gov/opacom/morechoices/mission.html>.

²⁶⁴ AuBuchon J, Birkmeyer JD, Busch MP. Safety of the blood supply in the United States: opportunities and controversies. *Annals of Internal Medicine* 1997;127(10):904-9.

underscores the observation of some at FDA and others in government that, in the US, any improvement in the safety of the blood supply is acceptable at virtually any cost.

One expert interviewed for this case study made the point that the two US economic analyses of the cost-effectiveness of NAT were not published until well after HIV and HCV NAT became available both under an FDA IND approval and under a general approval.^{265,266} Although this does not mean institutions could not have commissioned their own economic analyses, these economic analyses were not available, at least in published form, to decision-makers during their deliberations on this matter. However, according to another expert, even had these articles been available at the time of FDA decision-making regarding HIV and HCV NAT, they would likely have had no effect.

Decision-making by the American Public

In addition to obstacles to the use of economic evidence inherent in the FDA's mandate, all experts interviewed for this case study mentioned the extremely high premium placed by Americans on a safe blood supply as a reason why cost-effectiveness was not given more weight in decision-making regarding HIV and HCV NAT. The American public's fear of transfusion-transmitted infection, particularly HIV, was specifically cited by some experts as a major reason for the implementation of HIV and HCV NAT.

The importance that Americans place on ensuring a safe blood supply is expressed throughout the literature on blood safety technology and is used consistently to explain why technologies to improve blood safety have been implemented, despite extremely high costs per infection averted or QALY gained. The authors of both US economic analyses of the cost-effectiveness of HIV and HCV NAT reference fear of catastrophic disease as a reason for NAT's implementation regardless of its high cost.^{267,268} A review of the controversies associated with blood safety technology written prior to the implementation of NAT describes how HIV is perceived differently from other health threats, leading to a desire for extreme avoidance.²⁶⁹ For this reason, transfusion is viewed warily by much of the American public, and matters of cost-effectiveness do not reflect the true concerns of potential blood recipients. One interviewee for this study said that Americans' "fear of abstraction" makes them inherently distrustful of analyses that are meant to capture the costs and benefits of blood safety technologies.

The acceptance of NAT, despite its high cost per QALY gained, is not the only example of the American public's willingness to pay to avoid medical risk, particularly in situations that are considered to be out of the control of the individual. While roughly \$50,000-\$100,000 per QALY gained is a generally recognized, though informal in the US, upper threshold for a cost-effective intervention, the cost-effectiveness ratios of some widely used interventions in the arena of blood safety exceed \$2.0 million per QALY.²⁷⁰ HIV antigen testing and polymerase chain reaction testing were added to blood testing protocols in the US despite incremental

²⁶⁵ Jackson BR 2003.

²⁶⁶ Marshall DA 2004.

²⁶⁷ Jackson BR 2003.

²⁶⁸ Marshall DA 2004.

²⁶⁹ AuBuchon J 1997.

²⁷⁰ van Hulst M 2002.

cost-effectiveness ratios of \$2.3 million and \$2.0 million, respectively. Incremental cost-effectiveness ratios of other blood-related interventions, such as autologous blood donations for such surgical procedures as total hip replacement, coronary-artery bypass grafting, and abdominal hysterectomy, range from \$200,000 per QALY to \$1.4 million per QALY.²⁷¹ Certain categories of other widely accepted health care interventions also tend to have high cost-effectiveness ratios, including transplantation and intensive care interventions, whose cost-effectiveness ratios are on the order of \$100,000 to \$1.0 million per QALY gained, respectively.^{272,273}

Injury- and risk-reducing interventions outside health care are also commonly accepted despite extremely high cost-effectiveness ratios. For example, according to a report covering a wide range of life-saving interventions published in 1995, the ratio for seatbelts for passengers on school buses was estimated to be approximately \$2.8 million per QALY gained and the threshold used by the US Federal Aviation Authority for economic acceptability was about \$2.7 million per human life year saved.²⁷⁴

As noted by an expert interviewed for this study, most Americans are unlikely to be interested in lengthy explanations of how these types of decisions are reached. Understanding tradeoffs of costs and safety associated with blood safety or other technologies may require more attention than most people are willing or able to give, which poses another barrier to using economic evidence to influence views of the American public.

Decision-making at US Blood Banks

Although use of economic evidence varies among US blood banks, experts from several blood banks consulted for this case study described similar barriers to the use of economic evidence in decision-making regarding HIV and HCV NAT. As noted above, some blood banking experts expressed their obligation to society to implement HIV and HCV NAT, implying that a technology capable of saving lives should be utilized at any cost. Thus, cost-effectiveness analyses generally were not considered in decision-making. In addition, several experts described the political difficulty they would have faced had they decided to oppose the implementation of NAT.

3. Use of Economic Evidence in Decision-making Regarding Other Blood Safety Measures

Economic evidence, specifically cost-effectiveness analyses, appears to have played a larger role in decision-making regarding other blood safety measures, including the addition of HBV NAT to testing assays, West Nile virus (WNV) NAT and leukoreduction. In general, economic evidence seems to be given more weight in decisions regarding technologies that have a less direct association with reduced mortality or severe morbidity.

²⁷¹ Marshall DA 2004.

²⁷² Owens DK. Interpretation of cost-effectiveness analyses. *Journal of General Internal Medicine* 1998;13(10):716-7.

²⁷³ van Hulst M 2002.

²⁷⁴ Tengs TO, Adams ME, Pliskin JS, et al. Five-hundred life-saving interventions and their cost-effectiveness. *Risk Analysis* 1995;15:369-90.

Decision-making Regarding HBV NAT and Multiplex NAT for HIV, HCV and HBV

HBV NAT received FDA approval in 2005, 3 years after FDA's approval of HIV and HCV NAT. The clinical consequences of HBV differ substantially from those of both HIV and HCV, with the average morbidity associated with HBV infection much less than that of either HIV or HCV.²⁷⁵ Also, very few units of transfused blood infected with HBV actually result in persistent HBV infection requiring treatment, as infection with HBV results in chronic hepatitis infection in just 2-6% of adults.²⁷⁶ As opposed to HIV and HCV, which can be effectively screened for using MPNAT, HBV can only be effectively detected using IDNAT.²⁷⁷

Both economic analyses of NAT published in the US evaluated the cost-effectiveness of HBV NAT in relation to HIV and HCV NAT.^{278,279} One analysis calculated a cost-effectiveness ratio for HBV NAT of \$66 million per QALY gained, attributing the high ratio to the fact that so few HBV infections progress to a chronic symptomatic state requiring treatment.²⁸⁰ According to another study, the benefit of preventing one HIV infection is 40 times greater than that of preventing one HBV infection.²⁸¹ Both analyses concluded that the addition of HBV to HIV and HCV NAT worsens the overall cost-effectiveness of NAT.

Current FDA guidance considers HBV NAT optional.²⁸² According to one blood banking expert, none of the major US blood banks test blood using HBV NAT, and only 2-3 blood banks in the US use HBV NAT at all. Most of the experts interviewed for this study agreed that economic analyses, particularly of cost-effectiveness, contribute significantly to decision-making regarding whether or not to implement HBV NAT at blood banks. Some experts stated that cost has played a role in decision-making regarding HBV NAT at the FDA. According to one industry expert, there is currently a better understanding of the consequences and implications of not using economic evidence in decision-making relative to the understanding that existed during decision-making for HIV and HCV NAT. This was corroborated by another expert, who said that there is some acknowledgement that the blood safety industry cannot bear all possible improvements to existing tests and that decisions will have to be made about which tests are most important. One expert said that cost-effectiveness analysis of HBV NAT was used explicitly in the decision not to implement HBV NAT at a major US blood bank.

The role of economic evidence in decision-making regarding HBV NAT in government is reflected in recommendations issued by the HHS Advisory Committee on Blood Safety and

²⁷⁵ Donor screening assays for infectious agents and HIV diagnostic assays. Rockville, MD: US Food and Drug Administration, 2006. Accessed August 31, 2006. <http://www.fda.gov/cber/products/testkits.htm>.

²⁷⁶ Hepatitis B frequently asked questions. Atlanta, GA: National Center for HIV, STD, and TB Research, 2006. Accessed September 6, 2006. <http://www.cdc.gov/ncidod/diseases/hepatitis/b/faqb.htm#gen>.

²⁷⁷ Advisory Committee on Blood Safety and Availability Recommendations – August 2004. Washington, DC: Advisory Committee on Blood Safety and Availability, 2004. Accessed August 31, 2006. <http://www.hhs.gov/bloodsafety/resolutions/resaug04.html>.

²⁷⁸ Marshall DA 2004.

²⁷⁹ Jackson BR 2003.

²⁸⁰ Marshall DA 2004.

²⁸¹ Jackson BR 2003.

²⁸² Biswas R. Management of donors and units that test HBV NAT positive: current considerations. Gaithersburg, MD: Blood Products Advisory Committee, 2005. Accessed September 5, 2006. http://www.fda.gov/ohrms/dockets/ac/05/slides/2005-4164S1_07.ppt#381,2,Issue.

Availability. In its August 2004 recommendations, the Committee acknowledged the limited ability of HBV MPNAT to reduce risk of transfusion transmitted HBV relative to HBV IDNAT.²⁸³ The Committee also acknowledged that, while the average morbidity of HBV infection is far less than that of HIV or HCV, HBV MPNAT still incurs a cost comparable to that of NAT for those viruses. In addition, the committee stated that, while vaccination against HIV or HCV is not possible, vaccination is an effective way to prevent HBV. The recommendation concludes that, in regard to the general public health, health care dollars are better spent on expansion of the hepatitis B immunization program than on the introduction of HBV MPNAT. While it is unclear what influence this recommendation has had or will have on decisions made by the FDA, it appears that economic evidence is being considered more transparently in discussions of HBV NAT than in decision-making regarding HIV and HCV NAT.

According to several experts, the FDA is still in the process of deciding whether or not to license a multiplex NAT assay that tests concurrently for HIV, HCV and HBV. One blood banking expert believes that FDA approval of this multiplex assay is contingent solely on evidence that the additional panels will not decrease the test's sensitivity for detecting HIV. According to this expert, the cost-effectiveness of the assay, particularly the effect of the addition of HBV NAT, does not appear to be a factor in the consideration of approval of the multiplex assay. Another expert also expressed the view that decision-making regarding HBV NAT involves analysis of logistics and efficiency only, not cost-effectiveness.

Other experts hold the view that the FDA's considerations of a multiplex NAT assay that includes a test for HBV does involve at least some consideration of cost and cost-effectiveness. One expert said that the FDA is aware of the economic impact that adding an HBV assay to NAT would have on blood banks in the US. This expert speculated that, while the use of economic evidence in decision-making at the FDA regarding the addition of the assay is unclear, economic evidence is being used in deciding whether or not to license and recommend the use of the multiplex NAT. This view was corroborated by another expert who said that, although the FDA cannot engage BPAC in matters of cost-effectiveness directly, it does engage the committee in discussions regarding yield or the number of infections detected by HBV NAT. According to this expert, discussing the yield of HBV NAT is essentially the FDA's way of prompting consideration of costs and benefits associated with the test.

The extent to which cost-effectiveness analysis and other economic evidence are being used in decision-making regarding HBV NAT and the approval of a multiplex NAT assay is not well defined. However, it appears that consideration of cost and cost-effectiveness in those decisions is greater than in decisions made about HIV and HCV NAT by the FDA and by US blood banks.

Decision-making Regarding West Nile Virus NAT

In recent years, West Nile virus (WNV), which can cause encephalitis (or inflammation of the brain), has emerged as a transfusion-transmissible infection in the US blood supply.²⁸⁴ WNV

²⁸³ Advisory Committee on Blood Safety and Availability Recommendations – August 2004, 2004.

²⁸⁴ Custer B, Busch MP, Marfin AA, Petersen LR. The cost-effectiveness of screening the US blood supply for West Nile Virus. *Annals of Internal Medicine* 2005;143(7):486-92.

NAT has been available under FDA IND status since June 2003.²⁸⁵ WNV is transmitted by mosquitoes and, thus, the risk of infection with WNV via that route varies seasonally in most geographic locations, with the risk of infection highest during warmer months.²⁸⁶ As expressed by one expert whom we interviewed, the FDA called on industry to create a test to screen for WNV as soon as the virus was identified as transfusion-transmissible. According to this expert, the matter of cost or cost-effectiveness of implementing WNV NAT was not raised.

A study using results of WNV screening in 2003 found that, while WNV NAT is more cost-effective than HIV and HCV NAT, WNV still is not cost-effective.²⁸⁷ Investigators concluded that year-round national WNV IDNAT is not justified, based on comparison of effectiveness achieved versus resources consumed. According to this analysis, WNV MPNAT for half of the year is the most cost-effective strategy. Other cost-effective strategies include seasonally and geographically targeted individual donation testing. According to a separate study published in 2006, in low-transmission areas with short WNV seasons, using a questionnaire to screen for WNV is the most cost-effective approach.²⁸⁸ The authors concluded that year-round screening offers no further benefit relative to seasonal screening in any of the transmission settings tested.

Despite these findings, current FDA guidance recommends year-round WNV NAT.²⁸⁹ According to one expert, no yield cases (i.e., cases confirmed based on donor RNA or antibody seroconversion or viremia by another assay) have been detected over the first 3 years of screening prior to May or after November. One member of industry expressed frustration with current FDA guidance recommending year-round WNV NAT and expressed hope that the FDA will take into account current cost-effectiveness analyses and move to recommend seasonal testing soon. However, other experts did not expect to see any changes in the FDA's recommendations. One expert noted that, because there are regions in the US where mosquitoes breed year-round, there is always a risk of transmission-transfused WNV in some regions. For this reason, this expert did not expect the FDA to recommend seasonal testing. Another expert said that, from his perspective, there does not appear to be much pressure from US blood banks on the FDA to move to seasonal testing for WNV. According to this expert, blood banks must spend money to reconfigure their blood-testing protocols, so there is not much desire on the part of blood banks to change the current testing protocol. However, this expert did perceive merits of cost-effectiveness analyses of WNV NAT for allowing greater fine-tuning of decisions.

Decision-making Regarding Leukoreduction

Leukoreduction is the filtration and removal of white blood cells, or leukocytes, from whole blood prior to transfusion.²⁹⁰ Leukocytes provide no benefit to the recipient of a transfusion, but can carry viruses and other pathogens that can induce adverse effects such as febrile

²⁸⁵ Custer B, Busch MP, Marfin AA, Petersen LR. The cost-effectiveness of screening the US blood supply for West Nile Virus. *Annals of Internal Medicine* 2005;143(7):486-92.

²⁸⁶ Korves CT, Goldie SJ, Murray MB. Cost-effectiveness of alternative blood-screening strategies for West Nile virus in the United States. *PLoS Medicine* 2006;3(2):e21.

²⁸⁷ Custer B 2005.

²⁸⁸ Korves CT 2006.

²⁸⁹ Rios M, Akolkar P. West Nile Virus: update. Gaithersburg, MD: Blood Products Advisory Committee, 2006. Accessed September 5, 2006. http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4226S1_4.ppt#291,1,Slide 1.

²⁹⁰ Shapiro MJ. To filter blood or universal leukoreduction: what is the answer? *Critical Care* 2004;8(Suppl 2):S27-S30.

transfusion reactions and cytomegalovirus.²⁹¹ According to several industry experts, the benefits of universal leukoreduction, or leukoreduction of all blood donations, are still under debate, as is the cost-effectiveness of the technology. One expert interviewed for this case study said that, although he has been asked several times to evaluate the cost-effectiveness of leukoreduction, he consistently has declined, due to his inability to identify and quantify the clinical benefits it provides. Currently, the FDA does not require or recommend universal leukoreduction.²⁹² However, according to industry experts, several US blood banks currently use universal leukoreduction technologies on all blood.

Economic evidence, particularly analyses of cost, appears to have played a role in discussions regarding leukoreduction held by FDA advisory committees. This is evidenced in the proceedings of the HHS Advisory Committee on Blood Safety and Availability. The Summary of the PHS Advisory Committee on Blood and Availability Meeting, April 25-26, 2000, includes several references to the high cost of leukoreduction and the economic burden it places on hospitals and blood banks. The summary also includes sentiments expressed by blood safety experts about the need to separate economic evidence from scientific evidence regarding leukoreduction and to include economics in decision-making regarding leukoreduction.²⁹³ The minutes from a 2005 meeting of representatives from HHS, FDA and the Center for Biologics Evaluation and Research (CBER) includes reference to the high cost of leukoreduction and whether or not benefits outweigh these costs.²⁹⁴ However, one expert interviewed for this case study said that the FDA's decision whether to recommend universal leukoreduction still centers on clinical, not economic, evidence. Moreover, the extent to which these proceedings influenced or will influence decision-making at the FDA is unclear.

Economic evidence also appears to have played a role in decision-making regarding leukoreduction at US blood banks. An expert from the blood banking industry interviewed for this case study said that the decision to use leukoreduction at US blood banks despite lack of an FDA requirement is the result primarily of competition between blood banks to ensure the safest blood possible. However, according to this expert, US blood banks that have decided not to implement the technology have done so primarily for economic reasons. According to one industry expert, some blood banks have used economic analyses to determine that leukoreduced blood is used most cost-effectively when provided only to patients who require it, such as low birth-weight infants and transplant recipients.

Various explanations were given by experts as to why economic evidence has played a comparatively larger role in decision-making regarding leukoreduction than in decisions made about HIV and HCV NAT. Several key stakeholders identified the lack of a clear correlation between leukoreduction and improved safety as a reason for the increased use of economic evidence in decision-making regarding the technology. As opposed to HIV and HCV NAT, the

²⁹¹ Blajchman MA. The clinical benefits of the leukoreduction of blood products. *J Trauma* 2006;60(Suppl 6):S83-90.

²⁹² Update on leukocyte reduction of blood and blood components public workshop. Rockville, MD: Department of Health and Human Services, Food and Drug Administrations, Center for Biologics Evaluation and Research, 2005. Accessed September 6, 2006. <http://www.fda.gov/cber/minutes/leuko072005t.pdf>

²⁹³ Nightingale, SD. Summary of the PHS Advisory Committee on Blood and Availability Meeting, April 25-26, 2000: committee update. Silver Spring, MD: Advisory Committee on Blood Safety and Availability, 2006. Accessed September 5, 2006. <http://www.fda.gov/ohrms/dockets/ac/00/backgrd/3620b1a.pdf>.

²⁹⁴ Update on leukocyte reduction of blood and blood components public workshop, 2005.

less obvious clinical benefits of leukoreduction appear to have made more acceptable the use of economic evidence in decision-making.

4. Potential for Future Use of Economic Evidence in Decision-making

Among blood banking experts interviewed for this study, there was general agreement that there is potential for increased use of cost-effectiveness and other economic analyses in decision-making regarding NAT and other blood safety tests. The desire for increased use of cost-effectiveness analysis appears to owe, in part, to increasing pressure on blood banks to reduce the cost of blood while continuing to guarantee blood safety. One expert maintained, though, that the premium that Americans place on ensuring a safe blood supply has created a situation in which people expect that any improvement that can be made to blood testing will be made. For example, once the technology is available, this expert predicts an implementation of IDNAT at all blood banks in the US, despite studies showing the poor cost-effectiveness of IDNAT. Although there may be discussion of yield, this expert does not believe cost-effectiveness or other economic analyses will be used in the implementation of IDNAT.

Several experts discussed the need for an entirely new approach to analyzing the cost-effectiveness of NAT and other blood safety measures. New approaches might include a move away from the traditional focus on the incremental cost-effectiveness ratio of NAT, in which NAT only gains the value of the rare window cases it picks up, toward a new focus on what combination of testing yields the greatest net improvement in safety. One expert is pursuing the opportunity to conduct research to assess the current state of cost-effectiveness analyses of blood safety technologies and to specifically analyze the cost-effectiveness of technologies that were implemented prior to the widespread use of these analyses, such as serologic tests. According to this expert, the re-analysis of the cost-effectiveness of blood safety technologies is necessary in order to accurately assess the resources currently being spent on ensuring a safe blood supply. This expert added that analysis of the cost-effectiveness of NAT used alone without concurrent serologic testing also is needed, in order to understand the true economic impact of NAT. Such an analysis also would include an assessment of the factors that have contributed to the lack of attention given to cost-effectiveness analyses of blood safety technologies in the US.

Several experts cited other ways in which cost-effectiveness analyses of NAT and other blood safety technologies can be improved. Clearly, a key aspect is the American public's desire for zero-risk of transfusion-transmitted infections. Better means of conveying the need to weigh the actual level of risk of infection associated with transfusion and the magnitude of costs involved may improve acceptance by the public and policymakers of policies that reflect such tradeoffs. Also suggested was formation of an international working group to draft a set of methods, topics and perspectives that should be used in any economic analysis of blood safety technology. A working group would help to advance the field by calling for uniformity of economic analyses and their utility in the context of blood safety technologies. One expert identified the formation of such a group as a possible outcome of recent and ongoing international meetings of blood safety experts. Another expert suggested a potential move toward larger MPNAT testing pools, which could have a bearing on measures of cost-effectiveness.

Some experts mentioned the potential impact that pathogen reduction technology (PRT) could have on safety and cost tradeoffs in decision-making regarding blood safety. PRT, which is not yet approved by FDA, is designed to inactivate nucleic acids in blood irreversibly, thereby

blocking pathogen replication.²⁹⁵ Because pathogen reduction could eliminate significantly or entirely the need for NAT, the two forms of technology could compete, and economic analyses may be extremely important in deciding which technology to implement. According to one stakeholder, a PRT is nearing FDA approval.

Several experts discussed the increased need for cost-effectiveness analyses in resource-poor countries that are moving toward implementation of NAT. One expert in the blood banking industry referenced a forthcoming World Health Organization-level guidance, concluding that implementation of NAT is not cost-effective for resource-poor countries.

5. Differences in Use of Economic Evidence in Decision-making in the US and Internationally

The majority of experts interviewed for this case study agreed that cost-effectiveness and other economic analyses related to HIV and HCV NAT have been discussed more openly and used more transparently in Europe, Canada and Australia than in the US. One expert held a contrary view, expressing that; in general, Western Europe and Canada are much more risk-adverse than the US. According to this expert, technologies to improve the safety of the blood supply have been implemented in those countries more quickly and with less thought to cost-effectiveness relative to the US.

The National Center for Health and Clinical Excellence (NICE), which advises the UK National Health Service on medical practices and considers both clinical and economic evidence, has not issued guidance on NAT.²⁹⁶ A review of documents issued by Canadian Blood Services found no reference to cost-effectiveness of HIV or HCV NAT.²⁹⁷ A review article published in 2005 of the use of NAT in Western Europe found that use of HIV and HCV NAT was widespread throughout the majority of Western European countries. This review mentions the controversy surrounding the utility of HBV NAT and cites findings indicating that the expected benefits to be realized from HBV NAT, specifically HBV MPNAT, are small both in regard to discarded donations and clinical impact. The review also references the debate surrounding the cost-effectiveness of NAT, but says that no country reviewed had decided to withdraw the test at the time of publication.²⁹⁸ Thus, the extent to which cost-effectiveness has influenced decision-making regarding HIV and HCV NAT and other blood safety technologies in Western Europe and Canada is unclear.

Although evidence to corroborate either opinion is not widely available, one expert specifically cited a current major focus on the cost-effectiveness of NAT in Europe, particularly in The Netherlands, UK and France. Another expert attributed the prominent role of economic evidence in NAT decision-making to the UK's national budget for health care, where clinical

²⁹⁵ Nobilette JB. Bacterial contamination – overview of an important recipient adverse reaction. *Transfusion Medicine Quarterly* 2003;5:1-4.

²⁹⁶ Our guidance. London, England: National Institute for Health and Clinical Excellence, 2006. Accessed September 11, 2006. <http://www.nice.org.uk/page.aspx?o=ourguidance>.

²⁹⁷ Nucleic acid testing. Ontario, Canada: Canadian Blood Services, 2006. Accessed September 11, 2006. http://www.blood.ca/centreapps/internet/uw_v502_mainengine.nsf/9749ca80b75a038585256aa20060d703/8df e21e7e9a6322f85256ab100687de2?OpenDocument.

²⁹⁸ Laperche S 2005.

and economic evidence in support of a technology must be strong in order for it to be implemented in the NHS. Slower adoption of HIV and HCV NAT in the UK also may reflect, in part, the lower prevalence of HIV and HCV in the UK, diminishing the likelihood of infected blood and the potential gain in safety to be realized from blood testing.

E. Conclusions and Policy Implications

1. *Role of Economic Evidence in Decision-making*

Economic evidence does not seem to have played any role in FDA decision-making regarding HIV and HCV NAT. These technologies appear to have been licensed and recommended by the FDA, due solely to their ability to further ensure the safety of the blood supply. While one expert discussed a presentation made to BPAC regarding the cost-effectiveness of HIV and HCV NAT during FDA decision-making, the majority of experts interviewed for this case study concurred that economic evidence played no role in decision-making.

In contrast, economic evidence appears to have played some role in decision-making at US blood banks regarding use of HIV and HCV NAT. According to several blood banking experts consulted for this case study, cost-effectiveness analyses played a role in the decision of how and when to implement HIV and HCV NAT, particularly at blood banks that test blood for client blood collection agencies. Cost-effectiveness and other economic analyses also appear to have played some role in decision-making regarding other blood safety technologies.

2. *Policy Implications*

The pattern of decision-making regarding HIV and HCV NAT and other blood safety technologies reveals a strong emphasis on the primary importance of optimizing safety on the part of the FDA and the American public. This is despite general acknowledgement of the limited economic resources available to devote to health improvements and safety. FDA's mandate to ensure the safety and effectiveness of technologies is cited consistently by experts as an obstacle to the use of economic evidence in decision-making. It does not appear that the FDA's mission likely is to change to include economic considerations for specific technologies; this seems even less probable in the context of a perceived threat to public safety. As such, it appears unlikely that policy decisions made at the FDA regarding HIV and HCV NAT or other blood safety technologies will entail consideration of economic evidence in the near future.

There does appear to be potential for increased use of cost-effectiveness analyses and other forms of economic evidence by US blood banks in decision-making regarding other blood safety technologies, such as HBV NAT, WNV NAT and leukoreduction. While the influence that economic evidence has or will have on decision-making regarding these technologies is unclear, decision-making regarding blood safety technologies that are directly linked less to decreased mortality or severe morbidity is more likely to involve open discussion of economic evidence. Moreover, it appears that US blood banks are, in general, more open to the use of economic evidence in decision-making. For this reason, policies created by US blood banks increasingly may rely on cost-effectiveness and other economic analyses. If the FDA continues to provide reliable information about the accuracy of blood testing technologies and other sources continue to provide epidemiological and economic information, US blood banks and related organizations can continue to conduct their own cost-effectiveness analyses. Such analyses, in the context of competition and

other market factors, could influence blood banking policies regarding when and how to use blood safety technologies. Thus, while the FDA does not explicitly consider cost effectiveness in decisions pertaining to market approval, blood banks likely are to continue to use economic evidence to guide policies that will affect the adoption and use of these technologies in the health care market.

CASE STUDY II: RELENZA/ZANAMIVIR IN THE US AND THE UK

A. Magnitude and Importance

Each year, influenza, commonly referred to as the flu (i.e., “seasonal” flu),¹ affects millions of Americans and contributes to significant resource utilization, productivity losses and associated costs. For some, influenza may be little more than a nuisance, marked by fever, fatigue, aches and pains; however, for certain high-risk populations, influenza poses a more serious health risk.

According to the CDC, approximately 5-20% of Americans (15-60 million people) fall ill with influenza each year.² More than 200,000 of those who contract the virus are hospitalized due to related complications (e.g., bacterial and viral pneumonia) and approximately 36,000 die.³ While influenza can affect anyone, certain groups of people are considered to be at higher risk for infection. Children, the elderly, people with chronic respiratory, cardiovascular or renal disease, those with diabetes mellitus and those with compromised immune systems particularly are susceptible to the virus. Treatment strategies for these populations may differ from those recommended for the population at-large.⁴

In addition to significant morbidity and mortality as a result of the virus, influenza is associated with a considerable economic burden. In the US, the estimated direct costs of influenza, including physician visits, medications and hospital stays, may approach \$5 billion per year. When indirect costs such as for lost workdays and productivity are factored in, the annual cost of influenza in the US may be on the order of \$12-14 billion or more.^{5,6}

Several strategies for prevention and treatment of influenza currently are available. Inoculation is well documented as a safe and effective way to prevent influenza in most people, except for those with contraindicating conditions (e.g., an egg allergy).⁷ Inoculations can be administered hypodermically, using inactivated virus or through a nasal-spray, using a live, attenuated strain of the virus. The latter is approved by FDA only for use in persons ages 5 to 49, while the injection is suitable for most age groups, including small children and the elderly.⁸

¹ This discussion refers to “seasonal” or “interpandemic” flu, the typical flu epidemics caused by viruses that have been circulating for decades and change only slightly from year to year. In contrast, pandemic influenzas are caused by rare, new strains to which the majority of the world’s population has little or no immunity.

² Key facts about influenza and the influenza vaccine. Atlanta, GA: Centers for Disease Control and Prevention, 2005. Accessed August 1, 2006. <http://www.cdc.gov/flu/keyfacts.htm>.

³ Ibid.

⁴ Guidance on the use of zanamivir, oseltamivir and amantadine for the treatment of influenza. London, the UK: National Institute for Health and Clinical Excellence, 2003. Accessed July 3, 2006. <http://www.nice.org.uk/page.aspx?o=TA058guidance>.

⁵ Monto AS. Epidemiology and virology of influenza illness. *Am J Manag Care* 2000;6(5 Suppl):S255-64.

⁶ The cost of influenza. Brussels, Belgium: The Solvay Group, 2006. Accessed August 1, 2006. <http://www.solvay-influenza.com/aboutinfluenza/costofinfluenza/0,,2655-2-0,00.htm>.

⁷ Key facts about influenza (flu) vaccine. Atlanta, GA: Centers for Disease Control and Prevention, 2006. Accessed August 25, 2006. <http://www.cdc.gov/flu/protect/keyfacts.htm>.

⁸ Antiviral/antiflu agents. Hartford, CT: Aetna, Inc., 2006. Accessed July 3, 2006. http://www.aetna.com/products/rx/data/antiviral_antiflucpb.html.

In addition to prevention strategies, antiviral medications may be recommended for high-risk patients who have contracted influenza. While treatments should not be viewed as substitutes for inoculations, they may provide a means of shortening the duration of the infection or, in some cases, help stave off the infection altogether.⁹ Two primary classes of antiviral medications currently are used, including adamantanes (also known as M2 ion channel inhibitors) and neuraminidase inhibitors. Currently, the CDC advises against the use of adamantanes for seasonal flu, including the drugs Symmetrel (amantadine) and Flumadine (rimantadine), because of increasing viral resistance to this class of drugs and their lack of efficacy against influenza B.¹⁰ However, the neuraminidase inhibitors Tamiflu (oseltamivir) and Relenza (zanamivir) have both demonstrated marginal success in hastening the cessation of influenza symptoms.¹¹ While both (in addition to Symmetrel) are approved as means of chemoprophylaxis (prevention or protection against symptoms using drugs), Tamiflu is considered by many to be more effective in this capacity.^{12,13}

B. Overview of the Technology

This case study focuses on one of the neuraminidase inhibitors, Relenza, produced by GlaxoSmithKline (GSK), which was approved by the FDA in 1999 as a treatment for influenza.¹⁴ Randomized controlled trials (RCTs) suggest that the drug may shorten the duration of influenza symptoms (by between 0.78 and 1.99 days) if administered within 48 hours of the onset of symptoms; however, some have recommended a shorter window for treatment of only 30 or 36 hours.^{15,16,17}

There is also some evidence that Relenza reduces influenza-related medical complications such as secondary infections.¹⁸ While the efficacy of this antiviral in high-risk populations remains unproven, the evidence for such an indication has improved in the years since it was first approved.^{19,20} In the US, Relenza is approved for use in patients over 7 years of age and is not

⁹ Recommendations for using antiviral agents for influenza. Atlanta, GA: Centers for Disease Control and Prevention, 2006. Accessed August 3, 2006. <http://www.cdc.gov/flu/professionals/treatment/recommendations.htm>.

¹⁰ CDC recommends against the use of amantadine and rimantadine for the treatment or prophylaxis of influenza in the US during the 2005–06 influenza season. Atlanta, GA: Centers for Disease Control and Prevention, 2006. Accessed August 1, 2006. <http://www.cdc.gov/flu/han011406.htm>.

¹¹ Ibid.

¹² Recommendations for using antiviral agents for influenza, 2006.

¹³ Coverage position: oral influenza antiviral therapy. Bloomfield, CT: CIGNA Healthcare, 2006. Accessed July 3, 2006. http://www.cigna.com/health/provider/pharmacy/coverage_positions/ph_4006_coveragepositioncriteria_flu_antiviral.pdf.

¹⁴ At the time of Relenza's approval, GSK was GlaxoWellcome.

¹⁵ Guidance on the use of zanamivir, oseltamivir and amantadine for the treatment of influenza, 2003.

¹⁶ McKimm-Breschkin JL. Management of influenza virus infections with neuraminidase inhibitors: detection, incidence, and implications of drug resistance. *Treat Respir Med* 2005;4(2):107-16.

¹⁷ Da Silva PR, Nguyen VT, Hayward AC. Logistic issues and potential prescribing costs associated with use of neuraminidase inhibitors for the treatment of influenza in primary care. *J R Soc Med* 2003;96(4):66-9.

¹⁸ Guidance on the use of zanamivir, oseltamivir and amantadine for the treatment of influenza, 2003.

¹⁹ Prescribing information: Relenza. Research Triangle Park, NC: GlaxoSmithKline, 2006. Accessed July 3, 2006. http://us.gsk.com/products/assets/us_relenza.pdf.

²⁰ Burls A, Clark W, Stewart T. Zanamivir for the treatment of influenza in adults: a systematic review and economic evaluation. *Health Technology Assessment* 2002;6(9):a-83.

limited to use in high-risk patients. In the UK, Relenza is recommended only for those patients over 12 years of age and considered to be high-risk.^{21,22}

Due to the way in which Relenza is metabolized, the drug is administered through an inhaler rather than orally. Aside from presenting operating difficulties for many patients (particularly the elderly), this can lead to respiratory side effects, and patients with histories of respiratory conditions are advised not to use it.^{23,24} The limitations associated with the inhaler reportedly have limited the commercial success of Relenza. Prior to recent worldwide concerns about pandemic flu, Relenza's share of the influenza antiviral market had fallen to approximately 1%.^{25,26} Other factors that may have limited the commercial success of Relenza include the entrance of Tamiflu into the market less than one year after Relenza was introduced and the relatively small reduction in duration of symptoms provided by both drugs.²⁷

Recent research supports Relenza's efficacy against H5N1 flu strains which, at present, are considered to be the most likely cause of the next pandemic.²⁸ These findings come as reports are surfacing that Tamiflu-resistant strains of H5N1 are beginning to emerge.²⁹ As the number of H5N1 cases mount, Relenza has experienced an upsurge in sales as government health agencies seek to stockpile antiviral drugs in the event of a pandemic.³⁰ Because of the uncertainty surrounding pandemic flu, evaluating the cost-effectiveness of using Relenza for this purpose is speculative. However, the use of Relenza in seasonal flu has been the subject of multiple cost-effectiveness analyses, as described below.

C. Economic Value of the Technology

In order to assess the economic evidence regarding Relenza, we searched the relevant literature and databases. Our search yielded 16 pertinent studies, including 11 cost-effectiveness or cost-benefit analyses. In all of these economic analyses, Relenza was used as a treatment for the flu, not for prevention.

²¹ Relenza (zanamivir). Rockville, MD: Food and Drug Administration, 2006. Accessed August 1, 2006. <http://www.fda.gov/cder/news/relenza/default.htm>.

²² Guidance on the use of zanamivir, oseltamivir and amantadine for the treatment of influenza, 2003.

²³ Ibid.

²⁴ Relenza (zanamivir), 2006.

²⁵ Noona, R. Interview: Glaxo faces A\$430 Biota claim on flu drug. Yahoo! Australia and New Zealand Finance. July 27, 2005. Accessed August 8, 2006. <http://au.biz.yahoo.com/050727/18/p/6adq.html>.

²⁶ Biota values claim against GSK at A\$308 to A\$430. PRNewsire. Accessed August 25, 2006. <http://www.prnewswire.com/cgi-bin/stories.pl?ACCT=104&STORY=/www/story/07-26-2005/0004075649&EDATE=>.

²⁷ Elias P. Firms in dispute over antiviral drug. Kansas City Star. Accessed August 28, 2006. <http://www.kansascity.com/mld/kansascity/business/14357980.htm>.

²⁸ Avian flu H5N1 stopped by flu drug Relenza. Medical News Today. February 20, 2004. Accessed August 8, 2006. <http://www.medicalnewstoday.com/medicalnews.php?newsid=6043>.

²⁹ Woznicki, K. Avian flu virus showing resistance to Tamiflu. MedPage Today. September 30, 2005. Accessed August 8, 2006. <http://www.medpagetoday.com/PublicHealthPolicy/PublicHealth/tb/1850>.

³⁰ Avian flu boost for Biota as governments build stockpiles. Sydney Morning Herald. October 3, 2005. Accessed August 8, 2006. <http://www.smh.com.au/news/business/avian-flu-boost-for-biota-as-governments-build-stockpiles/2005/10/02/1128191605170.html>.

Because cost-effectiveness studies often are not generalizable outside of the country in which they are performed, we have broken down and discussed the studies by country.³¹ Of the 11 analyses, 3 were conducted under US conditions, 5 were conducted under British conditions and 3 were conducted under conditions of other countries, as described below. In addition to reviewing the relevant literature, we spoke with experts such as practicing clinicians, health economists and representatives from the pharmaceutical industry. These discussions provided a more thorough understanding of the cost-effectiveness of Relenza and the role economic evidence has played in pertinent policy decisions in the US and the UK.

1. Studies in the American Context

Our search yielded 3 studies that examined the economic impact of Relenza on the American health system. All of the articles were decision models, using previously collected data to define risks and predict costs and outcomes.

Two models compared the cost-effectiveness of Relenza with that of Symmetrel. Both studies showed that, while Relenza is more clinically effective than Symmetrel, it is less cost-effective. One modeling study found that, compared to Symmetrel, Relenza's incremental cost-effectiveness ratio (ICER) is about \$133,000 per QALY gained by healthy adults.^{32,33} The other modeling study compared alternative testing and treatment regimens in a scenario involving a population of 32-year olds (the average age of patients in neuraminidase inhibitor effectiveness studies). The study determined that, compared to no treatment, flu testing and taking Symmetrel had an incremental cost of \$11.60 per quality-adjusted day gained. Compared to taking Symmetrel, taking Relenza (with no flu test) cost \$185 per quality-adjusted day gained, while taking Tamiflu (with no flu test) cost \$235 per quality-adjusted day gained.^{34,35}

One cost-benefit analysis examined the net benefit of antiviral treatment by determining people's willingness to pay for a day of flu relief and estimating the financial costs of that therapy. In this study, monetary values were assigned to symptom relief and side effects from medication. Using previously published data, this analysis found that, compared to the base case of no vaccination and no antiviral treatment upon infection, Relenza is cost-beneficial. However, while Relenza was more cost-beneficial than Tamiflu, it was less cost-beneficial than Flumadine; vaccination and Relenza intervention had a net benefit (defined as benefit less total costs) of \$30.13 per patient, while no vaccination and Relenza intervention had a net benefit of \$1.97. Alternatively, vaccination and no treatment upon infection had a net benefit of \$29.39,

³¹ What is cost-effectiveness? Accessed September 12, 2006.

<http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=pih.section.96>

³² Rothberg MB, He S, Rose DN. Management of influenza symptoms in healthy adults. *J Gen Intern Med* 2003;18(10):808-15.

³³ This study assessed the drugs' effectiveness by their reduction in the duration of the flu, reduction in the use of antibiotics for flu-related bacterial complications, and their adverse effects. It was assumed that none of the drugs studied could reduce flu-related hospitalizations or deaths. Costs were defined as expenses relating to medicinal therapies and physician visits, as well as lost wages.

³⁴ Smith KJ, Roberts MS. Cost-effectiveness of newer treatment strategies for influenza. *Am J Med* 2002;113(4):300-7.

³⁵ This analysis measured effectiveness in avoided days of illness and quality-adjusted days gained, which accounted for partial symptom relief in the absence of recovery. The authors assumed that antivirals did not reduce flu-related complications and had no effect on flu-like illnesses. The costs were defined as doctor visits, medicinal expenses, and lost wages.

while vaccination and Flumadine intervention (the most cost-beneficial strategy) had a net benefit of \$30.97. The study also reported that a patient's willingness to pay for a day of flu relief was \$15.49. The authors concluded that vaccination and treatment with Flumadine is more cost-beneficial than any other regimen, including those integrating Relenza, although they urged head-to-head trials to determine more accurately the optimal course of treatment.^{36,37}

Certain epidemiological and other factors are important to consider when evaluating the relevance and meaning of these findings. For example, because Symmetrel does not target influenza B strains, Relenza may become comparatively more cost-effective under conditions where the proportion of influenza B strains is increasing.³⁸ Furthermore, all 3 of these studies were performed in 2002 or 2003, prior to the CDC's recommendation that Symmetrel and Flumadine not be used as antivirals due to increasing rates of Symmetrel- and Flumadine-resistant flu strains.³⁹ It is possible that, when the deleterious effect of resistance is included in future decision models, Relenza may prove more cost-effective.

2. Studies in the UK Context

British governmental bodies and researchers have investigated the cost-effectiveness of Relenza in the UK. The results of these reviews depend on which populations are studied (i.e., healthy adults, high-risk patients, children or the general population) and which outcomes are measured. Recent analyses suggest that Tamiflu may be less costly and more cost-effective in healthy adults. However, this does not appear to be so in the case of high-risk populations.^{40,41}

NICE Guidance Regarding Relenza

In 2003, NICE issued a guidance on the cost-effectiveness of Relenza and other antivirals in various populations based on data from RCTs and previous cost-effectiveness analyses. According to the guidance, the incremental cost per QALY gained (CQG) for healthy adults from treatment with Relenza (versus no antiviral therapy) ranges from £30,000 to £100,000 if hospital admission and mortality data are not included in the analysis. If these variables are included, the CQG ranges from £8,000 to £27,000. For high-risk adults, the NICE analysis also found that the CQG from Relenza treatment ranges from £19,000 to £82,000 when hospital admission and mortality data are not included in the analysis. If these variables are included, the CQG ranges from £3,700 to £17,000.^{42,43}

³⁶ Lee PY, Matchar DB, Clements DA, et al. Economics analysis of influenza vaccination and antiviral treatment for healthy working adults. *Ann Intern Med* 2002;137(4):225-31.

³⁷ This study defined costs as treatment expenses and the cost of visits to the physician. Benefits were the value of workdays recovered as well as the value (derived by willingness to pay) of symptom relief/avoidance.

³⁸ Rothberg MB 2003.

³⁹ CDC recommends against the use of amantadine and rimantadine for the treatment or prophylaxis of influenza in the US during the 2005-06 influenza season, 2006.

⁴⁰ Sander B, Gyldmark M, Hayden FG, et al. Influenza treatment with neuraminidase inhibitors: cost-effectiveness and cost-utility in health adults in the UK. *Eur J Health Econ* 2005;6(3):244-52.

⁴¹ Guidance on the use of zanamivir, oseltamivir and amantadine for the treatment of influenza, 2003.

⁴² Ibid.

⁴³ The NICE guidance measures effectiveness in relief of symptoms and resumption of normal activity. ICERs vary depending on whether or not reductions in hospitalizations and mortality are considered and on whether or not

The NICE guidance also compared Relenza and Tamiflu and found that Tamiflu appears to be more cost-effective than Relenza in healthy adults, though their CQG ranges overlap. In contrast, for high-risk adults, Relenza appears to be slightly more cost-effective than Tamiflu, although their CQG ranges also overlap.

Because NICE did not recommend the use of Relenza in children, no data were presented on the drug's cost-effectiveness in this population. NICE guidelines are revisited regularly, usually 1-3 years after their initial issuance, suggesting that the antiviral guidance may be up for review soon.⁴⁴

Other UK Analyses

Other studies have been performed in the UK. An analysis drawing from a systematic review determined that, when flu is circulating in a community, the incremental CQG of using Relenza compared to placebo is £65,000 for healthy adults and £54,000 for high-risk adults. The authors claimed that, "the data available suggest that [Relenza] may prove useful when used judiciously in at-risk patients."^{45,46} A similar systematic review concluded that, compared to standard treatments, the use of Relenza had ICERs of £31,529 per QALY gained for healthy adults, £17,289 per QALY gained for high risk patients, and £16,819 for those in nursing homes. The authors of this study addressed the discrepancy between these results and those of the other systematic review; while many factors may affect the values, the authors noted that they assumed that flu testing was more accurate than did the other researchers.^{47,48}

As part of another study, a simulation model was used to compare the cost-effectiveness of Relenza and Tamiflu in healthy adults in the UK.^{49,50} Using previously published data, the model found Tamiflu to be less expensive than Relenza and more cost-effective. This study did not evaluate the cost-effectiveness of Relenza for high-risk patients.

In an analysis based on data from a clinical trial conducted by GSK, researchers examined the cost-effectiveness of Relenza in high-risk patients compared to placebo. This study found that

general practitioner patient volume is affected by Relenza's availability. Costs are determined from the perspective of the UK National Health Service.

⁴⁴ Barnett D. Clinical effectiveness and cost effectiveness of zanamivir (Relenza): translating the evidence into clinical practice, a National Institute for Clinical Excellence view. *Philos Trans R Soc Lond B Biol Sci* 2001;356(1416):1899-903.

⁴⁵ Burls A 2002.

⁴⁶ This study's primary endpoint was time until symptom alleviation. As this analysis was a systematic review, a variety of secondary endpoints were considered in the included studies. Cost was defined as the expense of a five-day course of treatment with Relenza.

⁴⁷ Turner D, Wailoo A, Nicholson K, et al. Systematic review and economic decision modeling for the prevention of influenza A and B. *Health Technology Assessment* 2003;7(35):iii-170.

⁴⁸ In this study, effectiveness was measured primarily by Relenza's effect on the duration of the flu and its success at preventing flu-related complications. Costs considered were those of medicinal therapy, doctor visits, hospitalizations, and lost productivity.

⁴⁹ Sander B 2005.

⁵⁰ The authors assessed effectiveness by measuring the amount of time until a patient returned to normal activity. Costs included the expense of antivirals, resource utilization, and patients' lost of productivity due to absence from work.

the incremental cost per QALY is £3,900 if inpatient costs are omitted and £7,490 if they are included. Based on the finding, the authors concluded that Relenza is cost-effective.^{51,52}

3. Studies Based in Other Countries

We identified 3 cost-effectiveness analyses pertaining to Relenza that were performed outside the US and the UK. Certainly, cost-effectiveness studies are difficult to compare across countries. Aside from differences in currencies, costs in different countries vary with the structure of each nation's health system, availability and access of technology, payment systems and epidemiology and other population-based factors.⁵³

Canadian researchers estimated the cost-effectiveness of Relenza in the general Canadian population as well as in high-risk groups, using previously published studies and databases. Assuming that a small proportion (approximately 14%) of flu cases are diagnosed, the investigators found that treatment with Relenza has an ICER of CA\$195,000-235,000 compared to using over-the-counter medications for symptomatic relief. Assuming that a higher proportion of cases are diagnosed (approximately 35%), the CQG drops to \$77,000-95,000. This analysis supports the importance of flu prevalence in determining the cost-effectiveness of an intervention; the higher the prevalence, the more likely it is that Relenza will prove effective in patients who present with flu-like symptoms. The authors concluded that Relenza is cost-effective if it can lead to a significant reduction in hospital costs and flu can be accurately and widely diagnosed. They did not report their figures separately for the general population and high-risk groups.^{54,55}

Using clinical trial data, an Australian modeling study found that the use of Relenza in high-risk patients had an incremental CQG of AU\$11,715 compared to no antiviral treatment. The authors stated that, "treatment with [Relenza] for this population is cost-effective, based on an AU\$78,000 per QALY benchmark."^{56,57}

Lastly, a French analysis found that treatment with Relenza without testing for the flu appears to be more cost-effective than pursuing treatment only after a positive test. Specifically, the

⁵¹ Griffin AD, Perry AS, Fleming DM. Cost-effectiveness analysis of inhaled zanamivir in the treatment of influenza A and B in high-risk patients. *Pharmacoeconomics* 2001;19(3):293-301.

⁵² In this study, effectiveness was measured as time to symptom alleviation and return to normal activity and avoidance of complications requiring antibacterial medication. Costs considered included the expense of the drug and doctor visits.

⁵³ What is cost-effectiveness? Bethesda, MD: National Institutes of Health, 2006. Accessed November 9, 2006. <http://www.ncbi.nlm.nih.gov/books/bv.fcgi?rid=pih.section.96>.

⁵⁴ Brady B, McAuley L, Shukla VK. Economic evaluation of zanamivir (Relenza) for the treatment of influenza (structured abstract). Ottawa, ON: Canadian Coordinating Office for Health Technology Assessment, 2006. Accessed August 25, 2006. http://www.cadth.ca/media/pdf/119_zanamivir_tr_e.pdf.

⁵⁵ This analysis measured effectiveness as Relenza's effect on symptom alleviation, return to normal activities, and flu-related complications. Costs included unit costs for medication, physician visits, hospitalization, and treatment of flu-related complications.

⁵⁶ Mauskopf JA, Cates SC, Griffin AD, et al. Cost effectiveness of zanamivir for the treatment of influenza in a high-risk population in Australia. *Pharmacoeconomics* 2000;17(6):611-20.

⁵⁷ The primary effectiveness endpoint in this study was time until symptom alleviation; the primary cost measures were expenses related to medication, doctor visits, and hospitalizations.

study reported that such a strategy results in a higher average number of flu days averted and a lower cost to society.^{58,59}

4. Limitations

While these studies shed light on the cost-effectiveness of Relenza, some important limitations should be noted. Efforts to assess the cost-effectiveness of Relenza have been subject to inconsistent inputs and endpoints across studies. As a result, no one consensus on the cost-effectiveness of Relenza has emerged. According to one cost-effectiveness review, there exists no agreement, “on what probabilities to assign to the key risks and benefits that form the basis of these studies.”⁶⁰ In particular, estimates on the risk of flu infection in a studied population vary, greatly influencing the results of the models. Measurements of cost also are variable; to many, the cost of the drug is merely the average wholesale price (approximately \$50), while to others the costs include the increased number of patient visits to general practitioners that result from the availability of a flu treatment.^{61,62} Some analyses offset these costs by estimating what Relenza saves various stakeholders when it reduces the number of hospital admissions and the length of hospital stays and allows faster return to work resumption of productive lives. These uncertainties likely will carry over to economic analyses of Relenza as a potential therapy for the next pandemic flu.⁶³

Many of the published models calculate risks, costs and benefits for different age groups, rendering comparisons less accurate. Furthermore, the comparators are not consistent; some studies compare the administration of Relenza to other antivirals, while some compare it to placebo and others incorporate additional variables such as rapid flu testing.^{64,65,66} In addition, estimates are in a number of different currencies, including American dollars, Australian dollars and British pounds. This set of studies spans almost 7 years without accounting for inflation, currency exchange or other market forces, making it difficult to compare the results. Lastly, the measurement of cost-effectiveness ratios in the available literature is incongruous. While some of the studies utilize QALYs, others use quality-adjusted life days.^{67,68,69,70} Because of the

⁵⁸ Schwarzinger M, Housset B, Carrat F. Bedside rapid flu test and zanamivir prescription in healthy working adults: a cost-benefit analysis. *Pharmacoeconomics* 2003;21(3):215-24.

⁵⁹ This study measured effectiveness primarily by duration of illness. The costs considered were those of medicinal therapies, flu-related complications, and lost workdays.

⁶⁰ Schmidt AC. Antiviral therapy for influenza: a clinical and economic comparative review. *Drugs* 2004;64(18):2031-46.

⁶¹ Colgna R, Michocki R, Greisman L, Wolff T. Antiviral drugs in the immunocompetent host: part II. treatment of influenza and respiratory Syncytial virus infections. *American Family Physician* 2003;67(4):763-9.

⁶² Anti-flu drug rejected for NHS use. *BBC News*. October 1, 1999. Accessed August 9, 2006. <http://news.bbc.co.uk/2/hi/health/462531.stm>.

⁶³ Goodman C, Mukherjee D, Faulkner E. How effective would antiviral vaccination and antiviral drug prevention and treatment strategies be for reducing the impact of the next influenza pandemic? Copenhagen: World Health Organization Regional Office for Europe, Health Evidence Network, 2006. Accessed October 3, 2006. http://www.euro.who.int/HEN/Syntheses/pandemicflu_antivirals/20060106_14.

⁶⁴ Sander B 2005.

⁶⁵ Griffin AD 2001.

⁶⁶ Schwarzinger M 2003.

⁶⁷ Rothberg MB 2003.

⁶⁸ Mauskopf JA 2000.

⁶⁹ Burls A 2002.

⁷⁰ Smith KJ 2002.

manner in which these estimates are determined, quality-adjusted life days cannot simply be multiplied by 365 to yield QALYs.

While various modeling analyses and other studies have examined the cost-effectiveness of Relenza and other influenza antiviral medications, the lack of standardization of values for the inputs makes comparing these models very difficult. Experts interviewed as part of this case study indicated that additional studies would be helpful. Greater consensus among the academic and governmental communities regarding how to define risks, costs and benefits would be most beneficial. This does not mean that the goal of such consensus is to yield a single, standard finding or guideline to which all decision-makers would adhere. Certainly, epidemiological, technological, health care delivery, economic and social circumstances differ among and within countries. Furthermore, as world health agencies begin preparing for a possible pandemic flu outbreak, current models may become less relevant, and continued research is needed as circumstances evolve. The role of cost-effectiveness studies in decision-making is summarized below.

D. Critical Appraisal of Relevant Decisions

In order to assess the ways in which decision-makers in the UK and US have used cost-effectiveness in reviewing Relenza, we will review relevant decisions by country, focusing on governmental agencies and private stakeholders. This analysis reflects, in part, the division of responsibility that occurs in both countries' health systems.

1. Decisions in the United States

Decision-makers in the US have made little or no use of cost-effectiveness analysis or other economic evidence in evaluating Relenza. This is true of particularly government health agencies, whereas the decision-making processes of private organizations (e.g., commercial payers) tend to be less transparent, leaving some uncertainty regarding the role of economic evidence.

US Food and Drug Administration

The FDA's main role for health care products is to ensure the safety and efficacy of marketed products. Its mandate does not explicitly include assessing the cost-effectiveness of new medications that are up for market approval.⁷¹ As one academic researcher interviewed for this case study pointed out, the review process does not even require that new medications demonstrate any improvement (clinically or economically) over existing therapies, only that they outperform placebo and are demonstrably safe. As noted by a former FDA reviewer, FDA approval relied only on reviewers deeming Relenza to be effective and safe, despite claims by GSK that the drug would have a large-scale economic and public health impact because of the far-reaching effects of flu. Although these arguments were made, there is no indication that the FDA used economic evidence as part of its decision-making process.

One expert suggested that recent legislation may help to explain FDA's reticence regarding use of economic evidence. The Prescription Drug User Fee Act (PDUFA) requires pharmaceutical

⁷¹ FDA's mission statement. Rockville, MD: Food and Drug Administration, 2006. Accessed August 31, 2006. <http://www.fda.gov/opacom/morechoices/mission.html>.

companies seeking approval for their products to finance much of the FDA's investigation and review process.⁷² As such, one researcher we interviewed suggested that the Agency has become somewhat dependent on this source of revenue and may be unwilling to impose conditions that are viewed as unfavorable by the pharmaceutical industry. However, others consider this to be a narrow view, as PDUFA has a wider scope and is intended to accomplish many goals, such as increasing the timeliness of the approval process.⁷³ This expert further posited that comparing drugs (clinically or economically) may be highly undesirable for pharmaceutical companies because of the high risks and small potential gains such head-to-head trials pose. This researcher also suggested that the prospect of cost-effectiveness analyses providing the basis for lowering drug prices gives reason for pharmaceutical companies to oppose its use.

Centers for Medicare & Medicaid Services

CMS does not formally consider costs or cost-effectiveness in its decisions. (See Exhibit 1 below for a brief overview of CMS' statutory mandates related to economic evidence and its history regarding use of cost-effectiveness in coverage decisions). Furthermore, prior to 2006, CMS did not cover the use of prescription drugs that were not physician-administered (aside from a small number of exceptions).⁷⁴ Since the implementation of the Medicare Prescription Drug, Improvement, and Modernization Act (MMA), Medicare has begun covering oral and other non-physician-administered pharmaceuticals under Part D, which is largely administered by large private contractors.

There are no indications that economic evidence factored into CMS' limited decision-making for the drug. However, during January through May 2005 (and before implementation of Part D), CMS performed a demonstration wherein it assisted beneficiaries who did not have drug coverage policies to purchase Relenza and Tamiflu. According to former CMS Administrator Mark McClellan, the demonstration was to, "provide useful evidence on how prescription drug coverage affects the health and costs for Medicare beneficiaries ahead of the drug benefit in 2006."⁷⁵ No assessment of the demonstration is available yet and, thus, it is not possible to assess to what extent (if at all) issues of cost or cost-effectiveness were considered.

⁷² Prescription drug user fee act (PDUFA). Rockville, MD: Food and Drug Administration, 2006. Accessed September 11, 2006. <http://www.fda.gov/CBER/pdufa.htm>.

Prescription drug user fees – overview. Rockville, MD: Food and Drug Administration, 2003. Accessed November 6, 2006. <http://www.fda.gov/oc/pdufa/overview.html>.

⁷⁴ Tips and tools for people with Medicare and those who care for them. Baltimore, MD: Centers for Medicare & Medicaid Services, 2005. Accessed September 11, 2006. <http://www.medicare.gov/medicarerreform/drugbenefit.asp>.

⁷⁵ Medicare demonstration project pay for flu medicines. Baltimore, MD: Centers for Medicare & Medicaid Services, 2005. Accessed August 31, 2006. <http://www.cms.hhs.gov/apps/media/press/release.asp?counter=1309>.

Exhibit 1: Medicare's Mandate and History Regarding Use of Economic Evidence

Medicare's coverage determinations are guided by statute, providing that the program may cover only those services and items deemed, "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member."⁷⁶ In an effort to increase the transparency and clarity of the criteria used to determine whether these conditions are met, Congress requested in 2003 that CMS publicize those factors used in making national coverage determinations. However, debate persists regarding the true meaning and interpretation of the "reasonable and necessary" limitation.⁷⁷

Some experts contend that cost-effectiveness and other cost-related factors could be considered under the "reasonable" part of the clause, referencing the substantial economic burden to various stakeholders if economic evidence is wholly disregarded. At various points over the past two decades, CMS has attempted to define the criteria used to establish whether or not a service or item is "reasonable and necessary," and has even considered including CE information in this criteria.⁷⁸ In 1989, CMS issued a proposal in the *Federal Register* to include CE as a factor in coverage determinations.^{79,80} However, because of mistrust of CE analytic methods, political pressure from various interest groups, concerns about harming the physician-patient relationship, and other cultural and social factors, this proposal encountered resistance from various stakeholders and was not adopted.^{81,82,83} Today, CMS does not formally consider CE or other economic evidence in making coverage determinations for particular technologies.^{84,85} However, CMS senior staff have stated that a technology's potential economic impact on Medicare may be considered when determining whether it should be subject to a national coverage determination.⁸⁶ It remains unclear whether, or to what extent, economic evidence will be incorporated into Medicare policy decisions, but statutory interpretations will almost certainly be relevant.

Centers for Disease Control and Prevention

While the CDC has issued several recommendations regarding antivirals (including Relenza), these advisories have been in the context of clinical effectiveness and do not appear to be based on economic evidence.^{87,88} Although antivirals are not covered in this publication, the CDC does compile economic efficiency evidence for the *Guide to Community Preventive Services*. The Guide's rationale for using economic analyses is as follows:

"Systematic reviews of economic evaluations are completed for those interventions that are either Strongly Recommended or Recommended by the Task Force on Community Preventive Services. This approach was chosen because effectiveness is a prerequisite for cost effectiveness; therefore, effectiveness should generally be shown before economic efficiency is

⁷⁶ 42 USC § 1395.

⁷⁷ Bagley GP, Maxwell R. Linking Medicare coverage to research participation: reasonable and necessary? Washington, DC: Washington Legal Foundation, 2005. Accessed December 19, 2005. http://www.medicarerguide.com/MDRG/2005/200506_BagleyWLPwhitepaper.pdf.

⁷⁸ Neumann PJ. Using cost-effectiveness analysis to improve health care. Oxford, England: Oxford University Press, 2005.

⁷⁹ Neumann PJ, Rosen AB, Weinstein MC. Medicare and cost-effectiveness analysis. *N Engl J Med* 2005;353(14):1516-22.

⁸⁰ Medicare program: criteria and procedures for making medical services coverage decisions that relate to health care technology. *Federal Register* 1989;54(30):4302-18.

⁸¹ Neumann PJ 2005.

⁸² Stanton MS. Implantable cardioverter defibrillators: an excellent case study. *Health Affairs* 2005;24(1):52-4.

⁸³ Neumann PJ 2005.

⁸⁴ Neumann PJ, Rosen AB 2005.

⁸⁵ Garber AM 2004.

⁸⁶ O'Riordan M. Reaction to Medicare ICD decision: experts dismayed full MADIT II criteria not included in coverage. *Heartwire*. June 13, 2003. Accessed September 6, 2006.

⁸⁷ Recommendations for using antiviral agents for influenza, 2006.

⁸⁸ CDC recommends against the use of amantadine and rimantadine for the treatment or prophylaxis of influenza in the US during the 2005-06 influenza season, 2006.

assessed. Information about our steps for obtaining and evaluating evidence for review of economic evaluations is available in our Methods section.”⁸⁹

Private Payers

A review of publicly available coverage positions from private payers revealed that Relenza generally is reimbursed as a treatment for flu-like symptoms. These documents make no mention of cost, cost-effectiveness or resource utilization. However, private payers are not required to make their decision-making processes transparent, so that assessing which factors motivate coverage decisions is a difficult task. Operating in competitive markets, private payers have incentives to use premiums wisely and may not want to disclose any cost-effectiveness analyses that they conduct. At the same time, private payers need to attract and maintain desirable shares of the market by offering attractive benefits packages, which are likely to include immunizations and treatments to shorten or diminish symptoms.

Health Care Providers

The adoption of Relenza (and other antivirals) may have been limited by physicians using economic evidence. A survey of doctors in Massachusetts and Texas found that 39% of those polled did not prescribe antivirals. Of these, between 25% and 40% listed the fact that the drugs were too expensive as a reason for not prescribing them.⁹⁰ Physician responsibility and liability may pose barriers to the use of cost-effectiveness analysis or other economic criteria in making treatment decisions, particularly to withhold treatment that could be beneficial to patients. Furthermore, a fear of malpractice litigation may create incentive for physicians to over-use health technologies (regardless of cost-effectiveness) in order to insulate themselves from claims of negligence.

2. Decisions in the United Kingdom

The use of cost-effectiveness and other economic evidence is more openly embraced in the UK than in the US. The UK government features a distinct division of responsibility. One agency, the Medicines and Healthcare products Regulatory Agency (MHRA), in conjunction with the European Union’s European Medicines Agency (EMA), is responsible for ensuring safety and efficacy of medicines. Another agency (NICE) is charged with promoting sound health practices, evaluating programs, resolving issues of resource utilization and determining cost-effectiveness. The great majority of Britons receive their health care from the National Health Service (NHS). About 12% of the UK population has supplementary private insurance.⁹¹

⁸⁹ Guide to community preventive services. Atlanta, GA: Centers for Disease Control and Prevention, 2006. Accessed September 1, 2006. <http://www.thecommunityguide.org>.

⁹⁰ Rothberg MB, Bonner AB, Rajab MH, et al. Effects of local variation, specialty and beliefs on antiviral prescribing for influenza. *Clinical Infections Disease*, 2006;42(1):95-9.

⁹¹ Health care systems in eight countries: trends and challenges. European Observatory on Health Care Systems. April 2002. Accessed September 15, 2006. <http://www.lse.ac.uk/collections/LSEHealthAndSocialCare/pdf/finalreport.pdf>.

The Medicines and Healthcare Products Regulatory Agency and the European Medicines Agency

The MHRA is charged with, “ensuring that medicines and medical devices work, and are acceptably safe.”⁹² The agency works with the European Union’s EMEA as part of the UK’s membership in the European federation. The responsibilities of MHRA do not include cost-effectiveness analysis, and the existence of NICE frees it to focus only on matters of safety and efficacy. In 1999, MHRA granted Relenza marketing authorization, a decision that appears to have been made independent of any economic findings.⁹³

National Institute for Health and Clinical Excellence

Established by the UK’s Department of Health, NICE is an independent organization serving England and Wales, responsible for providing guidance to the NHS on, “the promotion of good health and the prevention of ill health.”⁹⁴ While NICE guidances are not binding, they typically are highly influential in the NHS. These guidelines also can be controversial, as was the case when the newly-established NICE offered its first guidance in 1999, a technology appraisal of Relenza.⁹⁵

In 1999, NICE determined that Relenza’s efficacy in high-risk populations was not sufficiently demonstrated through clinical trials. As a result, NICE was not able to justify supplying the drug through the NHS.⁹⁶ Prior to NICE’s guidance, the National Prescription Centre issued a bulletin warning that Relenza could, “increase expectations dramatically,” and greatly increase volume in general practitioners’ offices with people presenting with influenza-like symptoms.⁹⁷ This potential influx of patients was cause for concern, because many patients actually would not be suffering from flu and could prevent other patients who required immediate medical attention from being seen in a timely manner. Some experts expressed that, for the average patient, the flu represented more of an inconvenience than a medical emergency and that many such patients would not benefit from visiting general practitioners’ offices.

Despite concerns regarding patient volume and the potential £115 million annual cost to British tax payers, NICE chairman, Sir Michael Rawlins, claimed that cost “hardly arose” in the decision-making process.^{98,99} In an open letter, Rawlins wrote that NICE’s decision was motivated by three factors: 1) Relenza’s limited effect in patients; 2) its undemonstrated clinical

⁹² About us. London, England: The Medicines and Healthcare products Regulatory Agency, 2006. Accessed September 1, 2006. http://www.mhra.gov.uk/home/idcplg?IdcService=SS_GET_PAGE&nodeId=20.

⁹³ Summary of the Committee on Safety of Medicines meeting held on April 14th, 1999. London, England: The Medicines and Healthcare products Regulatory Agency, 2006. Accessed September 1, 2006.

⁹⁴ About NICE. London, England: The National Institute for Health and Clinical Excellence, 2006. Accessed September 1, 2006. <http://www.nice.org.uk/page.aspx?o=aboutnice>.

⁹⁵ Relenza: the implications. British Broadcasting Corporation, October 1, 1999. Accessed September 1, 2006. <http://news.bbc.co.uk/2/hi/health/462721.stm>.

⁹⁶ Relenza: a drug too far? British Broadcasting Corporation, October 26, 2000. Accessed September 1, 2006. <http://news.bbc.co.uk/2/hi/health/990232.stm>.

⁹⁷ Cost warning on flu drug. British Broadcasting Corporation, September 2, 1999. Accessed September 1, 2006. <http://news.bbc.co.uk/2/hi/health/435874.stm>.

⁹⁸ Relenza: a drug too far?, 2000.

⁹⁹ Cost “hardly arose” in the NICE Relenza decision. *The Pharmaceutical Journal* 2000;264(7079):88.

benefit in high-risk populations; and 3) with these factors in mind, the imposition it would place on general practitioners during their busiest period of the year.¹⁰⁰

NICE's guidance, which was accepted by the NHS, was criticized by several different constituencies, including those who believed that the cost of the drug was what kept the NHS from offering it.¹⁰¹ The committee that drafted the guidance was accused of rationing health care, and Relenza's manufacturer, UK-based GSK, even threatened to close a manufacturing plant in the UK and questioned, "the need to continue innovation in the UK."¹⁰²

In late 2000, NICE revisited the subject of Relenza and issued a revised guidance. The decision authorized the prescription of the drug to high-risk patients who presented within 36 hours of the onset of symptoms, provided that the current prevalence of flu is above a specified threshold (i.e., 50 consultations per 100,000 people in the population). Aside from the challenges of adhering to such conditions in order for a provider to prescribe the drug, NICE attributed the change in guidance to its commitment to evidence.¹⁰³ But others argued that there was no new evidence demonstrating Relenza's efficacy and that NICE merely was bowing to public pressure, political forces and pharmaceutical industry lobbying.¹⁰⁴

In 2003, NICE issued its most recent guidance regarding Relenza, along with Tamiflu and amantadine, as described above. The guidance reviewed the clinical evidence regarding the drugs' efficacy and estimated their incremental cost-effectiveness as compared to placebo. The report concluded that Relenza and Tamiflu are appropriate only for at-risk children and adults who present within 48 hours of first experiencing influenza-like symptoms (Amantadine was not recommended for influenza). NICE acknowledged that the cost-effectiveness of the drug is not a concrete figure, as cost per QALY gained varies considerably depending on which variables are included and what valuations are used. NICE concluded that the cost of the drug is within reason, but was not a clearly cost-effective intervention.¹⁰⁵

The effect of NICE guidance is not entirely clear. One study examined the prescribing patterns in one NHS trust following various NICE technology appraisals. This study found that, "there was an increase in the prescribing of drugs studied immediately after NICE guidance, with the exception of [Relenza]." According to the study, after NICE's 2000 revised guidance was issued, prescriptions did not rise significantly.¹⁰⁶ That Relenza is the exception to this pattern may be the result of the controversy that surrounded the drug's initial review by NICE.

Although cost effectiveness generally is more accepted in the UK than in the US, NICE's use of the method faces a variety of barriers. First, while the consideration of economic evidence is within the organization's mandate, NICE places primary emphasis on clinical evidence. The

¹⁰⁰ Cost "hardly arose" in the NICE Relenza decision. *The Pharmaceutical Journal* 2000;264(7079):88.

¹⁰¹ Relenza: a drug too far?, 2000.

¹⁰² Jones C. Pill Fever. *NowToronto*, January 13, 2000. Accessed September 1, 2006. <http://nowtoronto.com/issues/19/20/News/feature.html>.

¹⁰³ Smith R. The failings of NICE. *British Medical Journal* 2000;321:1363-4.

¹⁰⁴ Is NICE providing clear and credible guidance? London, UK: House of Commons, 2002. Accessed September 5, 2006. <http://www.publications.parliament.uk/pa/cm200102/cmselect/cmhealth/515/51504.htm>.

¹⁰⁵ Guidance on the use of zanamivir, oseltamivir and amantadine for the treatment of influenza, 2003.

¹⁰⁶ Wathen B, Dean T. An evaluation of the impact of NICE guidance on GP prescribing. *British Journal of General Practice*, 2004;54(499):103-7.

Agency is well aware that basing its guidance on strict cutoffs set at a particular ICER would fuel concerns about rationing of care. Others view rationing as inevitable, but question the means by which NICE performs this duty. Some critics argue that the evidence NICE collects should be only one variable in decision-making, considered along with the priorities of patients and the community.¹⁰⁷ Others believe that NICE, an organization of experts, should not be swayed by external forces, and its objectivity is undermined when politics, industry and media affect its decision-making process.¹⁰⁸ Lastly, as is the case for other cost-effectiveness analyses, estimates of clinical and economic effects in NICE's analyses are sensitive to variations in many variables and fall in wide ranges. Viewed as rough approximations, the ICERs of many technologies may approach or fall under acceptance thresholds, making it more difficult to deny coverage of these technologies.

3. Critical Comparison

The use of cost-effectiveness analysis and other forms of economic evidence in decisions related to Relenza's approval and coverage has varied greatly between the US and UK. However, critical review of these processes reveals that stakeholders in both countries have expressed discomfort with its use in setting health care policies.

Federal agencies in the US do not appear to have used economic evidence in their decisions regarding Relenza, which would be consistent with the limited scope of their mandates. In the UK, separate agencies exist for assessing the safety and efficacy of a drug and for the review of a drug's effect (including, but not exclusively, economically) on the health of the public and the country's greater health system. NICE, the agency established to accomplish the latter of the two objectives, did use economic evidence when reviewing Relenza for the NHS. NICE's chairman expressed that cost was not the driving factor behind the original recommendation against the NHS covering Relenza, pointing instead to its questionable efficacy in high-risk populations and the strain it would place on the NHS. In the years following its initial guidance, NICE gradually expanded its recommended use of Relenza. While the Agency claimed these modifications were related to reviews of the available evidence, others considered that NICE was being swayed, at least in part, by public and private criticisms.

Finally, while the UK largely has a nationalized health care system, the US system relies more heavily on a competitive market with multiple private payers. The decision-making processes of American private payers are not transparent and, thus, it is difficult to ascertain to what extent or in which circumstances economic evidence affects their coverage decisions.

E. Conclusions and Policy Implications

1. Role of Economic Information in Key Decisions

The role of cost-effectiveness analysis in Relenza's approval, adoption and diffusion varied greatly between the US and the UK. While the US did not use economic information in its Relenza-related decision-making, the UK used such evidence in its decision regarding whether, and if so, under which conditions, to offer the drug through the NHS.

¹⁰⁷ Smith R 2000.

¹⁰⁸ Is NICE providing clear and credible guidance?, 2002.

In the US, governmental actors did not consider the available economic evidence when reviewing Relenza. The FDA assessed the drug's safety and efficacy before approving it, but did not solicit nor review economic data. Because Relenza is not a physician-administered pharmaceutical, CMS did not cover it when it first came to market in 1999. Since MMA's implementation in 2006, Medicare now covers prescription drugs; however, this is done mostly through formularies managed by pharmacy benefit managers and private payers, so that CMS has not made a national coverage determination pertaining to Relenza. The CDC, which occasionally does report on the economic efficiency of interventions, has not performed any economic analyses on Relenza. CDC advisories regarding Relenza appear to be based solely on clinical concerns.

Measuring the extent to which Relenza's adoption and diffusion in the US were affected by cost-effectiveness analysis is slightly more difficult, because of the private sector's less transparent decision-making processes. Publicly available coverage decisions from private payers indicate that Relenza is covered by private insurers. However, in one study, physicians cited the high cost of antivirals (Relenza among them) as a reason for not prescribing them.

In the UK, cost-effectiveness played a more prominent role in Relenza's adoption and use. The MHRA approved the drug, focusing only on issues of clinical efficacy and safety; however, NICE used cost-effectiveness as one of several variables when crafting its recommendations on the drug to the NHS. Based on concerns about Relenza's efficacy in high-risk patients, the strain that providing it would place on general practitioners, and its cost to the health system, NICE initially recommended against the NHS's distribution of the drug. NICE later changed its position, recommending Relenza's distribution, but only to certain well-defined high-risk populations.

2. Policy Implications

While there exists no statute prohibiting American federal health agencies from using economic evidence in their decision-making processes, the mandates of these organizations do not explicitly call for such analyses. In discussion with experts regarding the regulation and coverage of Relenza, it was suggested that health agencies in the US have been reluctant to use cost-effectiveness analysis to inform their policymaking, as doing so would create additional responsibilities and could put them in the position of rationing care, in the view of some stakeholders.

In the UK, while economic evidence complements the use of clinical evidence and other factors in determining which technologies are provided by the NHS, it appears that NICE still is subject to criticism for this approach. As evidenced by the controversy surrounding NICE's Relenza guidances, ensuring that the viewpoints of various stakeholders are appreciated by NICE while insulating the committee from "pressure groups" remains a significant challenge.

While the extent to which US and UK health agencies use economic evidence is vastly different, similar concerns and controversies regarding cost-effectiveness analysis surround governmental actors in both countries. In the case of Relenza, US health care agencies did not use economic evidence and did not experience these concerns and controversies. In the UK, where economic evidence did play a role in decision-making, health agencies were obliged to face their critics and present and defend their methods. NHS continues to abide by NICE's recommendations and NICE continues to appraise practices and technologies.

CASE STUDY III: DRUG-ELUTING STENTS

A. Magnitude and Importance

Cardiovascular disease (CVD) is the leading cause of mortality among men and women in the United States.¹ Preliminary mortality findings from the American Heart Association show that CVD accounted for 37.7% of all deaths in 2003, with nearly 2,500 Americans dying as a result of CVD each day.² In addition to the public health implications of CVD, estimates indicate that total direct annual costs associated with CVD in the US will reach \$257.6 billion and total indirect costs will reach \$145.5 billion in 2006. This is an increase of more than \$270 billion in total costs since 2003.^{3,4}

Coronary artery disease (CAD) is the most common form of CVD, and 13 million Americans currently are diagnosed with the disease. CAD is caused by the gradual buildup of fatty deposits, or plaque, in the coronary arteries, a process also known as atherosclerosis.⁵ After attempting conservative care, such as lifestyle changes and medical management, coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention (PCI) are the two primary methods of treatment for CAD. CABG is an invasive procedure that involves thoracotomy (surgery through the sternum to open the chest wall) and transplantation of segments of arteries or veins from the legs or other parts of the patient's body to the heart to enable blood flow to bypass blocked sections of coronary arteries.

The main form of PCI is percutaneous transluminal coronary angioplasty (PTCA), which usually involves threading a balloon-tipped catheter via a small incision in an artery in the leg to the site of the coronary artery blockage and inflating the balloon to open the arterial channel (lumen). The balloon then is deflated and the catheter retracted from the body. The more invasive CABG procedure usually provides a definitive outcome of blood flow around the original blockage. However, restenosis (re-narrowing or re-blockage) of the arteries, caused by the migration and proliferation smooth muscle tissue in the arterial lining, occurs in approximately 40% of patients within months of the minimally invasive PTCA procedure.^{6,7}

In order to reduce the rate of restenosis, researchers developed stents, which are small, tube-shaped metal "scaffolds" delivered by the same type of balloon-tipped catheters and placed in the artery to maintain the arterial lumen following the procedure. While these bare metal stents succeed in reducing restenosis in many cases, restenosis still occurs in and around the stents,

¹ Thom T, Haase N, Rosamon W, et al. Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2006;113:85-151.

² Heart disease and stroke statistics—2006 update. Dallas, Texas: American Heart Association, 2006. Accessed August 2, 2006. <http://www.americanheart.org/presenter.jhtml?identifier=3000090>.

³ Ibid.

⁴ Heart disease and stroke statistics—2003 update. Dallas, Texas: American Heart Association, 2003.

⁵ What is coronary artery disease? Bethesda, MD: National Heart, Lung, and Blood Institute, 2006. Accessed August 2, 2006. http://www.nhlbi.nih.gov/health/dci/Diseases/Cad/CAD_WhatIs.html.

⁶ Stenosis and restenosis of coronary arteries. Dallas, TX: American Heart Association, 2006. Accessed August 2, 2006. <http://www.americanheart.org/presenter.jhtml?identifier=4706>.

⁷ Dangas G, Kuepper F. Restenosis: repeat narrowing of a coronary artery. *Circulation* 2002;105(22):2586-7.

resulting in an “in-stent restenosis” (ISR) rate of about 25%.⁸ As such, PCI with conventional PTCA or with bare metal stents provides only a partial solution to coronary artery restenosis.⁹

The relative numbers of CABG and PCI procedures have shifted over the years, with technological advances and changes in the supply and demand for these procedures. In recent years, the number of PCI procedures performed in the US has increased, while the number of CABG procedures has flattened or decreased somewhat among adults ages 45-64.¹⁰ In 2003, an estimated 664,000 PCI procedures were performed in the US, having more than tripled since 1987. Much of the growth in PCI procedures in recent years is due to the introduction of stents to the original PTCA procedure. Between 1996 and 2000 the rate of coronary stent insertion as part of PCI increased by 146% and, by 2003, 84% of PCI patients received stents.¹¹

B. Overview of the Technology

To supplement the mechanical support of bare metal stents, researchers have sought various means to maintain the arterial lumen, including biochemical ones. A highly successful approach that was brought to the market recently is the drug-eluting stent (DES). Building on the bare metal stent technology, these stents are coated with drugs that interrupt the biological processes that cause restenosis.¹² The first DES for use following angioplasty was approved by FDA in 2003.¹³ In the seminal 2003 SIRIUS RCT in support of FDA approval, 1,058 patients undergoing PCI treatment were implanted with either a sirolimus-eluting stent (SES) or a bare metal stent.^{14,15} Nine months after implantation, the restenosis rate among patients implanted with SES was just 4.1%, significantly less than the rate of 16.6% among patients implanted with bare metal stents.¹⁶ Based on the results of the set of TAXUS RCTs, DES coated with paclitaxel received FDA approval in 2004.¹⁷

Results from RCTs and follow-up studies of both SES and paclitaxel-eluting stents (PES) have been largely favorable.¹⁸ A systematic review of 28 RCTs for the prevention of ISR published in

⁸ Dangas G, Kuepper F. Restenosis: repeat narrowing of a coronary artery. *Circulation* 2002;105(22):2586-7.

⁹ How is coronary artery disease treated? Bethesda, MD: National Heart, Lung, and Blood Institute, 2006. Accessed August 2, 2006. http://www.nhlbi.nih.gov/health/dci/Diseases/Cad/CAD_Treatments.html.

¹⁰ Health, United States, 2005, with chartbook on trends in the health of Americans. Hyattsville, MD: National Center for Health Statistics, 2005. Accessed August 2, 2006. [http://www.cdc.gov/nchs/data/05.pdf](http://www.cdc.gov/nchs/data/hus/05.pdf).

¹¹ Heart disease and stroke statistics – 2006 update, 2006.

¹² Ibid.

¹³ FDA approves drug-eluting stent for clogged heart arteries. Rockville, MD: US Food and Drug Administration, 2003. Accessed August 2, 2006. <http://www.fda.gov/bbs/topics/NEWS/2003/NEW00896.html>.

¹⁴ SIRIUS is the name of the SIRollmUs-Eluting Balloon Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions Trial.

¹⁵ Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patient with stenosis in a native coronary artery. *New England Journal of Medicine* 2003;349(14):1315-23.

¹⁶ Holmes DR, Leon MB, Moses JW, et al. Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomized trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. *Circulation* 2004;109:634-40.

¹⁷ Taxus express 2 paclitaxel-eluting coronary stent system (monorail and over-the-wire) – P030025. Rockville, MD: US Food and Drug Administration, 2004. Accessed August 4, 2006. <http://www.fda.gov/cdrh/pdf3/P030025a.pdf>.

¹⁸ Eisenberg MJ, Konnyu KJ. Review of randomized clinical trials of drug-eluting stents for the prevention of in-stent restenosis. *American Journal of Cardiology* 2006;98(3):375-82.

August 2006 found that DES consistently reduce rates of restenosis to a greater extent compared to bare metal stents.¹⁹ A clinical trial involving 536 patients in 15 countries over a period of 4 years found that implantation with PES results in lower rates of restenosis than implantation with bare metal stents.²⁰ An RCT of 352 patients from 35 clinical centers in Europe conducted over a period of 4 years showed that implantation with SES leads to lower rates of restenosis than implantation with bare metal stents.²¹ Stents coated with drugs other than sirolimus and paclitaxel, such as everolimus, have produced similarly favorable results.²²

DES implantation has increased remarkably in the past three years.²³ From April 2003 to December 2004, the DES implantation rate in the US increased nearly 60%.²⁴ By 2005, as many as 85% or more of all PCIs may have been performed using DES.²⁵ Notwithstanding their widespread use, the prevalence of DES implantation varies by socioeconomic status, geographic location, sex and other demographic factors in the US. For instance, some accounts suggest that the transition from bare metal stents to DES has been slower in rural hospitals. Older patients and patients without health insurance are reported to be less likely to receive DES. Relative implantation rates of DES and bare metal stents also are reported to vary by race. While Caucasian and African American patients are equally likely to receive a stent, Caucasian patients reportedly are more likely to receive a DES.^{26,27} Outside of the US, the use of DES varies, ranging from 14% of total stent implants in Germany to 65% of total stent implants in Portugal, as reported in 2006.²⁸

Recently, the safety of DES have come into question. In 2005, reports of an association between implantation of DES and increased rates of in-stent thrombosis (blood clots) led to a dip in the use of DES in the US.²⁹ Studies presented at the March 2006 American College of Cardiology Annual Scientific Session and the September 2006 World Congress of Cardiology found that patients implanted with DES are at higher risk of thrombosis than patients implanted with bare

¹⁹ Eisenberg MJ, Konnyu KJ. Review of randomized clinical trials of drug-eluting stents for the prevention of in-stent restenosis. *American Journal of Cardiology* 2006;98(3):375-82.

²⁰ TAXUS II clinical trial follow-up data demonstrates excellent long-term outcomes at four years. Natick, MA: Boston Scientific, 2006. Accessed September 6, 2006. http://bostonscientific.mediaroom.com/index.php?s=press_releases.

²¹ Data suggest the CYPHER sirolimus-eluting coronary stent provides sustained clinical benefits in patients with coronary artery disease compared to bare metal stents. Barcelona, Spain: Johnson & Johnson, 2006. Accessed September 7, 2006. http://www.jnj.com/news/jnj_news/20060905_143702.htm;jsessionid=JSOWAIQ3MOQ2GCQPCB3WU3QKB2IIWTT1.

²² Abbott's XIENCE V drug-eluting coronary stent superior to TAXUS stent in Sprit II clinical trial. Abbott Park, IL: Abbott Laboratories, 2006. Accessed September 6, 2006. http://www.abbott.com/global/url/pressRelease/en_US/60.5:5/Press_Release_0345.htm.

²³ Rao SV, Shaw RE, Brindis RG, Klein LW. Patterns and outcomes of drug-eluting coronary stent use in clinical practice. *American Heart Journal* 2006;152(2):321-6.

²⁴ Ibid.

²⁵ Tung R, Kaul S, Diamon G, Shah P. Narrative review: drug-eluting stents for the management of restenosis: a critical appraisal of the evidence. *Annals of Internal Medicine* 2006;144(12):913-9.

²⁶ Rao SV 2006.

²⁷ QuickStats: use of stents among hospitalized patients undergoing coronary angioplasty, by race—United States, 2003. *Morbidity and Mortality Weekly Report* 2005;54(12):310.

²⁸ Kearney P, Stokoe G, Breithardt G, et al. Improving patient access to novel medical technologies in Europe. *European Heart Journal* 2006;27(7):882-5.

²⁹ Japsen B 2006.

metal stents.³⁰ Specifically, findings from the BASKET-LATE study³¹ and a meta-analysis of RCTs of DES³² found a small but significant increase in the rates of death and myocardial infarction in patients 18 months to 3 years following implantation with DES.³³ The risk of thrombosis was not found to diminish over time. The President of the American College of Cardiology responded to these findings by citing a shift from DES back toward bare metal stents in the US.³⁴

Major news publications have begun to publish articles regarding the potential risks of DES. A report in *The New York Times* included statements from leading cardiologists regarding increasing reluctance to use DES.³⁵ The FDA's Medical Devices Advisory Panel met in December 2006 to discuss issues related to in-stent thrombosis in DES and to consider whether to issue new safety guidelines for the devices.³⁶ It remains unclear how these findings or potentially forthcoming revisions to FDA guidance will influence rates of DES implantation in the US and abroad.

Changes in the assessed risks associated with DES, and potential changes in care, could shift its cost-effectiveness relative to bare metal stents or other treatments. For example, aside from the costs of DES and bare metal stents themselves, patients typically receive a combination of the antiplatelet drug clopidogrel (Plavix) and aspirin for several months to reduce or prevent clotting, after which clopidogrel therapy typically ceases. If further protection against clotting is desired in DES patients, use of this drug could be extended, increasing costs accordingly.

As of November 2003, the average acquisition cost to hospitals of DES was reported to be approximately \$2,700, and the average acquisition cost of bare metal stents was approximately \$700.³⁷ Questions remain as to whether DES are more cost-effective than bare metal stents. The following sections explore economic studies of DES and consider the extent to which economic evidence has played a role in decision-making regarding this technology.

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- ³⁰ Cheng M. New study raises doubts raised about drug-coated heart stents. Associated Press, September 3, 2006. Accessed September 5, 2006. http://www.boston.com/news/local/massachusetts/articles/2006/09/03/new_study_raises_doubts_raised_about_drug_coated_heart_stents/.
- ³¹ Pfisterer ME. BASKET-LATE: Late clinical events related to late stent thrombosis after stopping clopidogrel: drug-eluting vs bare-metal stenting. Abstract. American College of Cardiology Annual Scientific Session. March 14, 2006. Accessed December 1, 2006. <http://www.medscape.com/viewarticle/529648>.
- ³² Camenzind E. Safety of drug-eluting stents: insights from meta-analysis. Abstract. World Congress of Cardiology 2006. September 3, 2006. Accessed December 1, 2006. http://www.escardio.org/knowledge/congresses/CongressReports/hotlinesandctus/707009_Camenzind.htm.
- ³³ FDA statement on coronary drug-eluting stents. Rockville, MD: US Food and Drug Administration, 2006. Accessed November 8, 2006. <http://www.fda.gov/cdrh/news/091406.html>.
- ³⁴ Ibid.
- ³⁵ Feder BJ. Doctors rethink widespread use of heart stents. *New York Times*, October 21, 2006. Accessed November 7, 2006. <http://www.nytimes.com/2006/10/21/business/21stent.html?ei=5070&en=9b9d3249d952f732&ex=1163134800&adxnnl=1&adxnnlx=1163006798-YuN5YrK+ri+PkLxJ2dEHNA>.
- ³⁶ Circulatory systems devices panel of the Medical Devices Advisory Committee; notice of meeting. Rockville, MD: US Food and Drug Administration, 2006. Accessed November 7, 2006. <http://www.fda.gov/OHRMS/DOCKETS/98fr/E6-17519.htm>
- ³⁷ Greenberg D, Bakhai A, Cohen DJ. Can we afford to eliminate restenosis? Can we afford not to? *Journal of the American College of Cardiology* 2004;43(4):513-8.

C. Economic Value of the Technology

We identified 30 economic analyses relevant to DES, including 24 primary data studies and 6 secondary/synthesis studies. One of the primary data studies was an RCT, while 6 studies used data from RCTs that were conducted to evaluate the clinical efficacy of DES. Seventeen of the primary data studies involved economic modeling or decision-tree analyses to assess the cost-effectiveness of DES. Of the 30 relevant studies, 9 were conducted in the US.

1. Studies Conducted in the United States

Of the 7 primary data studies conducted in the US, 3 used patient data from RCTs that examined clinical efficacy and 4 used economic modeling to assess the cost-effectiveness of DES. Among the 3 studies using data from RCTs, 2 compared the cost-effectiveness of either SES or PES to bare metal stents and 1 compared the cost-effectiveness of SES to bare metal stents and to CABG. The study comparing SES to bare metal stents concluded that, although SES are not cost-saving relative to bare metal stents at 1 year, SES are reasonably cost-effective within the framework of the US health care system. The study comparing PES to bare metal stents concluded that, while treatment with PES resulted in slightly higher 1-year costs relative to bare metal stents, the cost-effectiveness ratio for PES is similar to that for other drug-eluting stent platforms. Lastly, the comparison of SES to both bare metal stents and to CABG found that DES are highly cost-effective relative to historical CABG results and reasonably cost-effective relative to historical bare metal stent results at 1-year follow-up.

Of the 4 US studies that used economic modeling, 1 found that DES are not cost-saving or cost-neutral, except when implanted in patients at high risk of restenosis, and 2 studies found that the costs of DES exceed current levels of reimbursement.^{38,39} In contrast, another analysis found that DES are cost-saving for patients undergoing PCI who have a bare metal stent target vessel revascularization (TVR) rate greater than 20% and cost-effective for all patients undergoing PCI whose bare metal stent TVR rate exceeds 12%.⁴⁰

The primary data studies conducted in parallel with RCTs include the cost-effectiveness analyses based on the SIRIUS and TAXUS-IV trials and the unpublished cost-effectiveness analysis based on data from the Arterial Revascularization Therapies Study (ARTS) I and II registries.^{41,42,43}

³⁸ Ruffy R, Kaden RJ. Projected health and economic benefits of the use of sirolimus-eluting coronary stents. *Advanced Studies in Medicine* 2003;3(6D):s602-11.

³⁹ Kong DF, Eisenstein EL, Sketch MH, et al. Economic impact of drug-eluting stents on hospital systems; a disease-state model. *Am Heart J* 2004;147(3):449-56.

⁴⁰ Greenberg D 2004.

⁴¹ Cohen DJ, Bakhai A, Shi C, et al. Cost-effectiveness of sirolimus-eluting stents for treatment of complex coronary stenoses: results from the sirolimus-eluting balloon expandable stent in the treatment of patients with de novo native coronary artery lesions (SIRIUS) trial. *Circulation* 2004;110:508-14.

⁴² Bakhai A, Stone GW, Mahoney E, et al. Cost effectiveness of paclitaxel-eluting stents for patients undergoing percutaneous coronary revascularization: results from the TAXUS-IV trial. *Journal of the American College of Cardiology* 2006;48(2):253-61.

⁴³ Cohen DJ. Cost-effectiveness of DES in multivessel disease: insights from ARTS I +II. Presentation given at Transcatheter Cardiovascular Therapeutics, October 2005, Washington, DC.

The first prospective economic evaluation of DES in the US used data from patients enrolled in the SIRIUS trial to assess the cost-effectiveness of SES versus bare metal stents.⁴⁴ Resource utilization and costs were examined over a 1-year period for all patients enrolled in the trial. For patients implanted with SES for treatment of a de novo (previously untreated) lesion, follow-up costs were reduced by \$2,751 per patient; however, overall aggregate costs after 1 year were \$309 higher for patients with SES. This study found that the incremental cost-effectiveness ratio (ICER) for SES is \$1,650 per avoided repeat revascularization, or \$27,540 per QALY gained. The investigators concluded that the cost-savings of SES do not fully offset the higher cost of SES. Because assessments of willingness-to-pay among potential PCI patients suggests a threshold of \$5,000-\$10,000 per repeat revascularization avoided, the investigators concluded that SES are reasonably economically attractive in the context of the US health care system.^{45,46} The investigators also concluded that SES might achieve cost-savings if the number of stents required per procedure decreases.

The cost-effectiveness analysis conducted alongside the TAXUS-IV trial compared aggregate health care costs for patients undergoing PCI with PES versus bare metal stents. As in the SIRIUS cost-effectiveness study, resource use and costs were assessed prospectively for all patients over a 1-year period. The study found an ICER of \$4,678 per avoided repeat revascularization, or \$47,798 per QALY gained. Although the cost savings associated with PES were not found to fully offset their initial costs, the study concluded that, because the cost-effectiveness ratio for PES is less than \$50,000 per QALY gained, the use of PES is reasonably cost-effective over a wide range of patients from a societal perspective.^{47,48} The investigators also found the cost-effectiveness ratio for PES in the population studied to be comparable to that of other DES technologies.

An unpublished analysis of the cost-effectiveness of SES versus bare metal stents and CABG was conducted as part of the ARTS-I and ARTS-II, which compared the clinical efficacy of bare metal stents to CABG and to SES, respectively.^{49,50} Investigators found that, for patients undergoing multivessel PCI, implantation with SES was less costly than CABG during initial hospitalization and after 1 year. From the perspectives of irreversible endpoints (e.g., death, myocardial infarction and stroke) and softer endpoints (e.g., repeat revascularization), SES was more cost-effective than CABG. In a comparison of SES to bare metal stents, investigators found SES to be significantly more costly during initial hospitalization. Despite the reductions in follow-up costs after SES implantation, investigators did not find SES to be cost-saving

⁴⁴ Cohen DJ 2004.

⁴⁵ Greenberg D, Bakhai A, Neumann PJ, Cohen DJ. Willingness to pay for avoiding coronary restenosis and repeat revascularization: results from a contingent valuation study. *Health Policy* 2004;70(2):207-16.

⁴⁶ Cohen DJ 2004.

⁴⁷ Bakhai A 2006.

⁴⁸ Mark DB, Hlatky MA. Medical economics and the assessment of value in cardiovascular medicine: part I. *Circulation* 2002;106(4):516-20.

⁴⁹ Cohen DJ 2005.

⁵⁰ CYPHER sirolimus-eluting coronary stent to be featured in late-breaking clinical trial presentations at 2005 American College of Cardiology Scientific Session. Miami, FL: Johnson & Johnson, 2005. Accessed September 7, 2006.
http://www.jnj.com/news/jnj_news/20050224_102215.htm;jsessionid=V3MGYUCXWV5TQCQPCB3WU3QKB2IIWTT1.

compared to bare metal stents at 1 year. However, for irreversible and softer endpoints, SES was found to be reasonably cost-effective after 1 year.

The 4 economic modeling studies published in the US were analyzed from the patient, payer or hospital perspective. An economic analysis published in 2004 modeled the economic impact on hospitals of DES over 5 years.⁵¹ According to the authors, without the introduction of an incremental reimbursement policy by CMS, Duke Medical Center would have lost \$8.1 million in the first year and \$8.7 million in each subsequent year. Although this study predicted that losses would still occur if an incremental reimbursement policy was introduced, it found that these losses would be smaller, with losses of \$4.75 million in the first year and \$5.6 million annually in following years. The study concluded that the incremental reimbursement proposed by CMS at the time would cover the cost of treating a single lesion at Duke Hospital only if an average of 1.5 stents were used per patient, a number the investigators stated likely would be surpassed. Another economic analysis used estimates of the financial contribution of cardiac services to hospitals around the US to estimate the impact of DES on revenue and expense for a sample hospital.⁵² The study concluded that, due to the high cost of DES and a decrease in the number of CABG procedures, most cardiac services will struggle to achieve a cost-expenditure balance at the end of the first year of DES implementation, even with adjustments in Medicare reimbursement.

In addition to these primary data studies, 2 systematic reviews have been published in the US using studies that have examined the cost-effectiveness of DES. A systematic review published in 2005 examined economic decision models that analyzed cost-effectiveness of DES from societal and hospital perspectives.⁵³ The study concluded that the savings associated with DES are not likely to offset their cost.

Authors of a 2006 systematic review that examined all studies pertaining to DES, bare metal stents, restenosis and cost-effectiveness published from 1999 to 2005 arrived at somewhat contrary findings. In addition to their higher cost, the authors reported that, although DES show promise in reducing angiographic (i.e., appearing on x-ray) and clinical restenosis, there is no compelling evidence of their benefit for such hard endpoints as heart attacks or mortality. The recent evidence that they are associated with slightly increased risk of in-stent thrombosis might, therefore, outweigh any other relative clinical benefit. As such, the authors concluded that substituting DES for bare metal stents is of questionable value.⁵⁴

2. Studies Conducted Outside the US

One RCT was conducted in Switzerland for the purpose of evaluating cost-effectiveness, including clinical outcomes, of DES compared to bare metal stents in real-world settings in unselected patients. The Basel Stent Kosten Effektivitats Trial (BASKET) found that total costs

⁵¹ Kong DF, Eisenstein EL, Sketch MH, et al. Economic impact of drug-eluting stents on hospital systems; a disease-state model. *American Heart Journal* 2004;147(3):449-56.

⁵² Chumer K, DeCerco J, Vaul J. Managing technological explosion in the medical management of coronary artery disease, part II. DES economic modeling: budgeting strategies for drug-eluting stent technology. *The Journal of Cardiovascular Management* 2002;13(4):16-20.

⁵³ Kong DF, Eisenstein EL. Decision models for assessing the cost effectiveness of drug-eluting stents. *Expert Opinion in Pharmacotherapy* 2005;6(6):965-74.

⁵⁴ Tung R 2006.

were higher with DES than with bare metal stents at 6 months. The study found that the lower costs of follow-up care for the DES did not compensate for their higher device costs. The incremental cost-effectiveness of DES compared to bare metal stents was greater than \$50,000 per QALY across all patients. However, subgroup analyses showed that DES were more cost-effective for elderly patients in specific high risk groups. The investigators concluded that the use of DES across unselected patients in real-world settings is not as cost-effective as been observed in studies involving patients selected with more specific indications.⁵⁵

Two other studies used RCT data to assess cost-effectiveness. Researchers in The Netherlands analyzed one-year resource utilization for patients enrolled in the RAVEL trial, which compared the clinical efficacy of SES to bare metal stents.^{56,57} This study concluded that the additional costs of the initial procedure using SES were almost completely covered by the decreased cost of follow-up care. A second study using RCT data, published in Germany, compared SES and PES and found that in patients at high risk of restenosis, SES were associated with lower costs after 9-12 months of follow-up.⁵⁸

In addition to these studies based on RCT data, 13 economic analyses of the cost-effectiveness of DES have been conducted in other countries. Ten of these studies compared the cost-effectiveness of DES to bare metal stents and 3 compared the cost effectiveness of DES to CABG. Eight of these studies reported that DES were only cost-effective if used in patients at increased risk of restenosis or other designated subgroups of patients. Similarly, 2 of the 3 systematic reviews concluded that the cost-effectiveness of DES would increase if they were used primarily in patients at high-risk for restenosis.^{59,60} In contrast, 3 economic analyses reported that use of DES is cost-effective relative to bare metal stents within the context of the health care system in each of Japan, Germany and Italy.^{61,62,63} Another study using a systematic

⁵⁵ Kaiser C, Brunner-La Rocca HP, Buswer PT, et al. Incremental cost-effectiveness of drug-eluting stents compared with a third-generation bare-metal stent in a real-world setting: randomised Basel Stent Kosten Effektivitats Trial (BASKET). *The Lancet* 2005;366(9503):2086.

⁵⁶ RAVEL is an acronym for RANdomised study with the sirolimus eluting Bx VELocity balloon expandable stent in the treatment of patients with de novo native coronary artery lesions.

⁵⁷ van Hout BA, Serruys PW, Lemos PA, et al. One year cost effectiveness of sirolimus eluting stents compared with bare metal stents in the treatment of single native de novo coronary lesions: an analysis from the RAVEL trial. *Heart* 2005;91:507-12.

⁵⁸ Elezi S, Dibra A, Folkerts U, et al. Cost analysis from two randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in high-risk patients with coronary artery disease. *Journal of the American College of Cardiology* 2006;48(2):262-7.

⁵⁹ Lord SJ, Howard K, Allen F, et al. A systematic review and economic analysis of drug-eluting coronary stents available in Australia. *Medical Journal of Australia* 2005;183(9):464-71.

⁶⁰ Hill R, Bagust A, Bakhai A, et al. Coronary artery stents: a rapid systematic review and economic evaluation. *Health Technology Assessment* 2004;8(35):iii-iv, 1-242.

⁶¹ Ikeda S, Kobayashi M. Economic evaluation of drug-eluting stents in Japan. *Keio Journal of Medicine* 2006;55(1):15-22.

⁶² Fricke FU, Silber S. Can PCI with drug-eluting stents replace coronary artery bypass surgery? A comparative economic analysis regarding both therapeutic options based on clinical 12-month data reflecting the German social health care insurance system. *Herz* 2005;30(4):332-8.

⁶³ Tarricone R, Marchetti M, Lamotte M, et al. What reimbursement for coronary revascularization with drug-eluting stents? *European Journal of Health Economics* 2004;5(4):309-16.

literature search and economic modeling concluded that, at their then-current cost, widespread use of DES was not cost-effective in Quebec.⁶⁴

3. Study Limitations

While these studies offer important insights regarding the cost-effectiveness of DES, several limitations have been noted by the authors and other researchers. The SIRIUS cost-effectiveness investigators acknowledged that the trial included a large percentage of patients with complex lesions, resulting in a relatively high rate of restenosis.⁶⁵ They recognized that the cost-effectiveness of DES implantation in patients at lower risk of restenosis is difficult to extrapolate from their findings. Conversely, the authors of the TAXUS-IV cost-effectiveness analysis acknowledged that their findings may not be applicable to patients at high risk of restenosis, whose average use of DES would be greater than that required by patients in their study.⁶⁶ Investigators from all 3 of the US studies conducted in parallel with RCTs acknowledged that their results were based only on 1-year follow-up data. Follow-up of only 1 year may have exaggerated the cost-effectiveness of DES relative to bare metal stents and to CABG if their clinical outcomes converge over time.^{67,68,69} The author of the unpublished manuscript analyzing cost-effectiveness using data from ARTS-I and ARTS-II acknowledged that findings were based on comparison with historical CABG and bare metal stent results and cited the need for studies employing contemporary controls.⁷⁰

These and other study limitations have been echoed by other researchers who question the often-cited conclusion that DES are cost-effective.^{71,72} The authors of one review examining evaluations of DES cautioned that the results of trial-based economic studies such as SIRIUS are limited in generalizability because the patients in the study are highly selected.⁷³ Another systematic review concluded that the extent of stent use often is underestimated, while the extent of restenosis following insertion of a bare metal stent and the reduction in restenosis following DES implantation often are overestimated, leading to an amplification of the cost-effectiveness of DES.⁷⁴ Some observers have noted the potential for bias and conflict of interest stemming from the fact that most studies examining the clinical efficacy of DES have been funded by stent manufacturers.⁷⁵

Non-US studies examining the cost-effectiveness of DES are similarly limited. The investigators who completed the cost-effectiveness study conducted with the RAVEL trial acknowledged the

⁶⁴ Brophy J, Erickson L. An economic analysis of drug eluting coronary stents: a Quebec perspective. Montreal, Canada: AETMIS, 2004. Accessed August 25, 2006.

<http://www.aetmis.gouv.qc.ca/site/download.php?059cca28f196fb38f30873d34a39efb7>.

⁶⁵ Cohen DJ 2004.

⁶⁶ Bakhai A 2006.

⁶⁷ Cohen DJ 2004.

⁶⁸ Bakhai A 2006.

⁶⁹ Cohen DJ 2005.

⁷⁰ Ibid.

⁷¹ Greenberg D 2004.

⁷² Tung R 2006.

⁷³ Greenberg D 2004.

⁷⁴ Tung R 2006.

⁷⁵ Ibid.

limits of its applicability, due to the small number of patients enrolled in the study and to the relative homogeneity of patients, the majority of whom were at low-risk for restenosis.⁷⁶ A leading expert consulted for this case study criticized BASKET for analyzing cost-effectiveness of DES based on only a 6-month follow-up of patients, a time frame that may capture the higher costs of DES without also capturing subsequent reductions in spending on follow-up care.

Although recent findings regarding in-stent thrombosis of DES have not yet been incorporated into published cost-effectiveness analyses, this may have an effect on the clinical costs and benefits associated with the technology. Certainly, any calculations of cost-effectiveness reflect data and assumptions available at the time and are subject to change as health benefits and costs shift. These recent findings linking DES to thrombosis bring to light the fact that premarket clinical trials cannot capture all of the potential risks associated with a medical intervention, due both to limitations on population size and study duration. This is particularly true when an adverse event is rare, as may be the case with DES.

D. Critical Appraisal of Relevant Decisions

In order to fully understand the role of economic evaluations in decision-making regarding DES, we consulted with industry and policy experts. We also reviewed guidance documents written by government and private organizations in the US and in other countries to assess the role of economic evaluations in policy decisions made about DES.

1. Use of Economic Evidence

Economic evidence appears to have played some role in decision-making regarding DES. However, much greater weight seems to have been given to clinical evidence, particularly during the initial approval and reimbursement processes.

Decision-making at the FDA

According to one industry expert, economic evidence, particularly evaluations of cost and cost-effectiveness, was provided to FDA by stent manufacturers during the initial DES approval process. This evidence included economic modeling, but did not include evaluations of ICERs. According to an industry expert, FDA did not explicitly request this information; instead it was provided by the stent manufacturing industry as an additional argument in favor of the approval of DES.

It is unclear whether the economic analyses provided by industry were used by the FDA. Some key stakeholders indicated that the FDA did not consider economic evidence at all during the DES approval process. Documents issued by the FDA regarding the approval of DES make no mention of cost, cost-effectiveness or other economic analyses.⁷⁷ Given other instances in which economic evidence pertaining to technologies under review was available to FDA, it might be assumed that the economic evidence provided to FDA regarding DES was not considered in

⁷⁶ van Hout BA 2005.

⁷⁷ CYPHER Sirolimus-Eluting Coronary Stent on RAPTOR Over-the-Wire Delivery System or RAPTORRAIL Rapid Exchange System- P020026. Rockville, MD: US Food and Drug Administration, 2003. Accessed September 7, 2006. <http://www.fda.gov/cdrh/PDF2/P020026.html>.

any formal way during the approval process. However, other key stakeholders indicated that FDA was aware of economic evidence pertaining to DES, but that if it was used at all, it would have been only supplementary to the focus on clinical evidence.

Decision-making at the Centers for Medicare & Medicaid Services

Based, in part, on the strong results of the pivotal RCTs described above, DES offer what may be a unique instance of coordination between FDA regulatory approval and CMS payment policies. In an unprecedented step, CMS assigned new codes to uniquely identify DES prior to FDA approval of the technology.⁷⁸ This timing enabled new coding and payment amounts to be in place when FDA gave approval for marketing of the technology, rather than at the time of the next annual round of updates by CMS. One expert, however, voiced concern over this coordination. He suggested that the usual delay between FDA approval and CMS payment policies can allow for a closer examination of a technology's impact, known or potential risks, and optimal use. This expert suggested that the lack of this delay in the case of DES may have enabled premature, insufficiently informed access by Medicare beneficiaries to the technology.

According to key stakeholders interviewed for this case study, the DES manufacturing industry worked very closely with CMS during this decision-making process to advocate increases in reimbursement for DES. In the view of stent manufacturers, the use of DES at hospitals would depend largely on availability of adequate reimbursement from payers. Given the treatment effect demonstrated in the RCTs, the size of the potential target population of DES and the potential economic impact on Medicare spending, industry stakeholders decided to bring both clinical and economic information to the attention of CMS. According to one key stakeholder, economic evidence provided by the stent manufacturing industry to CMS as part of industry's push for higher reimbursement included models of the economic impact that DES would have on bypass surgery using Medicare's own data set. These analyses showed that shifting a small percentage of patients from bare metal stents to DES would not result in economic losses if new codes were created by CMS to allow adequate reimbursement to hospitals for purchasing the new stents.

Although it appears that cost analyses were made available to decision-makers at CMS, the extent to which this evidence was considered in the new coding and payment decisions for DES is unclear. As recounted by one industry expert, cost-effectiveness and other economic analyses of DES were not requested by CMS. According to this expert, stent manufacturers provided economic analyses to CMS in support of higher reimbursement. One key industry stakeholder said that economic evidence regarding DES was also supplied to additional people within DHHS. Another key industry stakeholder stated that, drawing upon externally generated evidence and data, CMS conducted its own economic analyses to determine how reducing restenosis with DES might affect Medicare spending.

While there is no national coverage determination (NCD) for DES in particular, there is national Medicare coverage of DES for patients with coronary artery disease who meet certain criteria, per existing national coverage of PTCA.⁷⁹ The coding system specifically provides designated

⁷⁸ Firth BG. Making Medicare responsive to patients and innovation. Presentation to AdvaMed, 2003.

⁷⁹ National coverage determination for percutaneous transluminal angioplasty (PTA) (20.7). Baltimore, MD: Centers for Medicaid and Medicare Services, 2006. Accessed October 17, 2006.

codes for DES that allow for higher payment relative to bare metal stents.⁸⁰ Overall, experts whom we interviewed concur that current reimbursement levels for DES are fairly aligned with costs incurred by hospitals.

Decision-making Among Private Payers

The extent to which private payers use economic evidence in coverage determinations regarding DES is unclear. According to one stent industry expert, economic arguments in favor of DES similar to those presented to CMS have been made to private payers and generally have been favorably received. Current publicly-available policy determinations at major private payers, including Aetna, Cigna and Regence, provide coverage of DES for a variety of indications.^{81,82,83} However, the rationales for coverage of DES provided by each of these payers do not cite cost, cost-effectiveness or other economic factors. We identified no published information from these payers about resource use, such as surgeries or medications following implantation of DES, which might allow for an indirect assessment of costs or cost-effectiveness.

One industry expert interviewed for this case study indicated that cost-effectiveness analyses are used by private payers in making coverage decisions for technologies like DES, but consideration of these factors is not publicly acknowledged. This interviewee discussed the strong tendency of private payers to monitor and to be influenced by CMS coverage determinations. For this reason, many private payers may not have scrutinized the economic evidence surrounding DES after CMS announced its coverage decision regarding the technology.

Decision-making at Hospitals

In an effort to ensure hospitals are receiving adequate reimbursement and that revenue is not being lost due to incorrect coding, ongoing efforts are made by the stent industry to educate hospitals on how to code correctly for DES. At least one major stent manufacturer organizes approximately 15 instructional seminars annually at hospitals around the country.⁸⁴ According to one key stakeholder, efforts to ensure adequate reimbursement to hospitals for DES are well-received by hospital staff and administration.

According to one industry expert, hospitals continue to order large numbers of DES. The initial steep increase in the number of DES being implanted in the US has flattened recently, in part because of the technology's ability to reduce restenosis, diminishing the need for subsequent implantations in the same patients. Despite these trends and efforts to educate hospital staff

http://www.cms.hhs.gov/MCD/viewncd.asp?ncd_id=20.7&ncd_version=3&basket=ncd%3A20%2E7%3A3%3A Percutaneous+Transluminal+Angioplasty+%28PTA%29.

⁸⁰ Firth BG 2003.

⁸¹ Clinical policy bulletins, number 0621 (revised), drug-eluting stents. Hartford, CT: Aetna Incorporated, 2005. Accessed August 31, 2006. <http://www.aetna.com/cpb/data/CPBA0621.html>.

⁸² Cigna HealthCare coverage position, number 0092, drug-eluting stents for ischemic heart disease. Philadelphia, PA: Cigna Corporation, 2006. Accessed September 7, 2006. http://www.cigna.com/health/provider/medical/procedural/coverage_positions/medical/mm_0092_coverage_positioncriteria_drug_eluting_stents_for_ischemic_heart_disease.pdf.

⁸³ Medical policy, number 119, surgery section- percutaneous transluminal angioplasty and stenting (excluding carotid and intracranial). Portland, OR: The Regence Group, 2006. Accessed September 7, 2006. <http://www.regence.com/trgmedpol/surgery/sur119.html>.

⁸⁴ J&J: Getting paid up-front for new technology. *In Vivo: The Business and Medicine Report* 2003; 17(11):28.

regarding payment, there is no indication that hospitals are using cost or cost-effectiveness information to make decisions regarding the use of DES. It remains to be seen how the recent findings regarding increased incidence of thrombosis will influence use of DES at hospitals.

2. Barriers to the Use of Economic Evidence

Stakeholders cited FDA's mandate to monitor safety and efficacy and not cost as the main barrier to using economic evidence in decision-making regarding DES. That CMS does not formally consider cost-effectiveness analyses was identified as a second barrier.

One stakeholder identified CMS' current coding system for DES as an additional barrier to the availability of economic evidence. CMS' current coding system does not differentiate between types of DES and, therefore, does not allow CMS to track differences in follow-up care as a result of implantation with SES or PES. Without access to this data, it is not possible to assess the relative cost-effectiveness of different forms of DES using Medicare claims data.

3. Potential for Future Use of Economic Evidence in Decision-making

Our interviewees universally agreed that cost-effectiveness analyses of DES are important and useful, but they expressed mixed views toward future use of cost-effectiveness and other economic analyses regarding DES. Regarding whether FDA should use cost-effectiveness to analyze DES, some experts emphasized that FDA should be responsible only for evaluating the safety and efficacy of new medical technologies, not for evaluating technologies on the basis of cost or cost-effectiveness. One stakeholder expressed that the analyses required to determine cost-effectiveness are not sufficiently straightforward or standardized to be the charge of one government agency alone.

It is not yet clear how findings about the small but significant increased risk of thrombosis associated with DES will influence the use of DES.^{85,86} The health and economic tradeoffs inherent in using DES could shift as a result of these new findings. The introduction of new stents to the DES market also may affect these tradeoffs and related decision-making.

4. Currently Needed Economic Analyses

Experts cited several areas in which the methodology used in cost-effectiveness analyses and other economic analyses of DES might be improved or changed to increase the utility of such studies. One industry expert stated that analyzing the cost-effectiveness of DES in clinical trials has limited value, advocating that researchers take a broader look at the technology, specifically at whether or not the total amount of money spent on revascularization has increased or decreased since the advent of DES. Another key stakeholder stated that comparisons of the cost-effectiveness of DES and CABG are needed as operations involving bare metal stent implantation become obsolete.

Several experts cited inaccuracies that can arise in calculating ICERs when the price of the comparator drops significantly relative to the new technology, as has been the case with bare metal stents. Because ICERs measure change in cost relative to the change in outcome, and

⁸⁵ Cheng M 2006.

⁸⁶ Abbott's XIENCE V drug-eluting coronary stent superior to TAXUS stent in Sprit II clinical trial, 2006.

because the price of bare metal stents now is dramatically lower than the cost of DES, the resulting cost-effectiveness ratio appears quite large, resulting in what appears to be poor cost-effectiveness of DES. Similarly, one expert discussed the need for a uniform price point for bare metal stents to be used in cost-effectiveness analyses of DES, in order to allow for more consistent comparison of results.

5. International Differences in Use of Economic Evidence in Decision-making

As with other technologies, cost-effectiveness analysis and other economic analyses appear to have played a much larger role in decision-making regarding DES in other countries than in the US. In a 2003 guidance to the National Health Service on the use of coronary artery stents, the UK's NICE considered both clinical and economic evidence.⁸⁷ After reviewing 5 analyses of the cost-effectiveness of DES, NICE concluded that the routine use of DES for patients with low risk of restenosis was not justified. Descriptions of forthcoming updates to this guidance include plans to evaluate cost minimization, cost-effectiveness and economic models related to DES. The planned update to this review calls for NICE to develop its own economic model, to evaluate the cost-effectiveness of DES versus bare metal stents, as well as SES versus PES.⁸⁸

A key expert interviewed for this case study identified differences in the impact of policy decisions in the US and the UK as a reason for the different weight given to economic evidence in the two countries. Whereas there are many different payers in the US, the NHS is the primary payer in the UK,⁸⁹ creating what one expert interviewee called “decision homogeneity.” Because decisions made in the UK regarding DES and other health technologies will be used by a nearly universal health service that is subject to what amounts to a budget cap, greater weight is given to all forms of evidence, including cost-effectiveness and other economic analyses.

E. Conclusions and Policy Implications

1. Role of Economic Evidence in Decision-making

Economic evidence was available to decision-makers during both the FDA's approval process of DES and during CMS' decision to establish designated coding and higher payment levels for DES. However, it is unclear how this economic evidence was used at these agencies, if at all. It appears that any economic evidence in support of DES was viewed as secondary, or supplementary, to data on the treatment effect of DES.

Several studies conducted since the initial introduction of DES have tracked clinical and economic outcomes of implantation of DES versus bare metal stents. The initial surge in the rates of DES implantation immediately following their FDA approval seems to owe largely, if not entirely, to findings demonstrating the clinical superiority of DES.

⁸⁷ Guidance on the use of coronary artery stents. Technology appraisal 71. London, England: National Institute for Clinical Evidence, 2003. Accessed September 5, 2006.

http://www.nice.org.uk/pdf/TA71_coronaryarterystents_fullguidance.pdf.

⁸⁸ Ischaemic heart disease – coronary artery stents (review). London, England: National Institute for Clinical Evidence, 2006. Accessed September 5, 2006. <http://www.nice.org.uk/page.aspx?o=239915>.

⁸⁹ About the NHS- how the NHS works. London, England: National Health Service England, 2006. Accessed September 7, 2006. <http://www.nhs.uk/England/AboutTheNhs/Default.cmsx>.

While diffusion and adoption of DES rose sharply following their release, recent reports have been published highlighting potential safety concerns associated with DES, particularly a small but significant increased risk of in-stent thrombosis. It remains to be seen what effect these studies will have on the diffusion and adoption of DES and what implications these findings will have on the perceived health and economic tradeoffs presented by DES.

2. Policy Implications

The CMS decision to create unique codes for DES prior to their FDA approval is unprecedented and is an example of a unique interaction among FDA, CMS and industry. While it appears that economic evidence was made available during the decision-making process in support of DES, it is unclear who requested the evidence and whether it was used. While there does not appear to have been a comparable interaction among FDA, CMS and industry since then, this experience has encouraged earlier and more extensive interaction and information sharing among these stakeholders, including preparation and sharing of economic evidence.

CASE STUDY IV: IMPLANTABLE CARDIOVERTER-DEFIBRILLATORS

A. Magnitude and Importance

Sudden cardiac death (SCD) refers to death resulting from an abrupt loss of heart function.⁴⁹⁶ Approximately 450,000 deaths per year in the US, and half of all global cardiovascular mortality, are attributed to SCD.⁴⁹⁷ Although estimates vary, there is consensus among recent reviews that the majority of SCD is caused by ventricular tachycardia degenerating into ventricular fibrillation.^{498,499,500,501} The two primary risk factors for SCD are prior heart attack and coronary artery disease, which are linked to approximately 75% and 80% of SCD cases, respectively.^{502,503} Patients with heart failure, often caused by coronary artery disease, are 6-9 times more likely to suffer SCD than the general population.⁵⁰⁴ Given that annual costs associated with coronary artery disease in the US exceed \$140 billion, these conditions also pose a significant economic burden for individuals, the health care system and society.⁵⁰⁵

First-line agents in SCD prevention include pharmacotherapy with angiotensin converting enzyme (ACE) inhibitors.⁵⁰⁶ Clinical evidence suggests that ACE inhibitors decrease mortality in patient populations with heterogeneous degrees of heart failure, but that arrhythmic mortality may not be significantly affected.⁵⁰⁷ Clinical studies also have strongly suggested a positive effect of aldosterone receptor antagonists on reduction of moderate to severe heart failure in patients concurrently taking ACE inhibitors and diuretics.⁵⁰⁸ Finally, beta blockers

⁴⁹⁶ Sudden cardiac death. Dallas, TX: American Heart Association, 2006. Accessed August 15, 2006. <http://www.americanheart.org/presenter.jhtml?identifier=4741>.

⁴⁹⁷ Goldberger Z, Lampert R. Implantable cardioverter-defibrillators: expanding indications and technologies. *JAMA* 2006;295(7):809-18.

⁴⁹⁸ Ibid.

⁴⁹⁹ Lane RE, Cowie MR, Chow AWC. Prediction and prevention of sudden cardiac death in heart failure. *Heart* 2005;91:674-80.

⁵⁰⁰ Bryant J, Brodin H, Loveman E, et al. The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review. *Health Technol Assess* 2005;9(36):1-150, iii.

⁵⁰¹ Huikuri HV, Castellanos A, Myerburg RJ. Sudden death due to cardiac arrhythmias. *N Engl J Med* 2001;345(20):1473-82.

⁵⁰² Sudden cardiac death. Cleveland, OH: The Cleveland Clinic, Heart & Vascular Institute, 2005. Accessed August 17, 2006. <http://www.clevelandclinic.org/heartcenter/pub/guide/disease/electric/scd.htm>.

⁵⁰³ Sinha SK, Mehta D, Gomes JA. Prevention of sudden cardiac death: the role of the implantable cardioverter-defibrillator. *Mt Sinai J Med* 2005;72(1):1-9.

⁵⁰⁴ Thom T, Haase N, Rosamond W, et al. Heart disease and stroke statistics – 2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation* 2006;113(6):e85-151.

⁵⁰⁵ Ibid.

⁵⁰⁶ Lane RE 2005.

⁵⁰⁷ Naccarella F, Naccarelli GV, Maranga SS, et al. Do ACE inhibitors or angiotensin II antagonists reduce total mortality and arrhythmic mortality? A critical review of controlled clinical trials. *Curr Opin Cardiol* 2002;17:6-18.

⁵⁰⁸ Pitt B, Zannad F, Remme WJ, et al (randomized aldactone evaluation study investigators). The effect of spironolactone on morbidity and mortality in patients with severe heart failure. *N Engl J Med* 1999;341:709-17.

have been clinically proven to reduce mortality and morbidity in patients with chronic heart failure.⁵⁰⁹

Second-line pharmacological prevention of sudden cardiac death largely consists of antiarrhythmic agents (e.g., amiodarone) targeted at ventricular arrhythmia.⁵¹⁰ Clinical trials testing these pharmaceuticals have returned diverse results, with some finding reductions in mortality, and others concluding that these medications are ineffective and/or may induce arrhythmia.^{511,512,513} Validated by findings of multiple randomized controlled trials, implantable cardioverter-defibrillators (ICDs) have emerged in recent years as alternatives or complements to pharmacological prevention and have been incorporated into specialty society guidelines.

B. Overview of the Technology

The first ICD was implanted in a patient in 1980, and FDA granted approval for the use of ICDs in 1985 as a secondary prevention in cardiac arrest survivors.⁵¹⁴ To date, in excess of 400,000 ICDs have been implanted in patients all over the world.⁵¹⁵ The use of ICDs has grown steadily in the US and abroad, though recent estimates suggest that the use of ICDs in the US exceeds other countries by a significant margin.⁵¹⁶ Rather than attributing this finding purely to population health profile differences, experts suggest that the discrepancy may be due to greater acceptance of broadened clinical indications for ICDs in the US, international differences in thresholds of cost-effectiveness and cultural differences in the perception of SCD.⁵¹⁷

ICDs continuously monitor heart rhythm, provide pacing assistance to counter rapid heartbeat, and deliver shocks in response to sustained ventricular arrhythmia (potentially fatal irregular contractions of the ventricles of the heart). The shocks delivered are intended to disrupt the devolution of ventricular arrhythmia into ventricular tachycardia (abnormal rapidity) and its subsequent, highly fatal state, ventricular fibrillation (rapid, quivering, ineffectual contractions). Results of RCTs of ICDs largely are favorable, providing generally strong evidence that using the device reduces rates of overall and arrhythmic death compared with medical management. In the late 1990s, three RCTs investigated the effectiveness of ICDs compared to anti-arrhythmic medications in a population of cardiac arrest survivors. A meta-analysis of these studies showed that ICDs reduced total mortality by 27% and arrhythmic mortality by 51%, with strong

⁵⁰⁹ CIBIS-II Investigators. The cardiac insufficiency bisoprolol study II (CIBIS-II): a randomized trial. *Lancet* 1999;353(9146):9-13.

⁵¹⁰ Lane RE 2005.

⁵¹¹ Pitt B 1999.

⁵¹² Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352(3):225-37.

⁵¹³ Doval HC, Nul DR, Grancelli HO, et al. Randomised trial of low-dose amiodarone in severe congestive heart failure. Grupa de estudio de la sobrevivencia en la insuficiencia cardiaca en Argentina (GESICA). *Lancet* 1994;344:493-8.

⁵¹⁴ Decision memo for implantable defibrillators. Baltimore, MD: Centers for Medicare and Medicaid Services, 2005. Accessed September 14, 2006. <http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=148>.

⁵¹⁵ DeNoon D. When implanted heart devices fail. New York, NY: WebMD, 2006. Accessed October 12, 2006. <http://www.webmd.com/content/article/121/114295.htm>.

⁵¹⁶ Seidl K, Senges J. Worldwide utilization of implantable cardioverter-defibrillators now and in the future. *Card Electrophysiol Rev* 2003;7(1):5-13.

⁵¹⁷ Ibid.

statistical significance. These studies largely established the clinical evidence for use of the ICD as a secondary prevention for cardiac arrest survivors.⁵¹⁸

The population of potential ICD patients is limited by low survival rates of cardiac arrest.⁵¹⁹ Toward greater prevention of cardiac arrest, several clinical trials have been conducted to identify high-risk individuals who might benefit from the ICD as a primary prevention.⁵²⁰ The first round of these trials began in 1996 with the Multicenter Automatic Defibrillator Trial (MADIT), which investigated the effectiveness of the ICD in a patient population with left ventricular dysfunction after myocardial infarction (MI), a history of nonsustained ventricular tachycardia and inducible, nonsuppressible, ventricular tachyarrhythmia.⁵²¹ In 1999, the Multicenter Unsustained Tachycardia Trial (MUSTT) continued to explore the importance of the ICD as a primary prevention.⁵²² Taken together, the results of MADIT and MUSTT indicate a strong benefit of ICD use in a patient population with coronary artery disease, low left ventricular ejection fraction (a measure of the efficiency of the expulsion of blood from of the left ventricle) and inducible arrhythmia. Subgroup analysis from MUSTT, however, indicated poor predictability of electrophysiologic testing (i.e., arrhythmia inducibility) as a risk stratifier and, thus, as a potential clinical guideline for ICD use. MADIT-II, published in 2002, confirmed earlier findings from MUSTT on electrophysiologic testing.⁵²³ The most recent clinical trial of ICDs, the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), continued to expand the potential patient populations for primary prevention with ICDs, showing equivalent effectiveness in patients with ischemic and non-ischemic heart failure. In addition to evaluating the clinical effectiveness of ICDs, several cardiac factors (e.g., left ventricular ejection fraction, T-wave alternans) also were explored as part of these studies to predict which individuals likely are to experience the greatest benefit from ICDs, returning varied results.

The strong findings of these large RCTs helped to establish the use of ICDs for particular indications in mainstream cardiology. As of 2006, the American College of Cardiology/American Heart Association/European Society of Cardiology Guidelines for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death recommended ICD use for primary prevention in patients with left ventricular dysfunction as a result of a previous myocardial infarction, who suffer from New York Heart Association (NYHA) class II or III heart failure, have a left ventricular ejection fraction of 30% to 40%, and are expected to maintain a good functional state for at least one year post-implantation.⁵²⁴

Given the potential for their widespread use and their sizable unit cost, major third-party payers and policymakers anticipated that ICDs could have a large economic impact. For

⁵¹⁸ Goldberger Z 2006.

⁵¹⁹ Seidl K 2003.

⁵²⁰ Goldberger Z 2006.

⁵²¹ Moss AJ, Hall WJ, Cannom DS, et al. (Multicenter Automatic Defibrillator Implantation Trial investigators). Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. *N Engl J Med* 1996;335(26):1933-40.

⁵²² Buxton AE, Lee KL, Fisher JD, et al. (Multicenter Unsustained Tachycardia Trial Investigators). A randomized study of the prevention of sudden death in patients with coronary artery disease. *N Engl J Med* 1999;341(25):1882-90.

⁵²³ Goldberger Z 2006.

⁵²⁴ Zipes DP, Camm AJ, Borggrefe M, et al. ACC/AHA/ESC guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. *Journal of the American College of Cardiology* 2006;48(5):247-346.

example, it has been estimated that, at a unit cost of \$30,000, implanting ICDs in 230,000 US patients in a year would cost \$6.9 billion per year, or about 0.4% of national health care expenditures.⁵²⁵ Given the potential cost of treating patients with ICDs, many studies also have evaluated the cost-effectiveness of the device and its economic implications for the health system. Main findings from these studies are summarized below.

C. Economic Value of the Technology

We reviewed studies assessing the cost-effectiveness of ICDs. Twenty-four studies were identified that used cost-effectiveness analysis or cost minimization analysis of ICDs, ICD implantation procedures or ICD lead systems. These studies are described below according to whether they address primary or secondary preventive uses of ICDs. We also identified and reviewed 10 articles that examined various cost drivers of ICDs. Further, we interviewed experts such as practicing physicians, health economists and representatives from ICD manufacturers.

1. Secondary Preventive Uses of ICDs

Eight studies investigated the cost-effectiveness of ICDs for secondary prevention for cardiac arrest survivors. Of these studies, 4 were conducted in the US and 4 were conducted elsewhere (2 in Canada and 2 in the Netherlands). Three of the cost-effectiveness analyses used clinical data from RCTs, while the remaining studies used clinical data from observational studies or non-randomized controlled trials.

US-based Studies

US-based studies on ICDs as a secondary prevention generally have concluded that ICDs are cost-effective relative to conventional medical therapy.

An analysis published in 1990, based on data from the available literature, relevant databases and expert opinion, estimated that net cost-effectiveness of using ICDs in high-risk patients was \$15,000–\$25,000 per life-year saved (LYS) versus a comparison group that did not receive ICDs. The study predicted that the cost-effectiveness of the device would improve as its longevity increased.⁵²⁶

A 1992 analysis, based on actual variable cost figures and modeling predictions for 55-year old patients estimated that, as a secondary prevention, ICDs had an incremental cost-effectiveness ratio (ICER) of \$29,200 per QALY over treatment with amiodarone. This ratio was decreased substantially if the battery life of the ICD could be extended. While this model was not sensitive to age at ICD implantation, it was sensitive to the quality of life of patients taking amiodarone. Use of ICDs was the dominant strategy if the drug-taking population's quality of life was 40% lower than that of those receiving ICDs.⁵²⁷

Using Michigan Medicare data to construct a decision model, a 1995 study compared patients with ICDs to those monitored electrophysiologically while on antiarrhythmics. This study

⁵²⁵ Sinha SK 2005.

⁵²⁶ Kuppermann M, Luce BR, McGovern B, et al. An analysis of the cost effectiveness of the implantable defibrillator. *Circulation* 1990;81(1):91-100.

⁵²⁷ Larsen GC, Manolis AS, Sonnenberg FA, et al. Cost-effectiveness of the implantable cardioverter-defibrillator: effect of improved battery life and comparison with amiodarone therapy. *J Am Coll Cardiol* 1992;19(6):1323-34.

found that ICDs cost \$31,000 per life-year saved over a 6-year horizon, assuming a 4-year ICD battery life.⁵²⁸

A cost-effectiveness analysis published in 2002 examined the marginal benefit of ICDs over antiarrhythmic drugs in survivors of, “serious ventricular tachyarrhythmias.” This study found that the incremental cost per QCG by ICD implantation over a 3 year timeframe was \$66,677 compared to treatment with antiarrhythmic drugs. The model was sensitive to a patient’s left ventricular ejection fraction; for left ventricular ejection fraction $\leq 35\%$, the ICER for ICD implantation was \$60,967 per QALY gained; for left ventricular ejection fraction $>35\%$, the ICER rose to \$536,106 per QALY gained.⁵²⁹

Non-US Studies

In contrast to their US counterparts, studies conducted in other countries have come to more heterogeneous conclusions on the cost-effectiveness of secondary preventive use of ICDs. In 1996, 2 studies from the Netherlands found ICDs to be cost-saving relative to standard of care drug therapy. One of these analyses compared the cost-effectiveness of ICD implantation and conventional drug treatment in an unspecified hypothetical patient population, relying on data from a previously performed prospective study. Following patients for an average of 27 months, the researchers found the use of ICDs to be cost-saving as drug treatment cost US\$87 per day alive, while ICDs cost \$64 or \$51 per day of life, depending on the device’s battery life.⁵³⁰

The other Dutch study compared patients who had survived SCD, including those with ICDs implanted from the start or those being monitored on antiarrhythmic drugs and implanted later with ICDs as deemed appropriate.⁵³¹ Using ICDs from the start proved more cost effective than monitoring, costing US\$63 per day of life versus \$94 over a median follow-up period of 729 days. Prescribing only antiarrhythmic drugs was the least expensive strategy, but was associated with very high relative mortality.⁵³²

In Canada, however, 2 cost-effectiveness studies using data from the Antiarrhythmics Versus Implantable Defibrillators (AVID) RCT concluded that ICDs were not a cost-effective alternative to treatment with amiodarone, with an ICER of CA\$213,543 (approximately US\$140,000) per QALY gained.^{533,534} The model was sensitive to the number of risk factors. If patients had ≥ 2 of 3 risk factors (≥ 70 years old, left ventricular ejection fraction $\leq 35\%$ or NYHA class III heart

⁵²⁸ Kupersmith J, Hogan A, Guerrero P, et al. Evaluating and improving the cost-effectiveness of the implantable cardioverter-defibrillator. *Am Heart J* 1995;130(3 Pt. 1):507-15.

⁵²⁹ Larsen G, Hallstrom A, McAnulty A, et al. Cost-effectiveness of the implantable cardioverter-defibrillator versus antiarrhythmic drugs in survivors of serious ventricular tachyarrhythmias. *Circulation* 2002;105(17):2049-57.

⁵³⁰ Hauer RN, Derksen R, Wever EF. Can implantable cardioverter-defibrillator therapy reduce healthcare costs? *Am J Cardiol* 1996;78(5A):134-9.

⁵³¹ Wever EF, Hauer RN, Schrijvers G, et al. Cost effectiveness of the implantable defibrillator as first-choice therapy versus electrophysiologically guided, tiered strategy in postinfarct sudden death survivors: A randomized study. *Circulation* 1996;93(3):489-96.

⁵³² Ibid.

⁵³³ O’Brien BJ, Connolly SJ, Goeree R, et al. Cost-effectiveness of the implantable cardioverter-defibrillator: results from the Canadian Implantable Defibrillator Study (CIDS). *Circulation* 2001;103(10):1416-21.

⁵³⁴ Sheldon R, O’Brien BJ, Blackhouse G, et al. Effect of clinical risk stratification on cost-effectiveness of the implantable cardioverter-defibrillator: the Canadian implantable defibrillator study. *Circulation* 2001;104(14):1622-6.

failure), ICDs cost \$65,195 per year of life gained.⁵³⁵ The relatively high cost-effectiveness ratios may have arisen because the duration of AVID was cut from 10 years to less than 5 years under an early stopping rule after researchers identified a 38% risk reduction in the ICD group.⁵³⁶ Early stopping rules are essential for ethical reasons; however, these rules can negatively affect cost-effectiveness studies. Specifically, AVID's reduction in study time likely under-represents the effectiveness of ICDs by failing to account for long-term survival. Thus, the CQG may appear higher than it actually is, due to the large initial fixed cost of implantation. Modeling techniques that could project cost and health outcomes over a greater time period might result in findings of greater cost-effectiveness of ICD implantation.

2. Primary Preventive Uses of ICDs

In contrast to the few cost-effectiveness analyses of ICDs for secondary prevention, 16 cost-effectiveness analyses have been performed on ICDs as a primary prevention. Of these, 12 were US-based and 6 were based on results from RCTs, including MADIT, MADIT-II and SCD-HeFT.

US-based Studies

The first US studies on the cost-effectiveness of ICDs as a primary prevention examined patients presenting with ventricular tachycardia (VT) or ventricular fibrillation (VF). In a 2002 study, records of Medicare patients with histories of VT or VF receiving and not receiving ICDs were reviewed over a 9 year period. The researchers found that ICDs were associated with significantly lower mortality than conventional care and cost \$78,400 per life-year gained.⁵³⁷

An analysis published in 1998 was based on the expanded indications of the patient population data from the MADIT RCT. MADIT included patients with a past myocardial infarction; left ventricular ejection fraction $\leq 35\%$; unsustained VT and NYHA class I, II or III heart failure. Patients who received ICDs were compared to patients who received conventional medical therapy as indicated by their individual physician. Compared to conventional therapy, ICDs had an incremental ICER of \$27,000 per LYS, which the investigators found to be cost-effective. This model was sensitive to the cost of the device and its implantation.⁵³⁸

A 2001 decision model used data from the Myocardial Infarction Triage and Intervention registry and the available academic literature to examine the cost-effectiveness of ICDs and amiodarone treatment in a population of patients with a history of myocardial infarction without sustained ventricular arrhythmia. The study did not compare the use of ICDs to amiodarone therapy, rather it compared each strategy to no treatment. The researchers found ICDs to be the most effective and costly treatment strategy. However, ICDs had to decrease arrhythmic death by 50% (as compared to no treatment) to reach a commonly accepted ICER of

⁵³⁵ Ibid.

⁵³⁶ Antiarrhythmics versus implantable defibrillators. Bethesda, MD: National Library of Medicine, 2005. Accessed August 17, 2006. <http://www.clinicaltrials.gov/ct/show/NCT00000531>.

⁵³⁷ Weiss JP, Saynina O, McDonald KM, et al. Effectiveness and cost-effectiveness of implantable cardioverter defibrillators in the treatment of ventricular arrhythmias among Medicare beneficiaries. *Am J Med* 2002;112(7):519-27.

⁵³⁸ Mushlin AI, Hall WJ, Zwanziger J, et al. The cost-effectiveness of automatic implantable cardiac defibrillators: results from MADIT-Multicenter Automatic Defibrillator Implantation Trial. *Circulation* 1998;97(21):2129-35.

\$75,000. Of note, the model was quite sensitive to a patient's left ventricular ejection fraction, with cost-effectiveness falling when left ventricular ejection fraction was higher.⁵³⁹

Using data from the relevant literature, expert opinion, Medicare/Medicaid fee schedule payments and the Bureau of Labor Statistics, a 2004 model calculated the cost-effectiveness of ICDs against that of standard drug therapy in a population of patients with congestive heart failure. The model found that the incremental CQG was \$122,947 and was sensitive to "patient utility" and the rate of sudden death among patients with congestive heart failure. The researchers concluded that treatment with ICDs is not cost-effective.⁵⁴⁰

In 2004, the Blue Cross and Blue Shield Association Technology Evaluation Center (BCBSA TEC) commissioned a cost-effectiveness study using clinical data from MADIT-II, the most definitive RCT on primary preventive use of ICDs to date. Patients in MADIT-II had coronary artery disease and left ventricular ejection fraction less than or equal to 30% and experienced a 31% reduction in mortality as a result of ICD use. At \$50,900 per QALY (compared to conventional treatment), BCBSA TEC found that ICDs in the MADIT-II population were cost-effective. Further analysis indicated that ICDs were particularly cost-effective in patients who had survived SCD (\$48,400 per QALY) but less cost-effective in patients screened only for a prior MI (\$59,900 per QALY) or patients screened for congestive heart failure (\$64,300 per QALY). The authors state that the model is most sensitive to ICD efficacy in preventing sudden cardiac death, ICD impact on quality of life, cost of the device, frequency of replacement and age of patient. The authors concluded that MADIT-II may increase substantially the number of people eligible to receive ICDs.⁵⁴¹

The TEC investigators continued their research on this issue by refining and then applying their model to the clinical findings of 8 major RCTs (including SCD-HeFT).⁵⁴² Across these studies, the cost-effectiveness of ICDs ranged from \$34,000 to \$70,200 per QALY.⁵⁴³ In comparison to a cost-effectiveness threshold of \$100,000 per QALY, the authors judged the ICD to be relatively cost-effective in patients with prior VT or VF, patients with a prior MI and left ventricular ejection fraction $\leq 35\%$ and in patients with nonischemic dilated cardiomyopathy with left ventricular ejection fraction $\leq 30\%$. Applying SCD-HeFT data to their model, the TEC investigators also suggested that the expansion of primary preventive ICD implantation may be cost-effective in patients with nonischemic cardiomyopathy and reduced left ventricular function.⁵⁴⁴ A separate study performed by different researchers in 2004 estimated that, if patient inclusion criteria were expanded, ICDs could be cost-effectively implanted in nearly 600,000 current at-risk patients in the US.⁵⁴⁵

⁵³⁹ Sanders GD, Hlatky MA, Every NR, et al. Potential cost-effectiveness of prophylactic use of the implantable cardioverter defibrillator or amiodarone after myocardial infarction. *Ann Intern Med* 2001;135(10):870-83.

⁵⁴⁰ Chen L, Hay JW. Cost-effectiveness of primary implanted cardioverter defibrillator for sudden death prevention in congestive heart failure. *Cardiovasc Drugs Ther* 2004;18(2):161-70.

⁵⁴¹ Sanders GD, Owens DK, Hlatky MA. Special report: cost-effectiveness of implantable cardioverter-defibrillators in a MADIT-II population. Chicago, IL: Blue Cross Blue Shield Association, Technology Evaluation Center, 2004. Accessed October 17, 2006. http://www.bcbs.com/tec/vol19/19_03.html.

⁵⁴² Sanders GD, Hlatky MA, Owens DK. Cost-effectiveness of implantable cardioverter-defibrillators. *N Engl J Med* 2005;353(14):1471-80.

⁵⁴³ *Ibid.*

⁵⁴⁴ *Ibid.*

⁵⁴⁵ Jauhar S, Slotwiner DJ. The economics of ICDs. *N Engl J Med* 2004;351(24):2542-4.

In 2005 and 2006, there were 3 additional cost-effectiveness analyses of ICDs using MADIT-II clinical data and/or MADIT-II inclusion/exclusion criteria.^{546,547,548} These studies all yielded cost-effectiveness ratios for ICDs of less than \$100,000 per QALY in patients with a prior MI and reduced left ventricular function.^{549,550,551} For instance, one cost-effectiveness analysis using the MADIT-II findings found ICDs to be particularly cost-effective in patients who are microvolt T-wave alternans non-negative. This finding suggested further potential for risk stratification of the MADIT-II population through T-wave alternans testing.⁵⁵²

A recent modeling exercise compared the cost-effectiveness of ICDs to amiodarone therapy in patients with stable, moderately symptomatic heart failure, NYHA classification II or III and left ventricular ejection fraction $\leq 35\%$. Using data from SCD-HeFT, hospital billing information and the Medicare fee schedule, the model estimated the cost-effectiveness of ICDs to be \$41,530 per QALY compared to medical therapy. The investigators also found that amiodarone had little effect on mortality reduction, despite costing more than other forms of medicinal treatment.⁵⁵³

Evidence from these studies and conclusions from other systematic reviews indicate that the implantation of ICDs is cost-effective in patients with previous cardiac arrest, patients with reduced left ventricular ejection fraction and ischemic cardiomyopathy (typically characterized by a prior MI) and patients with non-ischemic cardiomyopathy and reduced left ventricular ejection fraction.⁵⁵⁴ While T-wave alternans testing is a possible risk stratifier that may identify patients most likely to benefit from ICD implantation, further study likely is needed.⁵⁵⁵

Non-US Studies

Four non-US studies have investigated the cost-effectiveness of ICDs as a primary prevention, with heterogeneous results. A Canadian model, based on relevant studies and Canadian cost figures, found ICDs to be cost-effective in an unspecified population, with an ICER of \$42,070-\$50,949 (Canadian dollars; depending on annual discount rate) per life-year saved compared to medical therapy.⁵⁵⁶ This figure only incorporated hospital costs, but the authors assumed that professional costs (e.g., physician visits) were similar between ICD implantation and conventional medical therapy. The model was most sensitive to the reduction in mortality attributed to ICD implantation. The authors concluded that ICDs are efficacious, but that each health institution must decide for itself whether or not to provide ICDs for primary

⁵⁴⁶ Al-Khatib SM, Anstrom KJ, Eisenstein EL, et al. Clinical and economic implications of the Multicenter Automatic Defibrillator Implantation Trial-II. *Ann Intern Med* 2005;142(8):593-600.

⁵⁴⁷ Zwanziger J, Hall WJ, Dick AW, et al. The cost effectiveness of implantable cardioverter-defibrillators: results from the Multicenter Automatic Defibrillator Implantation Trial (MADIT)-II. *J Am Coll Cardiol* 2006;47(11):2310-8.

⁵⁴⁸ Chan PS, Stein K, Chow T, et al. Cost-effectiveness of a microvolt T-wave alternans screening strategy for implantable cardioverter-defibrillator placement in the MADIT-II eligible population. *J Am Coll Cardiol* 2006;48(1):112-21.

⁵⁴⁹ Al-Khatib SM 2005.

⁵⁵⁰ Zwanziger J 2006.

⁵⁵¹ Chan PS 2006.

⁵⁵² Ibid.

⁵⁵³ Mark DB, Nelson CL, Anstrom KJ, et al. Cost-effectiveness of defibrillator therapy or amiodarone in chronic stable heart failure: results from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). *Circulation* 2006;114(2).

⁵⁵⁴ Stanton MS, Bell GK. Economic outcomes of implantable cardioverter-defibrillators. *Circulation* 2000;101(9):1067-74.

⁵⁵⁵ Chan PS 2006.

⁵⁵⁶ McGregor M, Chen J. Use of the implantable cardiac defibrillator (ICD) at the McGill University Health Centre (MUCH). Montreal, QC: McGill University Health Centre, 2003. Accessed October 17, 2006. <http://www.mcgill.ca/files/tau/icd.pdf>.

prevention.⁵⁵⁷ An additional Canadian systematic review found the cost-effectiveness of ICDs to depend on characteristics of the patients treated and identified patients at high risk for VT and VF as most likely to benefit from ICD implantation.⁵⁵⁸ Similarly, in 2000 and 2005 the University of Southampton (UK) reviewed evidence from US, UK and other countries for the National Health Service.^{559,560} Both of these studies found that ICDs had heterogeneous cost-effectiveness ratios across populations and that further risk stratification was needed to identify patients most likely to benefit from ICD primary preventive use.^{561,562}

3. ICD Cost Drivers

To better understand the costs of ICDs, we reviewed 10 articles examining various cost drivers and spoke to several experts from relevant fields. Experts reported that the cost of ICDs has decreased little or remained unchanged over time. They suggested new features that have been added to the device have helped to maintain its price. However, one representative from an ICD manufacturer claimed that, despite such new features, the unit price of ICDs had not kept pace with medical inflation.

Other cost drivers were investigated by several research teams, to discover ways in which the cost-effectiveness of ICDs might be improved. Five teams identified nonthoracotomy implantation of the ICD as a significant cost-saver, and 1 of these teams found even greater savings from pectoral implantation as opposed to abdominal ICD implantation.^{563,564,565,566,567} Two studies identified electrophysiologic studies (EPS) as a minimally cost-advantageous risk stratifier, and another study suggested that, if EPS is used, ICD implantation should be done in the same visit rather than

⁵⁵⁷ Ibid.

⁵⁵⁸ Lynd LD, O'Brien BJ. Cost-effectiveness of the implantable cardioverter defibrillator: a review of current evidence. *J Cardiovasc Electrophysiol* 2003;9(Suppl):S99-S103.

⁵⁵⁹ Parkes J, Bryant J, Milne R. Implantable cardioverter defibrillators: arrhythmias: a rapid and systematic review. *Health Technology Assessment* 2000;4(26):1-69.

⁵⁶⁰ Bryant J, Brodin H, Loveman E, et al. The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review. *Health Technology Assessment* 2005;9(36):1-150, iii.

⁵⁶¹ Parkes J 2000.

⁵⁶² Bryant J 2005.

⁵⁶³ Cardinal DS, Connelly DT, Steinhaus DM, et al. Cost savings with nonthoracotomy implantable cardioverter-defibrillators. *Am J Cardiol* 1996;78(11):1255-9.

⁵⁶⁴ Venditti FJ Jr., O'Connell M, Martin DT, Shahian DM. Transvenous cardioverter defibrillators: cost implications of a less invasive approach. *Pacing Clin Electrophysiol* 1995;18(4 Pt. 1):711-5.

⁵⁶⁵ Luceri RM, Zilo P, Habal SM, David IB. Cost and length of hospital stay: comparisons between nonthoracotomy and epicardial techniques in patients receiving implantable cardioverter defibrillators. *Pacing Clin Electrophysiol* 1995;18(1 Pt. 2):168-71.

⁵⁶⁶ Williamson BD, Man KC, Niebauer M, et al.. The economic impact of transvenous defibrillation lead systems. *Pacing Clinical Electrophysiology* 1994;17(12 Pt. 1):2297-303.

⁵⁶⁷ Gold MR, Froman D, Kavesh NG, et al. A comparison of pectoral and abdominal transvenous defibrillator implantation: analysis of costs and outcomes. *J Int Cardiol Electrophysiol* 1998;2(4):345-9.

separately to reduce cost.^{568,569,570} Finally, 1 study suggested that pre-implantation discharge testing of ICDs can be eliminated without increased patient risk to save significant cost.⁵⁷¹

A retrospective study of patients with ischemic (due to poor blood flow in the heart muscle) ventricular arrhythmias examined the effect of two different treatment strategies involving CABG surgery and ICD implantation on treatment outcomes and costs. The analysis found no significant difference in outcomes or costs between performing these procedures concurrently and performing only the CABG first, then relying on future electrophysiologic testing to determine if an ICD was necessary.⁵⁷² Experts interviewed for this case study identified this area as significantly lacking in cost-effectiveness research and a new front for investigating the cost-effectiveness of medical interventions.

D. Critical Appraisal of Relevant Decisions

1. Food and Drug Administration

The FDA first approved the implantable defibrillator in 1985 for secondary prevention in cardiac arrest survivors.⁵⁷³ According to some experts interviewed for this case study, the high near-term mortality rates for cardiac arrest survivors prompted FDA to approve the technology despite a lack of robust supporting clinical evidence. This reflects the fact that the threshold for approval can change depending on whether a technology offers a new option to patients who otherwise would have no remaining options. That is, FDA may consider the risk-to-benefit ratio relative to existing treatment alternatives for a population when determining an appropriate evidence threshold for approval. In contrast to the patient population for secondary prevention using ICDs, the much larger potential patient population for primary prevention using ICDs called for a more rigorous level of evidence. On May 17, 1996, FDA first approved the ICD for primary prevention of SCD, i.e., in patients with previous heart attacks who are at high risk for SCD due to ventricular arrhythmias. The indications approved by FDA were consistent with the inclusion/exclusion criteria of MADIT.⁵⁷⁴

We identified no evidence of the matter of cost or cost-effectiveness entering discussion regarding ICDs at the FDA prior to 2000. On June 20, 2000, the Circulatory System Devices Panel of the FDA's Medical Devices Advisory Committee met to discuss "functional indication" approval of ICDs (a statement that describes what the device does without specifying a patient

⁵⁶⁸ O'Donoghue S, Platia EV, Brooks-Robinson S, Mispireta L. Automatic implantable cardioverter-defibrillator: is early implantation cost-effective? *J Am Coll Cardiol* 1990;16(5):1258-63.

⁵⁶⁹ Hallstrom AP, Stein PK, Schneider R, et al. Characteristics of heart beat intervals and prediction of death. *Int J Cardiol* 2005;100(1):37-45.

⁵⁷⁰ Pires LA, Ravi S, Lal VR, Kahlon JP. Safety and potential cost savings of same-setting electrophysiologic testing and placement of transvenous implantable cardioverter-defibrillators. *Clin Cardiol* 2001;24(9):592-6.

⁵⁷¹ Lurie KG, Iskos D, Fetter J, et al. Prehospital discharge defibrillation testing in ICD recipients: a prospective study based on cost analysis. *Pac Clin Electrophysiol* 1999;22(1 Pt. 2):192-6.

⁵⁷² Lee JH, Folsom DL, Biblo LA, et al. Combined internal cardioverter-defibrillator implantation and myocardial revascularization for ischemic ventricular arrhythmias: optimal cost-effective strategy. *Cardiovasc Surg* 1995;3(4):393-7.

⁵⁷³ Decision memo for implantable defibrillators. Baltimore, MD: Centers for Medicare and Medicaid Services, 2005. Accessed September 14, 2006. <http://www.cms.hhs.gov/mcd/viewdecisionmemo.asp?id=148>.

⁵⁷⁴ FDA approval of wider use of implantable defibrillator. *FDA Medical Bulletin* 1996;(26)3.

population).⁵⁷⁵ At this meeting, one panelist cited adverse cost implications from misuse of ICDs under a functional use approval. However, this panelist noted that physicians using guidelines and expert decision-making were unlikely to abuse broader FDA-approved indications.⁵⁷⁶ Consistent with overwhelming panelist consensus regarding the clinical effectiveness of ICDs, the FDA approved ICDs for functional use in 2005.⁵⁷⁷

All experts interviewed for this case study noted that the FDA rarely, if ever, considers economic evidence in their approval decisions. However, an expert from a major implantable medical device company observed that the cost of ICD devices appeared to expedite FDA review of a lower-cost ICD. On May 15, 2003, the FDA issued a press release citing rapid approval of a new, \$10,000 per unit Biotronik ICD. In the press release, FDA Commissioner Mark McClellan was quoted as saying, “FDA is committed to helping patients get access to safe and effective new medical technology quickly, at affordable prices. Lower cost ICDs will mean that these critical life-saving devices will be more affordable and accessible for many patients who need them.”⁵⁷⁸ One expert interviewed for this case study noted that this type of press release was unprecedented and reflects the heightened awareness and permeation of cost into FDA actions on ICDs. Thus, while matters of cost and cost-effectiveness do not appear to have explicitly affected FDA decisions on device approval, they may have played a role in expediting the review of at least one less expensive ICD model.

2. Medicare

Coverage for Secondary Prevention

CMS first provided Medicare coverage of ICDs in 1986 for cardiac arrest survivors previously experiencing ventricular fibrillation.⁵⁷⁹ As noted by some observers, the decision to pay for ICD implantation in survivors of cardiac arrest (i.e., secondary prevention) was not a difficult one, and neither cost-effectiveness nor clinical effectiveness data were particularly critical to Medicare’s decision to cover the device. Indeed, “the ICD appeared to be an exception to the general rule about needing a randomized trial to prove the effectiveness of therapy.”⁵⁸⁰ According to some experts interviewed for this case study, cardiac arrest survivors had sufficiently poor near-term survival rates that any intervention was assumed to be more likely to provide benefit than harm. Furthermore, the size of the patient population that was eligible to receive an ICD for secondary prevention under Medicare probably was not large enough to elicit concerns about cost impact to Medicare. CMS’ coverage revisions in 1999 that expanded the criteria for secondary prevention appear to have been similarly uncontroversial.⁵⁸¹

⁵⁷⁵ Open public hearing of the Circulatory System Devices Panel meeting, Medical Devices Advisory Committee. Rockville, MD: US Food and Drug Administration, 2000. Accessed September 15, 2006.

<http://www.fda.gov/ohrms/dockets/ac/04/transcripts/Pages%20from%204033t1-01.pdf>.

⁵⁷⁶ Ibid.

⁵⁷⁷ Draft guidance for industry: functional indications for implantable cardioverter defibrillators. Rockville, MD: US Food and Drug Administration, 2005. Accessed September 14, 2006.

<http://www.fda.gov/cdrh/ode/guidance/1304.html>.

⁵⁷⁸ FDA approves lower cost implantable defibrillator. Rockville, MD: US Food and Drug Administration, 2003. Accessed September 14, 2006. <http://www.fda.gov/bbs/topics/NEWS/2003/NEW00906.html>.

⁵⁷⁹ McClellan MB, Tunis SR. Medicare coverage of ICDs. *N Engl J Med* 2005;352(3):222-4.

⁵⁸⁰ Hlatky MA, Sanders GD, Owens DK. Evidence-based medicine and policy: the case of the implantable cardioverter defibrillator. *Health Affairs* 2005;24(1):42-51.

⁵⁸¹ Ibid.

Coverage as a Primary Prevention

The MADIT-II RCT was terminated in late 2001, after showing strong clinical effectiveness of ICDs in patients with a prior MI and left ventricular ejection fraction $\leq 30\%$.⁵⁸² Device manufacturers quickly sought to capitalize on these findings and requested Medicare coverage of ICDs for primary prevention of SCD. In early 2003, the Medicare Coverage Advisory Committee (MCAC) convened to address and advise on this issue.

MCAC identified three main caveats associated with the MADIT-II data that had a bearing on coverage, including: 1) clinical results from centers participating in the study were heterogeneous (albeit conclusively positive on ICD use in the aggregate); 2) certain subpopulations of the MADIT-II cohort appeared to benefit from ICDs more than others; and 3) the ongoing SCD-HeFT trial had the potential to better clarify appropriate primary preventive ICD use. Despite these caveats, MCAC unanimously recommended coverage for using ICDs for primary prevention of SCD for all beneficiaries meeting the MADIT-II study criteria.⁵⁸³

As recounted by some observers, “when the FDA approved ICDs for MADIT II indications and the public Medicare Coverage and Advisory Committee voted unanimously in February in favor of extending Medicare coverage, it appeared that CMS approval was a foregone conclusion.”⁵⁸⁴ However, comments at the time by the CMS Chief Medical Officer, Sean Tunis, suggested that the agency interpreted the MCAC finding to be inconclusive: “[CMS is] quite aware that many of the critics of MADIT II stayed home from the [MCAC meeting]. We [have been] in contact with many of them since, and they make equally good comments.”⁵⁸⁵ In June 2003, CMS appeared to act contrary to the MCAC recommendation and issued an NCD that modified the MADIT-II criteria by adding a requirement of delayed electrical conduction through the left ventricle (a QRS restriction).⁵⁸⁶ According to some sources, this electrophysiological restriction cut the number of eligible Medicare beneficiaries in half.⁵⁸⁷

Significant debate exists on the rationale behind Medicare’s QRS restriction. The CMS Chief Medical Officer expressed skepticism at the MADIT-II results and argued that the MADIT-II study insufficiently stratified the patient population by risk.⁵⁸⁸ Some authors echoed Dr. Tunis’ evaluation of clinical uncertainty in the scientific community regarding the benefit of ICDs in the entire MADIT-II population.⁵⁸⁹ Furthermore, experts consulted for this case study suggested that unpublished results from a retrospective analysis of MADIT-II data played a key role in CMS’ decision-making process. This retrospective analysis reportedly identified patients with prolonged QRS intervals as the most likely to benefit from ICDs and was a key factor in CMS’ decision to issue the QRS restriction.⁵⁹⁰

⁵⁸² Impact of the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II). St. Paul, MN: Guidant Corporation, 2006. Accessed September 6, 2006. <http://www.guidant.com/physician/madit/>.

⁵⁸³ Hlatky MA 2005.

⁵⁸⁴ Ibid.

⁵⁸⁵ Peck P. CMS draws heat as coverage of MADIT II ICD decision draws near. NewsRhythms. May 28, 2003. Accessed August 30, 2006. <http://www.medscape.com/viewarticle/456391>.

⁵⁸⁶ Hlatky MA 2005.

⁵⁸⁷ Jauhar S 2004.

⁵⁸⁸ O’Riordan M 2003.

⁵⁸⁹ Hlatky MA 2005.

⁵⁹⁰ Ibid.

While CMS officials largely have maintained that the NCD was based on clinical data, representatives of the medical device industry, professional associations and others have alleged that the QRS restriction was motivated by cost considerations. As compiled by one report, Douglas Zipes, past president of the American College of Cardiology called the decision “inappropriate.” Arthur Moss, primary author of the MADIT-II study, called the retrospective analysis a “fishing expedition,” adding that, “[t]hey looked through all the data until they found something that agreed with what they wanted to do, which was try to reduce the number of patients who would get ICDs.”⁵⁹¹ Others have argued that, “the central issue in this debate, of course, is money,” and that the decision, “disturbed many cardiologists, who believed that the restriction was simply a way to limit the use of an expensive medical device.”⁵⁹²

In response to these arguments, Sean Tunis told public audiences that, “it is about the money,” that, “economics – not evidence – may be the deciding factor,” and that there is little wiggle room in the Medicare budget for ICDs. According to Tunis, “[a]s money goes to higher tech services and newer benefits, we are led in [the] direction of under compensating for primary care, home health care, etc.”⁵⁹³ In the view of one of our interviewees from the medical device industry, these cost concerns were the motivating factor behind the QRS restriction.

Steve Phurrough, director of the CMS Coverage and Analysis Group, has argued that cost magnitude data played a role in CMS decision-making on ICDs through heightened scrutiny of clinical data. He was quoted as saying, “[i]f an ICD were a buck and a quarter, would we have gone through this entire process of reviewing the evidence at all? Maybe not. But because it’s a bit more than a buck and a quarter we wanted to make sure the evidence was clear and that it was a benefit. We don’t use cost to decide the evidence issue but we do use cost to decide if this is important enough to address.”⁵⁹⁴ Some experts we interviewed agreed with this explanation, expressing that, though ICDs were hotly debated because of their cost, the need to review the clinical findings motivated the ICD national coverage determination.

While these explanations may be mutually exclusive, an interviewee from a major implantable medical device company suggested that CMS intended for its retrospective subset analysis and selective consideration of RCTs to tilt the decision toward additional restrictions. This process obfuscated what the interviewee considered to be strong clinical evidence for the MADIT-II inclusion/exclusion criteria and was motivated, not by clinical ambiguity, but by cost concerns.

In 2005, CMS appeared to respond to 2 new RCTs, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) and Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure (COMPANION) by expanding covered clinical indications for use of ICDs in primary prevention.⁵⁹⁵ In 2006, the results of SCD-HeFT prompted CMS to expand Medicare coverage further to patients fitting many of this most recent study’s inclusion/exclusion criteria.⁵⁹⁶ However, CMS decided to expand coverage only to those patients experiencing non-ischemic dilated cardiomyopathy (NIDCM) for more than 9 months. According to an interviewee from a major implantable medical device company, CMS

⁵⁹¹ O’Riordan M 2003.

⁵⁹² Jauhar S 2004.

⁵⁹³ Ibid.

⁵⁹⁴ O’Riordan M 2003.

⁵⁹⁵ Hlatky MA 2005.

⁵⁹⁶ McClellan MB 2005.

used the results from 2 RCTs, SCD-HeFT and the Cardiomyopathy Trial (CAT), in order to make this decision. According to our interviewee, the CAT trial failed to recruit a sufficient population and was halted prematurely as a result. Results from this trial suggested that patients with NIDCM for less than 9 months experienced a clinical benefit from ICDs, whereas patients with NIDCM for greater than 9 months had little clinical benefit. The SCD-HeFT trial did not divide their patient population by duration of NIDCM diagnosis, but found statistically significant clinical benefit in all patients with NIDCM and ischemic dilated cardiomyopathy. In the view of the interviewee, the clinical evidence strongly pointed towards using the SCD-HeFT inclusion/exclusion criteria without regard to the CAT findings, but CMS emphasized the CAT findings to restrict the coverage decision and the patient population.

Impact of Cost-effectiveness Analyses

Our review of the literature, coupled with interviews of leading experts, revealed little to no impact of cost-effectiveness findings on CMS decision-making for particular technologies. Multiple sources, including those originating from CMS, expressed that potential cost to/impact on Medicare of a technology increased the likelihood that CMS would undertake a national coverage determination and increase the scrutiny of the available clinical evidence. Nevertheless, all of our sources stressed the primacy of clinical considerations within the benefit structure of Medicare.

Our experts posited a number of possible explanations for the irrelevance of cost-effectiveness analyses to CMS decision-making. Among these is that the “reasonable and necessary” criterion for NCDs usually is interpreted based on clinical evidence as it pertains to Medicare beneficiaries. While some suggest that “reasonable” could be interpreted to include matters of cost, none have observed this to be defined in terms of cost-effectiveness.

As noted by one expert, the reason that CMS does not employ a large staff of people with expertise in cost-effectiveness analyses and related areas is because reviewing economic evidence is not within the agency’s purview. Indeed, past attempts to incorporate cost-effectiveness evidence into coverage decisions have not been received favorably.

One expert observed that ICD cost-effectiveness studies have appeared to be heterogeneous and highly sensitive to a range of reasonable assumptions. One expert stated that the initial disparity between the studies, in addition to the sensitivity of the results to assumptions, has discouraged public sector officials from using cost-effectiveness evidence as a decision-making tool. This expert indicated that the BCBSA TEC report did not positively or negatively affect CMS’ NCD; rather, it was grouped with the other relevant cost-effectiveness evidence and intentionally ignored.

Another expert suggested that, if CMS were to use cost-effectiveness analyses, they should be used in determining both coverage and payment. If economic evidence were to be used only in determining coverage (but not payment), more costly technologies that yield better outcomes could, depending on their payment code assignment, still be reimbursed at the same level as cheaper, but less cost-effective alternatives. This could create a disincentive for hospitals to use some cost-effective technologies (and potentially deprive patients of their benefits), as doing so could result in a financial loss.

3. Private Payers

Our interviews with relevant academics and industry experts suggested that private payers were significantly more likely than public payers to use cost-effectiveness evidence in coverage decision-making. Our search of publicly available coverage policies indicated that major payers such as Aetna, Cigna, the Regence Group and numerous Blue Cross Blue Shield plans currently cover ICDs for patients meeting the SCD-HeFT criteria.^{597,598,599,600} We identified no direct evidence of cost-effectiveness evidence being used openly in private payer decisions; however, interviews with experts suggested that cost-effectiveness evidence was used in a supplementary role to clinical evidence. Our experts indicated that private payers sought out cost-effectiveness analyses that were explicitly based on RCT data. Private payers often gave these analyses to consulting physicians, who compared the study populations to private payers' patient demographics. Where a cost-effectiveness analysis reflected the payers' covered patient population, the analysis was more likely to become a factor in ICD coverage decisions. However, experts stressed that ICDs' life-saving potential was a significantly more important factor in private payer coverage decisions.

4. Non-US Payers

United Kingdom

The UK National Health Service (NHS) covers ICDs for indications that are similar to those covered by Medicare in 2003 (MADIT-II criteria with the QRS restriction).⁶⁰¹ While the findings of more recent clinical trials have prompted adjustments to Medicare's coverage criteria, the NHS scope of coverage appears to have been less responsive to these more recent findings.

The NHS' NICE issued a technology appraisal of ICDs in January 2006. In this appraisal, NICE explicitly used clinical and cost-effectiveness data.⁶⁰² Two independently conducted systematic reviews of the cost-effectiveness literature using an NHS perspective were cited as key inputs to NICE's recommendation.^{603,604} Upon reviewing the clinical and economic evidence, NICE recommended the use of ICDs in patients with a QRS wave ≥ 120 milliseconds and meeting the MADIT-II criteria. This conclusion is reflected in the NHS coverage decision. The similarities between the CMS NCD and the NICE technical appraisal are noteworthy, given that CMS made no explicit consideration of economic evidence while NICE did.

⁵⁹⁷ Biventricular Pacemakers for the Treatment of Congestive Heart Failure. Portland, OR: The Regence Group, 2003. Accessed August 25, 2006. <http://www.regence.com/trgmedpol/medicine/med75.html>.

⁵⁹⁸ Cardioverter-defibrillators. Hartford, CT: Aetna, Inc., 2005. Accessed August 25, 2006. <http://www.aetna.com/cpb/data/CPBA0585.html>.

⁵⁹⁹ Coverage position: implantable cardioverter defibrillator (ICD). Bloomfield, CT: CIGNA Healthcare, 2005. Accessed August 25, 2006. http://www.cigna.com/health/provider/medical/procedural/coverage_positions/medical/mm_0181_coveragerepositioncriteria_intrnl_extrnl_cardioverter_defibrillators.pdf.

⁶⁰⁰ Implantable cardioverter-defibrillator. Thousand Oaks, CA: Blue Cross of California, 2006. Accessed August 25, 2006. <http://medpolicy.bluecrossca.com/policies/SURG/ICD.html>.

⁶⁰¹ Arrhythmia-implantable cardioverter defibrillators. London, UK: National Institute for Health and Clinical Excellence, 2006. Accessed September 14, 2006. <http://www.nice.org.uk/page.aspx?o=TA95>.

⁶⁰² Ibid.

⁶⁰³ Bryant J 2005.

⁶⁰⁴ Buxton AE 1999.

Other Non-US Findings

While New Zealand often explicitly has considered cost-effectiveness data in coverage decisions, there is little documentation of the role economic evidence played in the country's ICD-related decisions. We identified 1 technology assessment of ICDs conducted in New Zealand, but little documentation on the role of cost-effectiveness evidence in coverage decision-making.⁶⁰⁵ In 2000, the Canadian Coordinating Office for Health Technology Assessment (now the Canadian Agency for Drugs and Technologies in Health) used guidelines from a 1999 meeting of the Canadian Cardiovascular Society and relevant economic evidence to determine that ICDs must be "allocated and rationed" so as to ensure "legitimacy and fairness" and the functioning of the regional and national health systems.⁶⁰⁶ Overall, few cost-effectiveness studies using non-US costs exist, largely limiting international comparison of the effect of cost-effectiveness evidence in health system decision-making for ICDs.

E. Conclusions and Policy Implications

ICDs have been breakthrough technologies with demonstrated significant life-saving potential. There is a focused and well-recognized body of literature on the cost-effectiveness of ICDs that provides a wide range of cost-effectiveness ratios, including favorable findings for certain clinical indications. We found little empirical evidence to suggest that findings of cost-effectiveness analyses had an impact on decision-making about ICDs in the US.

Our review of the literature, coupled with expert interviews, indicates that the FDA and CMS, along with other key public and private sector stakeholders largely have approved and covered these devices consistent with the best clinical data. However, there also is considerable evidence to suggest that information about the potential cost impact of using these devices has played an important, secondary role in decision-making.

At the FDA, clinical data have been the basis of approval decisions, though cost considerations appear to have accelerated approval of at least one lower cost ICD. At CMS, clinical data was the key factor in coverage decisions, though concerns about the potential impact on Medicare costs affected the level of scrutiny given to the relevant clinical evidence and might have affected the relative weight accorded to various clinical trials comprising this body of clinical evidence. There appears to be little, if any, direct evidence that the findings of cost-effectiveness analyses conducted by academic researchers, technology assessment organizations or others played a significant role in coverage decisions and no evidence that such findings played any role in FDA approval decisions.

In the US private sector, clinical data continued to be the primary factor, while cost-effectiveness information played a supplemental role in some instances. In the UK, cost-effectiveness evidence was used more explicitly, although there is ambiguity as to the degree to which potential cost impact truly informed decisions.

⁶⁰⁵ Outcomes of the use of the implantable cardiac defibrillator: a critical appraisal of the literature. Christchurch, NZ: New Zealand Health Technology Assessment, 1997. Accessed September 15, 2006. <http://nzhta.chmeds.ac.nz/publications/nzhta1.pdf>.

⁶⁰⁶ Noorani HZ, Connolly SJ, Talajic M, et al. Implantable cardioverter defibrillator (ICD) therapy for sudden cardiac death. *The Canadian Journal of Cardiology* 2000;16(10):1303-6.

Whether or not findings of cost-effectiveness analyses should be used in regulatory, payment or care decisions, interviews with our experts indicate that ambiguity about the role of economic factors in decision-making can have negative consequences. As expressed most strongly by those in the industry and the medical profession, such ambiguity can pose disincentives for device innovation and development by decreasing transparency and increasing uncertainty in the technology approval or coverage processes. For device makers, the experience with ICDs appears to have emphasized this problem, particularly due to mixed messages on the relative importance of health outcomes data and potential cost impact in coverage determinations.

Appendix C: Abbreviations

ACE	Angiotensin converting enzyme
AERS	Adverse Event Reporting System
AHRQ	Agency for Healthcare Research and Quality
AIDS	Acquired Immunodeficiency Syndrome
AMCP	Academy of Managed Care Pharmacy
ARTS-I	Arterial Revascularization Therapies Study I
ARTS-II	Arterial Revascularization Therapies Study II
ASPE	Assistant Secretary for Planning and Evaluation
AVID	Antiarrhythmics Versus Implantable Defibrillators
BASKET	Basel Stent Kosten Effektivitats Trial
BCA	Benefit-cost analysis
BCBSA TEC	Blue Cross and Blue Shield Association Technology Evaluation Center
BLA	Biologics License Application
BMS	Bare metal stent
BPAC	Blood Products Advisory Committee
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CAT	Cardiomyopathy Trial
CBA	Cost-benefit analysis
CBER	Center for Biologics Evaluation and Research
CBO	Congressional Budget Office
CCA	Cost-consequence analysis
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDHP	Consumer-driven health plan
CDRH	Center for Devices and Radiological Health
CE	Cost-effectiveness
CEA	Cost-effectiveness analysis
CED	Coverage with Evidence Development
CMA	Cost-minimization analysis
CMS	Centers for Medicare and Medicaid Services
COMPANION	Comparison of Medical Therapy, Pacing and Defibrillation in Heart Failure
CPSC	Consumer Product Safety Commission
CQG	Cost per QALY gained
CTA	Computed tomography angiography
CUA	Cost-utility analysis
CVD	Cardiovascular disease
DDMAC	Division of Drug Marketing, Advertising, and Communications

DEcIDE	Developing Evidence to Inform Decisions about Effectiveness
DEFINITE	Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation
DES	Drug-eluting stent
DHHS	Department of Health and Human Services
DoD	Department of Defense
DQTC	Drug Quality and Therapeutics Committee
ELs	Equivalent lives
EMA	European Medicines Agency
EO	Executive Order
EPA	Environmental Protection Agency
EPC	Evidence-based Practice Center
EPS	Electrophysiologic study
ESRD	End-stage renal disease
FCC	Federal Communications Commission
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act of 1997
FTC	Federal Trade Commission
GDP	Gross domestic product
GMP	Good manufacturing practices
GPO	Group purchasing organization
GSK	GlaxoSmithKline
HBV	Hepatitis B virus
HCT/P	Human cell, tissue, and cellular and tissue-based products
HCV	Hepatitis C virus
HERC	Health Economics Resource Center
HIV	Human immunodeficiency virus
HTA	Health technology assessment
ICD	Implantable cardioverter-defibrillator
ICER	Incremental cost-effectiveness ratio
IDE	Investigational Device Exemption
IDNAT	Individual donation nucleic acid testing
iFOBT	Immunoassay fecal-occult blood test
IND	Investigational new drug
IOM	Institute of Medicine
ISR	In-stent restenosis
LVAD	Left-ventricular assist device
LVRS	Lung volume reduction surgery
LYS	Life-year saved
MADIT	Multicenter Automatic Defibrillator Trial
MADIT-II	Multicenter Automatic Defibrillator Trial II
MCAC	Medicare Coverage Advisory Committee

MedPAC	Medicare Payment Advisory Commission
MeSH	Medical subject headings
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Myocardial infarction
MMA	Medicare Prescription Drug, Improvement, and Modernization Act of 2003
MPNAT	Minipool nucleic acid testing
MUSTT	Multicenter Unsustained Tachycardia Trial
NAT	Nucleic acid testing
NCD	National coverage determination
NCI	National Cancer Institute
NDA	New Drug Application
NHLBI	National Heart, Lung and Blood Institute
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIDA	National Institute on Drug Abuse
NIDCM	Non-ischemic dilated cardiomyopathy
NIMH	National Institute of Mental Health
NRC	Nuclear Regulatory Commission
NYHA	New York Heart Association
OC	Office of Compliance
OCP	Office of Combination Products
ODE	Office of Device Evaluation
OMB	Office of Management and Budget
OSB	Office of Surveillance and Biometrics
P&T	Pharmacy and Therapeutics
PBAC	Pharmaceutical Benefits Advisory Committee
PBM	Pharmacy benefits management
PBS	Pharmaceutical benefit scheme
PCI	Percutaneous coronary intervention
PDUFA	Prescription Drug User Fee Act
PEC	Pharmacoeconomics Center
PERIs	Pharmacoeconomics Research Institutes
PES	Paclitaxel-eluting stent
PET	Positron emission tomography
PMA	Premarket approval
PRT	Pathogen reduction technology
PTCA	Percutaneous transluminal coronary angioplasty
QALY	Quality-adjusted life year
R&D	Research and development
RAVEL	Randomised study with the sirolimus eluting Bx Velocity balloon expandable stent in the treatment of patients with de novo native coronary artery lesions

RCT	Randomized controlled trial
RFA	The Regulatory Flexibility Act of 1980
RICE	Research Initiative in Clinical Economics
SBA	Small Business Administration
SCD	Sudden cardiac death
SCD-HeFT	Sudden Cardiac Death in Heart Failure Trial
SCHIP	State Children's Health Insurance Program
SEC	Securities and Exchange Commission
SES	Sirolimus-eluting stent
SIRIUS	Sirolimus-Eluting Balloon Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions Trial
TVR	Target vessel revascularization
UMRA	Unfunded Mandates Reform Act of 1995
USPSTF	United States Preventive Services Task Force
VA	Department of Veterans Affairs
VF	Ventricular fibrillation
VHA	Veterans Health Administration
VOI	Value of information analysis
VT	Ventricular tachycardia
WNV	West Nile virus

Appendix D: Glossary

1. **Adoption** -uptake by health care providers, patients and other relevant groups of stakeholders
2. **Antibody test** - a blood test performed to detect a specific antibody, the product of the body's immunological response to an antigen
3. **Antigen test** - a blood test performed to detect the presence of an antigen, a substance capable of causing an immunological response
4. **Antiviral** - a drug targeting a viral infection
5. **Arrhythmia** - abnormal rhythm of the heart
6. **Assay** - an analysis used to determine the presence of a particular substance or biomarker or to quantify the amount of a substance or biomarker
7. **Cardiac arrest** - loss of heart function preceded by failure of heart's electrical system resulting in extremely fast heart rate and quivering/ineffectual contractions
8. **Consumer-driven health plan (CDHP)** - an employer-sponsored health plan in which employees are free to select the appropriate high deductible health plan for their specific needs; employers often will subsidize basic preventive services that fall below an employee's deductible
9. **Coronary artery bypass graft** - procedure in which an artery or vein from a patient's body is removed and used to bypass blocked portions of the coronary arteries in order to increase blood flow to the heart
10. **Coronary artery stent** - a wire-mesh tube that serves to keep open a previously-narrowed coronary artery
11. **Cost-benefit analysis (CBA)** - compares costs and benefits as quantified in common monetary units
12. **Cost-effectiveness** - ratio of costs to outcomes that can be assigned to health technologies/interventions
13. **Cost-effectiveness analysis (CEA)** - compares costs in monetary units with outcomes in quantitative non-monetary units, e.g., reduced mortality or morbidity, life-years saved
14. **Diffusion** - the spread of a new health technology from initial areas of use (e.g., geographic areas) to broader use
15. **Drug-eluting stent** - a metal device used to hold open an artery to facilitate necessary blood flow that releases a drug that prevents the formation of scar tissue and cell proliferation which could result in re-obstruction
16. **Evidence-based medicine** - the use of the best and most recent clinical evidence in decision-making related to patient care
17. **Fibrillation** - quivering/ineffectual contractions of the heart
18. **Group purchasing organization** - an organization that aims to assist health care providers in lowering their costs by aggregating health-related purchases and leveraging purchasing

- volume to negotiate discounts from manufacturers, distributors and other related health care stakeholders
19. **Guidance** - documents issued by authoritative bodies (e.g., FDA) to provide advice regarding clinical trial design, good manufacturing practices, proper use of technologies/interventions, and other topics
 20. **Health technology assessment (HTA)** - a systematic evaluation of properties, effects, and/or impacts of health care technology
 21. **Implantable cardioverter-defibrillator (ICD)** - a device that is connected to the heart of patients at risk for recurrent, sustained ventricular tachycardia or fibrillation, serving to sense cardiac rhythm, pace the heart, and provide electrical shocks as necessary
 22. **Incremental cost-effectiveness ratio (ICER)** - the marginal cost of one intervention over another divided by the marginal effect of that intervention over the other
 23. **Left ventricular ejection fraction** - the proportion of blood in the left ventricle that is pumped into the arteries
 24. **Leukoreduction** - the process of removing white blood cells from blood performed because white blood cells offer no benefit to blood recipients, but may carry infection
 25. **Myocardial infarction** - heart attack; blockage of arteries that prevents oxygenated blood from reaching the heart
 26. **National coverage determination (NCD)** - a national Medicare coverage decision by the Centers for Medicare and Medicaid Services for a particular device or technology deemed “reasonable and necessary,” relying on an evidence-based process
 27. **Nucleic acid testing (NAT)** - a blood screening method that identifies viruses by their genetic material rather than by their antibodies or antigens, allowing for earlier and more accurate detection
 28. **Percutaneous coronary intervention** - the reopening of a narrowed coronary artery with a catheter-guided balloon; also known as angioplasty
 29. **Prevalence** - the amount of disease existing in a given population at a particular point in time
 30. **Quality-adjusted life year (QALY)** - a measure that accounts for both mortality and morbidity, incorporating the effect of a given condition on a patient’s quality of life
 31. **Randomized controlled trial** - a study in which patients are randomly assigned to either an intervention or control group
 32. **Resource utilization** - use of health care services or interventions including inpatient visits (e.g., hospitalization) and outpatient visits (e.g., physician office visits), as well as use of medications and other medical supplies or equipment
 33. **Restenosis** - the re-narrowing of a blood vessel, such as often occurs in coronary arteries following angioplasty
 34. **Serologic tests** - blood tests to detect specific antibodies known to be caused by particular antigens
 35. **Sudden cardiac death (SCD)** - death resulting from cardiac arrest

36. **Tachycardia** - an abnormally fast heart rate
37. **Third-party payer** - any payer of health care services other than the person receiving the services; include private payers (e.g., Aetna) and the federal government (e.g., Medicare)
38. **Window period** - in blood-borne disease, the time between infection and production of antibodies during which a blood donor can be infected with a virus and still test negative on antibody screening tests

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