Proposed Recommendations for Designing Clinical Trials for “New Indications” of Approved Oncology Drugs for Treatment of Late Stage Disease

Release Date: September 14, 2010
Effectiveness Guidance Document Writing Team

C. Daniel Mullins, PhD; Russ Montgomery, MHS; Sean Tunis, MD, MSc

Acknowledgements

The writing team would like to thank the following individuals for the thoughtful comments and edits they provided on draft of this Effectiveness Guidance Document:

Amy P. Abernethy, MD
Associate Director, Duke Comprehensive Cancer Center and Associate Professor, Duke University School of Medicine

Jeff Allen, PhD
Friends of Cancer Research

Timothy D. Birner, PharmD, MBA
Sanofi-Aventis Medical Affairs

Don Husereau, BScPharm, MSc
Senior Advisor, Canadian Agency for Drugs and Technologies in Health (CADTH)

Sarah Garner, PhD, BPharm, MRPharmS
Associate Director, Research and Development, National Institute for Health and Clinical Excellence (NICE)

Benjamin Kim, MD, MPhil
Division of Hematology-Oncology, David Geffen School of Medicine at UCLA
Pardee-RAND Graduate School, RAND Corporation

Michael Kolodziej, MD
Chairman, Pharmacy and Therapeutics Committee, US Oncology

Keith D. Lind, JD, MS, BSN
Senior Policy Advisor, AARP Public Policy Institute

Joseph Lipscomb, PhD
Professor of Health Policy and Management and Georgia Cancer Coalition Distinguished Cancer Scholar
Rollins School of Public Health, Emory University

Karl Matuszewski, MS, PharmdD
Vice President, Editor-in-Chief, Gold Standard, Elsevier

Gerald K. McEvoy, PharmD
Assistant Vice President, Drug Information, American Society of Health-System Pharmacists
ACKNOWLEDGEMENTS (CONT’D)

The writing team would like to thank the following individuals for the thoughtful comments and edits they provided on draft of this Effectiveness Guidance Document:

Steven D. Pearson, MD, MSc, FRCP
Institute for Clinical and Economic Review (ICER), Massachusetts General Hospital and Harvard Medical School

Scott D. Ramsey, MD, PhD
REACH Group, Public Health Services, Fred Hutchinson Cancer Research Center

Grant Williams, MD
Williams Cancer Drug Consulting, LLC

Martin J. Zagari, MD
Global Health Economics Head, Amgen
EXECUTIVE SUMMARY

PREFACE

The Center for Medical Technology Policy (CMTP) supports the development of Effectiveness Guidance Documents (EGDs) to provide specific recommendations on the design of prospective studies that will inform decisions by patients, clinicians and payers. The recommended methods aim to achieve a balance between internal validity, relevance and feasibility. EGDs are intended to be analogous to Food and Drug Administration (FDA) guidance documents, but are focused on the design of clinical studies to support clinical and health policy decision making. EGD recommendations are developed through an extensive consultative process involving a broad range of experts and stakeholders. Full details about the EGD development process are available in an appendix to this document and at http://www.cmtpnet.org/cmtp-research/guidance-documents/EGDProcess.pdf.

The purpose of this EGD is to provide recommendations for the design and implementation of prospective clinical trials for FDA-approved oncology drugs used outside their current labeled indications for treatment of late stage disease. The principles and recommendations in this EGD were developed with input from patent advocacy groups, medical oncologists, pharmaceutical companies, US government agencies including the FDA, the Centers for Medicare & Medicaid Services (CMS), the National Cancer Institute (NCI), foreign government agencies involved in health technology assessment, public and private payers, drug compendia, clinical research entities, statisticians, academics, and professional societies such as the American Society of Clinical Oncology (ASCO). Representative from many of these groups discussed these methodological issues in detail at a meeting hosted by the Center for Medical Technology Policy in Baltimore on November 12, 2009. The following four key recommendations represent only a subset of the recommendations in this document:

- Whenever feasible, use actual survival, rather than a surrogate for survival, as the primary outcome
- Provide evidence of the validity of disease-free survival (DFS) or progression-free survival (PFS) as surrogates for survival within the targeted indication whenever the primary outcome is DFS or PFS
- Use a clinically-relevant dosing regimen for the comparator drug that allows for evidence-based comparisons
- Incorporate biomarkers within a trial with the expectation that their use within the trial will drive clinical practice and coverage decisions
INTRODUCTION

Purpose
The Center for Medical Technology Policy (CMTP) supports the development of Effectiveness Guidance Documents (EGDs) to provide specific recommendations on the design of prospective studies that will inform decisions by patients, clinicians and payers. The recommended methods aim to achieve a balance between internal validity, relevance and feasibility, with the goal of providing decision makers with studies that allow a reasonable level of confidence that the intervention improves net health outcomes. EGD recommendations address patient inclusion/exclusion criteria, choice of comparators, selection of outcomes, duration of follow-up and other key elements of trial design that are relevant to the specific topic of each guidance.

The target audiences for these study design recommendations include clinical researchers, product developers and research funding organizations. It is also anticipated that organizations developing evidence-based policies will consider these recommendations in their evidence reviews. EGDs are intended to be analogous to Food and Drug Administration (FDA) guidance documents, which are also targeted to product developers and clinical researchers, and provide guidance on the design of clinical studies that are intended to support regulatory decision-making. EGDs are intended to serve a comparable function, but are focused on the design of clinical studies to support clinical and health policy decision making. In this respect, they provide methodological roadmaps for the design of prospective comparative effectiveness research (CER) targeted to specific health technologies or services.

EGD recommendations are developed through an extensive consultative process involving a broad range of experts and stakeholders, including mechanisms for broad public review and comment. The process is guided by a technical working group (TWG) selected by CMTP staff, which consists of about 8-12 experts in clinical care and research methods specific to the clinical domain that is the focus of the EGD. Initial draft recommendations are developed by CMTP, with input from the TWG as well as interviews with numerous other experts and stakeholders. These are then discussed in detail during a day-long expert-stakeholder methods symposium involving approximately 45-60 participants including patients, consumers, clinicians, payers, regulators, product developers, researchers, and others. Revised draft EGD recommendations are then developed and circulated for broad public comment, after which the EGD recommendations are further refined and posted on the CMTP website. EGDs are updated as new scientific evidence, methodological advances and technologic improvements emerge.

Like FDA guidance, EGD recommendations are advisory rather than compulsory. To the extent that these methods are an accurate reflection of the information needs of patients, clinicians and payer, the recommendations deserve serious consideration by those who intend for their research findings to impact clinical and/or health policy decisions.

Full details about the EGD development process are available in an appendix to this document and at http://www.cmtpnet.org/cmtp-research/guidance-documents/EGDProcess.pdf. A list of the experts and stakeholders who provided input on this document is found on the acknowledgements page of this
document. A longer list of individuals who attended a stakeholders meeting that led to the development of these recommendations are included in Appendix B and at http://www.cmtpnet.org/cmtp-research/NewIndicationsMeetingParticipants.pdf.

Scope and Process of this EGD

The goal of this EGD is to provide a framework to guide the design and implementation of prospective clinical trials for FDA-approved oncology drugs used outside their current labeled indications to treat late stage disease. Oncologists currently select treatments for their patients using several sources such as FDA labeling, contemporary medical literature, guidelines, drug compendia, anecdotal information from colleagues, and continuing educational programs. Each of these sources provides useful information yet also reflects evidentiary gaps that make it difficult for end users to have sufficient information to make informed decisions regarding treatment decisions.

This EGD applies to the design of oncology drug trials for late-stage cancer drug therapies where there is a hypothesized survival benefit for the drug being examined in a “new indication.” The aim is to reflect the desires of patients, prescribers, payers, and compendia developers so that those who design future post-approval clinical trials will do so with these stakeholders in mind. Rather than providing an exhaustive list of all aspects of prospective clinical trial design, the EGD focuses on those aspects that will be most impactful in making the results that emerge from future trials in this area most meaningful and actionable.

While changes in registration trial design to improve efficiency and increase effectiveness data is a laudatory goal, recommendations for registration trials are outside the scope of this EGD; those interested in registration trial design may refer to the FDA Guidance for Industry on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.¹ For purposes of this EGD, prospective trials designed to evaluate “new indications” would focus exclusively on prospective randomized clinical trials that explore currently approved drugs in off-label uses. Trials that follow the guidance may or may not be intended to lead to a change in the FDA-approved label for the drug. It is our hope that many trials that follow this guidance could simultaneously meet the regulatory requirements of the FDA for new indications.

The principles in this EGD were developed following a meeting hosted by the Center for Medical Technology Policy in Baltimore on November 12, 2009. Participants at the meeting included representatives from patent advocacy groups, medical oncologists, pharmaceutical companies, US government agencies including the FDA, the Centers for Medicare & Medicaid Services (CMS), the National Cancer Institute (NCI), foreign government agencies involved in health technology assessment, public and private payers, drug compendia, clinical research entities, statisticians, academics, and professional societies such as the American Society of Clinical Oncology (ASCO). This meeting was funded through unrestricted contributions from Amgen, Bayer Pharmaceuticals, Genentech, and Sanofi-Aventis. CMTP maintains full authorship and editorial control over this EGD and all other materials.

¹ A drug compendium is a list of “medically-accepted indications” of drugs and biologics.
related to this initiative. A meeting summary, including a list of all meeting participants, may be found at: http://cmtpnet.org/cmtp-research/NewIndicationsFinalMeetingSummary.pdf

In addition to the one-day multi-stakeholder meeting, 12 key informant interviews were conducted prior to the November 12th meeting and 10 key informant interviews were conducted after the November 12th meeting. Discussions during the meeting and interviews were used to generate the initial recommendations contained on the following pages, which subsequently were sent for peer-review by meeting attendees and other select experts in relevant disciplines. The guidance reflects what we heard patient advocates, drug compendia representatives, payers, and prescribers state were reasonable and feasible recommendations for prospective clinical trials that would lead to the generation of “meaningful evidence” to inform decision-making by patients, consumers, prescribers and payers who are increasingly interested in understanding the comparative and “real world” effectiveness of pharmaceutical products. **While we are grateful to all who provided their opinions and feedback, we emphasize that the document has not been formally reviewed or approved by any person or agency mentioned in this document or the meeting summary.**

The guidance was informed by conversations from agencies throughout the world, yet much of this guidance reflects a greater emphasis on the current environment and views within the US. Recognizing that many clinical trials are multinational, some aspects of trial designs may need modification if the primary audience is outside the US.

Although some of this guidance may apply to other drugs used in cancer patients as well as non-drug technologies, the focus of this EGD is specific to chemotherapy and targeted therapies for treatment of late-stage disease where there is a hypothesized survival benefit. The guidance includes recommendations for selecting outcomes and comparators as well as other aspects of the clinical trial study design and analysis plan. There also are recommendations for recruiting study sites and patients.

**Pervasiveness of Oncology Drug Use Outside their FDA-Approved Indications**

The Government Accountability Office (GAO) reported that one-third of anticancer medication prescribing represented off-label use in 1991.² By 2005, off-label prescribing in oncology had increased to one-half to three-quarters, according to a 2005 survey by the National Comprehensive Cancer Network.³ Moreover, among medications used off-label, a study found that 73% lacked evidence of clinical efficacy and only 27% were supported by strong evidence.⁴ The lack of evidence on new indications and off-label uses for oncology drugs affects multiple stakeholders, including patients, clinicians, pharmaceutical companies, and private organizations that produce or evaluate evidence on new indications for oncology drugs. The widespread use of oncology drugs outside the indications approved by the FDA and the well-recognized lack of sufficient evidence for these off label uses warrants in-depth consideration of how best to close those evidence gaps and how to design trials to best accomplish that goal. The expedited review process, which is heralded by both the FDA and manufacturers as a means of getting drugs reviewed and approved in a shorter time frame, creates challenges for generating the depth of information that is desired by post- regulatory decision makers when the product is launched and may unintentionally encourage off-label use.
CMS and other payers may include reference to drug compendia and other published materials for recommendations on appropriate use of oncology drugs. These recommendations are generally considered to be based on scientific evidence, aggregated from peer-reviewed original literature on both labeled and off-label indications, though there has been concern, expressed in legislation by Congress (MIPPA 182(b)), that conflicts of interest may impair the impartiality of the compendia process itself and the underlying clinical research and publication processes upon which compendia rely. Nevertheless, systematic reviews document that even though a tremendous volume of research is generated each year, there is little useful information to guide clinical decision-making concerning the relative value of comparator treatments. Arguably, if there were more valid and reliable evidence available for review and if compendia were up-to-date, consistent, and standardized, this compendia model might serve as an optimal method for determining whether anticancer drugs are safe, effective, and useable outside of the FDA drug label. However, concerns about the current compendium process reinforce the need for improvements in the framework for evaluating uses of oncology drugs for new indications. Those involved in compendia processes agree that improvement in the way that post-regulatory trials are conducted would improve their ability to produce evidenced-based compendia recommendations.
RECOMMENDATIONS

This EGD is intended to address the concerns expressed by post-regulatory decision makers regarding their desire for more clinically meaningful evidence for medical decision-making. The following recommendations are intended to guide the design of future prospective trials for off-label uses of oncology drugs in order to address the desires of patients and their clinical providers, compendia, payers and policy makers across four content areas: Trial Design and Data Analysis, Patient and Site Recruitment, Comparators, and Outcomes.

TRIAL DESIGN and DATA ANALYSIS

Prospectively designing a trial allows the study design to fill an evidence gap by testing a hypothesis. Clinical trials designed to test the comparative survival and/or health-related quality of life (HRQoL) benefits of cancer therapies should collect all outcomes prospectively for both the drug being investigated for a “new indication” as well as the comparator drug. Using historical outcomes data for the comparator drug and doing an indirect comparison does not provide the same level of certainty regarding comparative net benefit as one derives from an active comparator trial. Differences in study design, inclusion/exclusion criteria, and changes in technology and treatment patterns over time introduce biases into indirect comparisons of treatment effect across clinical trials. As such, the process for selection of outcomes and comparators described below should be incorporated prospectively into active comparator clinical trials along with the following recommendations for study design and analysis for CER oncology studies investigating “new indications” for FDA-approved cancer drugs. Medical oncologists from academic medical centers and the community as well as other key stakeholders, such as patients or patient advocates, compendia and payers should be engaged in discussions surrounding trial design.

I. Design the study protocol to test the drug in the intended therapeutic application

Rationale. Many stakeholders believe that drug companies purposefully test their oncology agents in a narrow indication with the expectation that there will be expanded use once approved. The fact that there is an expectation in some circles that Medicare will reimburse for any use that is listed in one of the compendia promotes this belief. Even when new trials are conducted in different tumor sites, the post-approval trials often do not rigorously test the drug in its intended new indication. Insurers want assurance that the study design is deemed appropriate and vetted by clinical and methodological experts. Reimbursement agencies and insurers view peer-reviewed manuscripts as an integral yet sometimes flawed part of that process.

Implementation. The drug should be tested in the manner in which it is to be used; e.g. monotherapy, combination therapy, adjuvant therapy, etc. Similarly, the drug should be tested in the anticipated line of therapy (i.e. first, second or multiply pretreated). If the drug is anticipated to be administered in multiple ways (e.g. quick infusion versus slow infusion), then separate arms or trials for each intended use should be included within the trial. The duration of the trial and length of follow-up should permit reasonably complete data capture for the selected outcomes.
II. Pre-specify subpopulations of interest in order to avoid misinterpretation of spurious findings

**Rationale.** Evidence of benefit in a subpopulation from a post hoc analysis does not necessarily provide sufficient proof of value in that population. Post hoc analysis should be viewed as hypothesis-generating, not confirmatory evidence of causality. Payers frequently view post hoc analyses and retrospective analyses of treatment effect within subpopulations as “marketing tools” to promote unsubstantiated effectiveness claims. Pre-specifying subpopulations of interest reduces the ability to selectively report results and thereby adds to the credibility of the study.

**Implementation.**

- The selection of sub-populations should be informed by prior studies and current scientific evidence. In addition, certain priority populations, such as the elderly, racial/ethnic minorities, patients with comorbidities, or those with specific genetic markers should be pre-specified and justification for sub-populations included or excluded from sub-analyses should be provided.
- In some cases, it may be necessary and informative to perform post hoc analysis. There may be unanticipated safety concerns in certain subtypes of patients, which may only be uncovered through post hoc analyses. Any consideration of the results of such post hoc analysis should be mindful of the potential of over-interpretation of “false” safety signals in subpopulations with small sample sizes.

III. Incorporate biomarkers within a trial with the expectation that their use within the trial will drive clinical practice and coverage decisions

**Rationale.** Biomarkers might be used to identify the trial population (i.e., used as part of inclusion/exclusion criteria) or they might be used to identify subgroups that might have varying likelihood of treatment response. It should be clear how specific biomarkers are to be used within a trial (e.g., identification of people with various risk stratification versus treatment effect modification). Furthermore, rules concerning alterations in the incorporation and use of biomarkers during the implementation phase of a trial should be pre-specified whenever possible and justified in all cases.

**Implementation.** If biomarkers are used as part of the inclusion/exclusion criteria for trial enrollment, then the same biomarker tests should be anticipated as part of the criteria for coverage. In most cases, post hoc analysis of subgroups based upon biomarkers should be viewed as hypothesis generating, not confirmatory evidence of predictive response. Additional research from follow-up trials is essential to confirm the value of biomarkers in patient selection. However, KRAS provides a good example where post hoc analyses can be informative. Cetuximab and panitumumab are two EGFR-inhibiting monoclonal antibodies that were approved for the treatment of metastatic colorectal carcinoma in 2006. However, subsequent post hoc analysis of available data indicated that these therapies were not beneficial to a subset of patients with specific mutations in KRAS, a signaling transducer in the EGFR pathway. As such, it is now widely recommended that all candidates for the two EGFR-inhibitors should
be tested for these particular KRAS mutations, and if present, should not receive either of the therapies.9

IV. Use a blinded reviewer to assess PFS to reduce bias

Rationale. The use of a blinded reviewer provides a greater assurance that the manufacturer cannot influence the assessment of the primary outcome of interest.

Implementation.

• A blinded review process removes the need for a centralized independent verification process, which might be required if a blinded process is not used. For non-blinded trials, the FDA may recommend that PFS be verified using centralized independent verification tumor assessments.

• The frequency and timing of PFS measurements should be driven by expected median survival time of the trial population. The timing of PFS measurement is critical for valid and reliable comparisons.

V. Capture key covariates that may represent confounders of the relationship between treatment and outcomes, particularly in patient subgroups that were not explored in registration trials

Rationale. Capturing covariates allows analysis of the variance in treatment responses across individuals or subgroups, known as heterogeneity of treatment effect (HTE), and is particularly relevant for patient subgroups that were not included in the original registration trials. Prespecified subgroup analyses should consider biomarkers as well as clinical and demographic characteristics that have a scientific/historical basis (e.g. women in lung cancer) to determine whether health outcomes are consistent across subpopulations and whether observed differences in treatment effect are “real” or an artifact of confounding. It is not reasonable, however, to expect that the trial will be powered for each of these various subgroups.

Implementation.

• There are a variety of covariates that should be captured, some of which are consistent across trials and others which would be based upon the specific tumor site and CER study. Physiological age is an important potential confounder and exploration of the treatment effect among the elderly is useful. The influence of comorbidities, including renal and liver impairment, are almost always important to explore. Performance status, indicative of a patient’s ability to withstand treatment, is critical because age and comorbidities alone are not as informative as adjusting for performance status. Race/ethnicity and available socioeconomic status (SES) also are likely to impact treatment outcomes and should be captured at baseline.

• The patient’s clinical presentation, including tumor type, characterization, stage, and prior treatment exposures, may also impact survival and patient-reported outcomes (PROs). Therefore, this information should also be captured and addressed in the statistical analysis plan.
• If there are differences in treatments (e.g., dosing regimens, multimodal care, concomitant medicines), practitioners (e.g., physician specialty or practice patterns) or health care settings (e.g., location of care or cross-country/regional variations) within the trial that would impact the treatment effect, these should be recorded and examined during data analysis.

PATIENT and SITE RECRUITMENT

VI. Develop a recruitment strategy that addresses patients’ and physicians’ reluctance to participate in a trial of currently available drugs.

Rationale.

• A survey of cancer patients found misconceptions about randomization were very common.\textsuperscript{10} Many patients believe that randomization means they have a 50 percent chance of receiving a placebo, when in most cases the comparator arm receives the standard practice. The same study found that 85 percent of non-participating patients were unaware or unsure that participation in trials was an option, and that 75 percent were willing to enroll once educated. Among those participating in trials, 93 percent rate their overall experience as positive. Even with educational efforts, recruitment may be difficult.

• When a drug is already covered outside of a trial setting, the potential for coverage in the trial as an incentive for participation is lost. This is compounded by the fact that patients often prefer to avoid the extra time and other demands of trial participation. Similarly, physicians often feel pressure from patients who want their doctor to do what he or she feels is best for the patient – not randomize them to a trial where they have only a chance of getting the drug that their doctor thinks is best. Moreover, if the practicing medical oncologist is convinced of the benefit of a drug, perhaps due to the influence of a local thought leader, it probably does not matter that the drug has not demonstrated its value through a clinical trial; it will be used for the new indication and the physician is unlikely to see the need for a new trial.

Implementation.

• Patients are reluctant to participate in a randomization process that only provides the investigational treatment to some patients,\textsuperscript{11,12} especially when the drug is widely available and already covered and reimbursed due to compendia listings.\textsuperscript{13} A crossover design, or a protocol that allows switching over to another line of therapy upon progression, may help to recruit patients who are reluctant to participate in a trial where there is the high probability of receiving only placebo.

• An educational process for patients and prescribers is needed to highlight the benefits of generating new evidence and the realities of trial participation, especially in situations where a clinical benefit is already assumed by the oncologist.
VII. Recruit patients from a variety of clinical practice settings

Rationale. A majority of cancer patients are treated in community settings. However, a large majority of cancer patients enrolled in trials receive their care at academic medical centers, a fact which limits the generalizability of studies. By accruing patients from mostly academic settings, the patient population is likely to be more homogenous than real-world patient populations. In addition, important differences in treatment patterns between academic and community settings will not be reflected in the study. These factors restrict the potential for pragmatic/comparative effectiveness studies capable of generating evidence more generalizable to real-world practice. Expanding beyond academic medical centers allows the opportunity to broaden the patient population.

Implementation.

- When community-based sites are used in addition to academic medical centers as trial sites, appropriate training, resources, and a track record with recruiting for cancer trials are key predictors of sites’ ability to recruit patients. It may be necessary to spend time with physicians and support staff at less experienced clinical trial sites to demystify what serving as a trial site entails and requires.

- A report on effective implementation of cancer trials, compiled through a survey of cancer study sites with additional input from a technical working group of academic oncologists, states that a cancer trial site should have a board-certified or -eligible medical oncologist, at least one dedicated research coordinator (either a clinical research associate or a research nurse), a data manager, and a part-time research pharmacist. For post-regulatory trials of oncology drugs, it may not be necessary to have such personnel in-house. However, a coordinator or another staffer should be knowledgeable on informed consent, the risks and benefits to patients, and insurance coverage. In community settings with few accrued patients, these individuals likely will not spend all their time on trial-related work, but these roles need to be clear and assigned to appropriately trained staff.

- Limiting the amount of data collection within the trial can make participation easier for non-academic clinicians.

- Electronic data capture should help to improve the efficiency of conducting the trial, and emerging IT solutions should allow participating sites to utilize their existing EHR infrastructure rather than create a new one. If validated PROs are used, the electronic data capture version of these ePROs needs to be validated. In addition, interoperability between existing EHR infrastructure and the systems used for trial data capture is an essential component.

VIII. Provide appropriate incentives, including reimbursement, for clinicians to recruit patients from a variety of sites

Rationale.

- Surveys of oncologists conducted by the American Cancer Society (ACS) and others have identified several disincentives for clinician participation in cancer trials, including financial barriers, regulatory burdens, precertification protocols, awareness of clinical trial options, and negative physician perceptions about clinical trials. Studies suggest that clinician concerns are valid; on average,
reimbursement for NCI-sponsored trials covers less than half of per enrollee research expenses.\textsuperscript{19} While these issues affect all oncologists, they are particularly difficult for community oncologists, who have fewer financial, logistical, and staff resources to support their participation in trials.\textsuperscript{20} Additionally, participation in trials requires substantial work to comply with regulatory and documentation requirements – time which is rarely eligible for reimbursement.\textsuperscript{21} At the same time, physicians need more than just financial incentives; they need to understand the value for their practice and their patients.

- Payment for patients is less of an issue. Travel time and cost are important patient considerations, but patients will probably participate if their doctor recommends the trial. Moreover, significant payment to patients can create the ethical dilemma of coercion and should be avoided.\textsuperscript{22}

**Implementation.**

- At a minimum, break-even reimbursement for participating sites is required. In 2010, the Institute of Medicine recommended that the NCI “substantially” increase the per care reimbursement rate and provide additional funding for time spent developing and overseeing cancer trials and doing paperwork.\textsuperscript{23}

- Coverage with evidence development (CED) may provide incentives to encourage site and patient participation, especially when the drug is currently not covered by health plans for a given use. However, health plans are reluctant to help with identification of patients due to ethical and legal concerns, including HIPAA-related issues. There likely will be relatively few CED trials in the short run and CED trials should be prioritized and supported appropriately. Providers should be reimbursed in CED trials at a fair rate that includes time spent on administrative tasks and time spent by submitting data. It may be necessary for health plans and the institution leading the trial to provide additional financial incentives to support CED participation by clinicians.

**COMPARATORS**

**IX. Select comparator(s) from among commonly used FDA-approved drugs for the targeted new indication that decision makers deem to have the greatest clinical net benefit**

**Rationale.** There are relatively few instances in which only a placebo comparison would be acceptable for trials of FDA-approved drugs being examined outside currently labeled indications. Instead, trials should utilize active comparators that are FDA approved and commonly used for the targeted indication. If there are multiple comparators that meet these criteria, the comparator should be the FDA-approved agent with the greatest clinical net benefit for the targeted indication; clinical net benefit reflects both survival and HRQoL benefits as well as safety concerns. While a placebo arm may be required by the FDA in certain circumstances, it frequently will be unnecessary when an active comparator trial is designed to demonstrate superiority or non-inferiority in a post-approval trial.
Implementation.

- Comparators should be commonly used for the targeted indication, but the best comparator is not necessarily the market leader in terms of sales. Market size may reflect marketing practices of pharmaceutical manufacturers and/or rebates and discounts rather than the most favorable benefit-to-risk profile. Comparators with low net benefit profiles should be avoided because demonstrating superiority to such a comparator would not provide meaningful evidence of net benefit. Also, comparators with infrequent use are less informative for prescriber and payer decision-making since the trial results will not answer relevant questions about the comparative effectiveness of more commonly used drugs. The final selection of comparators should be informed by discussions with decision makers. Trial designers should bring together a panel of prescribers, payers, and informed consumers or patients/patient advocates to assist with the process of selecting a comparator.

- Comparisons to “current best care” should only be used when this type of standard of care reflects evidence-based clinical practice in the community. When a recently updated national consensus-based clinical guideline exists, the comparator treatment arm should reflect that guidance, not merely expert opinion or routine care. Analysis of up-to-date administrative claims data sets can be used to verify “standard of care.”

- Placebo comparisons may be acceptable when there are no approved therapies for the targeted indication in the targeted line of therapy. Typically, the “placebo” comparator should be Best Supportive Care.

X. Clearly define the comparator(s), including other components of treatment

Rationale. There is rapid progress in technologies and treatments for cancer, which makes it challenging to define a comparator for oncology CER studies. Related components of care and the manner in which a drug is administered can vary substantially and this variation will impact health outcomes. Multimodal care is becoming increasingly more common in treatment of late stage cancers. Therefore, it is important to incorporate and accurately describe related aspects of care, such as whether the drugs are administered in the adjuvant or neoadjuvant setting and whether surgery and/or radiation are permitted or required as part of the trial protocol. If surgery, radiation, or other drugs are part of the care within the trial, then the trial design should either minimize variation in these components of care or specifically incorporate the variation (e.g. type of radiation) as part of the pre-specified analysis plan.

Implementation. Recruitment of patients into oncology clinical trials is a major challenge, particularly for studies aimed at investigating FDA approved drugs used off-label. By engaging medical oncologists and their professional colleagues (e.g. surgical oncologists, radiation oncologist) in the study design, the appropriate comparator, including other components of treatment, can be appropriately incorporated so that the value of the evidence to be generated is clear. If the value of information derived from a trial is apparent, physicians who treat cancer patients will be more likely to actively recruit patients for the trial.
XI. Use a clinically-relevant dosing regimen for the comparator drug that allows for evidence-based comparisons

Rationale. Prescribing patterns and dosing schedules for chemotherapy agents often evolve with “real world” clinical experience with these drugs. Therefore, a study that utilizes the original FDA-approved dosing schedule for the comparator drug frequently will not reflect a meaningful comparison for the prescribing community. In some cases, subsequent trials will document the regimen with the most favorable clinical net benefit, while in other cases the preferred regimen will be based upon clinician consensus or expert opinion. While consensus without level-one evidence from clinical trials has its own problems, the use of outdated dosing regimens that do not reflect current standard of care are less helpful when making comparisons of two marketed drugs. The dosing for the comparator drug used in the clinical trial should reflect the regimen with the best net benefit, which frequently differs from the FDA label.

Implementation. Deviation from the FDA-labeled regimen for the comparator therapy are appropriate when evidenced-based medical information documents an enhanced net benefit from an alternative dosing regimen. In the absence of evidence from clinical trials, use of expert opinion regarding the best dosing regimen to examine for the comparator will appeal to some clinicians and not to others based on the strength of evidence as well as their own experiences with patients. Using an off-label dosing regimen that is not evidence based raises additional concerns; therefore, unless the off-label dosing regimen for the comparator drug is informed by a rigorous clinical trial that provides comparative benefit of different dosing regimens including the FDA-approved regimen, the regimen should be vetted by an expert consensus panel. A meeting with the FDA to discuss the justification for the specific dosing regimen used for the comparator should occur prior to finalizing the study protocol if regulatory review of the study is anticipated (i.e. if the study sponsor intends to request a change in the label for their drug based upon the trial results.)

OUTCOMES

It is important to collect outcomes that are most meaningful to decision makers. Frequently, there is a strong focus on assuring that outcomes are assessed in a valid manner without first determining whether the correct outcomes are being measured. In the off-label oncology space, one area of great concern is the debate on how to measure disease-free survival (DFS) or progression-free survival (PFS) when in fact these surrogates are not as ideal as actual ‘overall survival (OS)’ data. Patients, medical oncologists and payers want evidence of survival or PRO benefits, not just data on DFS or PFS, which may or may not translate into any meaningful impact on OS or HRQoL. There also is a desire to reduce the burden on patients and sites that enroll patients. This suggests that rather than collecting the complete list of data elements that were collected in the original registration trial and a battery of data and questionnaires, only those outcomes that are most critical should be collected in a post-marketing trial, even when a change in the labeled indication is sought. There is a tendency for oncology trial designers to collect more data than is necessary because not having sufficient data to address all FDA
questions and concerns reduces the likelihood of approval. In a post-approval environment, it should be easier to justify parsimony in data collection without sacrificing essential CER data for safety and effectiveness. The FDA issued a guidance in 2001 to assist manufacturers determine how to reduce data collection elements while still meeting FDA requirements.24

XII. Whenever feasible, use actual survival, rather than a surrogate for survival, as the primary outcome.

Rationale. Decision makers are frustrated by the widespread use of surrogate markers for survival in oncology trials. This is particularly true in the post-regulatory environment where trials for “new indications” sometimes look more like small Phase 2 safety studies rather than pragmatic Phase 3 studies, which would be more informative. If the manufacturer of a cancer therapy suspects that their therapy extends survival, then the survival benefit should be demonstrated through prospective randomized clinical trials. Many medical oncologist have come to believe that PFS and DFS as endpoints have evolved to become tumor response rates without meaningful outcomes. This is supported by empirical examples in which drugs have been approved based upon surrogates endpoints of PFS or DFS and subsequent studies failed to demonstrate survival benefits. For example, Iressa (gefitinib) was approved by the FDA in 2003 for small cell lung cancer using tumor response rate as a surrogate endpoint for survival, but that approval was later pulled after four studies showed no overall survival benefit.25 It is possible to have higher PFS and still have equivalent cancer-specific survival if the later tumor progression does not directly translate into survival benefits. Similarly, it is possible to have higher PFS and still have equivalent all-cause survival if toxicities lead to increased mortality from other causes.

Implementation.

- It is more feasible to measure survival when the median survival is short and when the survival advantage of a new drug would occur within the first 6-12 months of treatment. Similarly, because of the length of survival it is likely that survival is more frequently a reasonable outcome for second and third-line therapy trials than for first-line therapy trials.
- There is a debate surrounding whether cancer-specific mortality or all-cause mortality is more meaningful and much of this is related to the perspective of the decision maker. If one primary outcome is selected, we recommend the use of cancer-specific mortality as the primary outcome and agree that all-cause mortality also needs to be collected and reported as a secondary outcome. Physicians prefer cancer-specific mortality/survival data because it focuses on the primary research question of a CER oncology trial, which is to determine the impact of the drugs on the tumor. It is more pragmatic to focus on cancer-specific mortality. If there is a hypothesized cancer-specific survival benefit of one drug compared to another, then it is informative to also report all-cause mortality, but all-cause mortality is secondary to cancer-specific mortality. We recognize that many patients and payers prefer all-cause mortality/overall survival data; some argue that distinguishing between a death caused by the cancer, the treatment, or some complex relationship between the cancer, its treatment, and their combined impact on the patient is challenging. Furthermore, what the patient really wants is longer life and better health and better quality of life during their
remaining life. If there are serious toxicities associated with a cancer drug, it is possible that one comparator could be superior in terms of cancer-specific mortality and inferior in terms of all-cause mortality. However, from a purely practical standpoint particularly when a change in label is anticipated, the FDA can assess the cancer-specific survival and continue to monitor the safety and survival data after completion of the trial. From a trial design and data analysis standpoint, there are many factors that influence survival that are unrelated to the cancer treatments.

XIII. Provide evidence of the validity of disease-free survival (DFS) or progression-free survival (PFS) as surrogates for survival within the targeted indication whenever the primary outcome is DFS or PFS

Rationale. There are situations when it may not be feasible to power a study for actual survival, such as when the median survival is longer than two years or when the target population is very small. In such circumstances, DFS or PFS may be selected as the primary outcome for the trial; the justification for using DFS or PFS should not be merely the manufacturer’s desire for an expedited trial. To justify the use of DFS or PFS as a surrogate for survival, the trial designer should provide evidence of a reliable link between DFS or PFS and actual survival, PROs, or HRQoL for the specific cancer type, stage, and treatments being examined. Specifically, the FDA guidance states, “Whether an improvement in PFS represents a direct clinical benefit or a surrogate for clinical benefit depends on the magnitude of the effect and the risk-benefit of the new treatment compared to available therapies.”

Implementation.

- Trial protocols should clearly define and lay out the methodology for measuring and assessing DFS or PFS, including the length of time to measure PFS. The frequency and length of follow-up are specific to the trial; however, a minimum of 6 months of follow-up typically would be appropriate.
- When DFS or PFS is used as the primary endpoint, follow-on studies should be conducted, analyzed and published in the peer-reviewed literature, which may involve extensions of the clinical trials, observational studies, or registries, to capture actual survival. The specific study protocol for such follow-on studies should be specified in advance to ensure that such studies will be performed in a timely and informative manner. If a follow-on study is not feasible (e.g. due to drug supply issues) then a strong justification should be provided.

XIV. Select a parsimonious set of patient-centric outcomes that are most “clinically meaningful”

Rationale. The impact of oncology treatments on HRQoL and other patient-centric outcomes are often equally or more important than longevity among advanced stage cancer patients. For example, in late-stage lung cancer, therapies often provide only a few weeks of additional life so the toxicities of treatment and the impact of therapies on HRQoL are quite meaningful. In a post-regulatory environment, “real world” data on safety and efficacy already exist, which should guide the data collection for trials examining the agents in a new indication. Trial designers should focus on those PROs that are most meaningful to patients and prescribers when they are trying to compare the drug to an alternative drug that has been approved by the FDA for the targeted new indication. This may involve
HRQoL instruments as well as clinical outcomes, symptoms and adverse events. The desire to provide evidence of patient-centric outcomes that are “clinically meaningful” must be balanced with the desire for limiting the burden of data capture on patients and study sites. In particular, patients question why it is necessary to collect low-grade toxicity measures in a trial for a drug that already was approved by the FDA.

Implementation.

- Meaningful patient-centric data should be captured in all trials for new indications. Validated HRQoL instruments provide valid and reliable measures, but additional evidence, such as direct medical resource utilization, is needed to make the information “actionable” for private payers. Patients and payers often want symptoms and safety data related to HRQoL provided in a disaggregated form.

- The selection of metrics and relative emphasis on PROs and HRQoL for oncology CER and treatment decision-making vary across cancer type, histology and prognosis, and stakeholders.

- High-grade adverse events and safety data that impact patient health or HRQoL should be collected during the trial to supplement ongoing surveillance for safety/toxicities. The specific list of adverse events should be informed by prior evidence and reports for the drugs being studied and the specific cancers and patient populations being included. Prior evidence on the risk profiles of the drugs being compared should be used to limit the number of items collected. If the product has robust information on safety, there is a strong desire to reduce the burden of data collection; however, adverse events may differ by dosing schedule and frequency, so the desire to be parsimonious in collecting safety and adverse event data should be balanced with the clinical application. Parsimony will help with patient and site recruitment (see Patient and Site Recruitment section). In fact, this is consistent with an FDA guidance that states, “In supplemental efficacy applications that propose a new use for an already marketed drug in a similar population, additional data on grade 1-2 nonhematologic toxicity and grade 1-3 hematologic toxicity may not be important and may not need to be collected.”

- Collect data on direct medical resource utilization and patient burden of illness to inform the analysis of relative value. Direct medical resource utilization is an integral part of value assessment of oncology therapies and should reflect various perspectives as appropriate (e.g. insurer, patient). These are setting-specific.

- Patient burden of illness should reflect the patient burden beyond direct medical resource utilization.

- Clinicians often don’t understand HRQoL scales; therefore, such scales need to be translated into something more clinically relevant and meaningful.
REFERENCES


14 Cox and McGarry 2003.


Proposed Recommendations for Designing Clinical Trials for “New Indications” of Approved Oncology Drugs for Treatment of Late Stage Disease


19 The Lewin Group, 2005.

20 Institute of Medicine 2010.

21 Ibid.


23 Institute of Medicine 2010.


APPENDIX A:
GENERAL OVERVIEW

Purpose

Effectiveness Guidance Documents (EGDs) provide specific recommendations about the design of comparative effectiveness studies that will produce evidence that is useful to inform decisions by patients, consumers, clinicians, payers and policymakers. The intent of these documents is to describe the specific elements of clinical studies that would provide these “post-regulatory” decision makers with a reasonable level of confidence that the technology improves health outcomes. In this respect, they are intended to provide technology-specific methodological guidance for the generation of new evidence about comparative effectiveness.

Target Audiences

The primary target audiences for EGDs are produce developers and clinical researchers who are interested in designing clinical studies that will be informative to patients/consumers, clinicians and payers. They should also be useful to these decision makers themselves as they assess and appraise research that has already been conducted. They will be able to compare the design of available clinical studies to the recommendations contained in the EGD.

Scope

Each EGD will focus on a specific category of health care technologies, for example, radiation therapy for cancer, cardiac imaging for diagnosis of coronary disease, gene expression profiling for breast cancer, mechanical interventions for chronic wounds. Methodological considerations for the design of clinical studies will be specific to defined categories of technologies, and recommendations for study designs can be more concrete and specific when targeted to a well-defined group of related technologies. For therapeutic interventions, the primary focus will be on evidence of comparative clinical effectiveness and for diagnostic intervention the primary focus will be on comparative clinical utility.

Relationship to FDA Guidance Documents

EGDs are intended to be analogous to FDA guidance documents, which are also targeted to product developers and clinical researchers, and provide guidance on the design of clinical studies that are intended to support regulatory decision making. EGDs will serve a comparable function for product developers and clinical researchers, but are focused on the design of clinical studies to support post-regulatory decision making. These post-regulatory decision include individual clinical decisions made by patients/consumers, clinical recommendations made by clinicians, clinical policies generated by medical professional societies, and reimbursement decisions made by payers. Because the FDA has regulatory oversight over all health care technologies, that organization is naturally positioned to develop guidance documents providing recommendations on studies intended for regulatory approval. Because there has not been a single organization that represents the universe of post-regulatory decision makers, CMTP is providing a forum in which study design recommendations can be generated reflecting the perspective
of key decision makers (patients, clinicians, payers, and policy makers) in the design of comparative effectiveness research.

By including the relevant FDA regulatory experts in the EGD development process, it is hoped that EGDs will reflect optimal alignment between study design elements intended for regulatory approval and study design elements targeted to clinical and health policy decision making. This may help to reduce the need for multiple separate studies to address these different evidentiary purposes.

**Balancing Validity with Feasibility, Relevance, and Timeliness**

The EGD recommendations are not intended to describe the design characteristics of “gold standard” clinical studies. The recommendations aim to achieve a balance across a number of important considerations associated with these studies, including scientific validity, feasibility, time requirements cost. In other words, EGDs seek to achieve a balance between scientific consideration and practical considerations, recognizing the there is an inevitable trade-off between the level of certainty that can be achieved through clinical research with the cost/time/burden required to achieve that level of certainty. EGDs aim to strike a balance of a reasonable level of certainty at a reasonable level of burden. In order to determine what constitutes a reasonable balance, the process used by CMTP to produce EGDs (described in more detail below) integrates the perspectives of all knowledgeable and affected experts and stakeholders.

Because they do not describe “gold standard” studies, EGD recommendations are not intended to imply that further and more rigorous studies should not be done on any specific technology. Many important questions are likely to remain even after studies are completed that are consistent with the study design recommendations of the EGD, and further research will be valuable to pursue for most technologies. In some cases, coverage with evidence development will be a useful policy tool to facilitate additional studies of technologies for which there is evidence that meets the EGD recommendations.

**Development Process**

Product developers, payers, clinicians, patient representatives, researchers and other relevant experts participate directly in the development of EGDs through a multi-stakeholder workgroup process managed by CMTP. Potential topics for EGDs are selected by means of an internal process, with recommendations being sought from external stakeholders, horizon scanning materials, and recent technology assessments. CMTP employs a defined set of criteria to prioritize potential technology suggestions, giving weight to the (in)sufficiency of current clinical evidence, the potential clinical and economic impacts of the technology, and the improvability of evidence, among other factors.

Once the technology topic is chosen, CMTP senior staff contracts with technical consultants with expertise in the relevant area to be the primary authors of the EGD. Expertise can be demonstrated through experience in conducting trials on the topic, drafting a technology assessment or systematic review, or developing practice guidelines. Additional background research and direction will be provided to the primary authors by a “Technical Working Group” (TWG). This will be a group of 5-7 technical experts with familiarity in the topic area, such as members of scientific review committees, clinical
research investigators, authors of published scientific manuscripts, clinical trials methods experts, and governmental representatives with oversight responsibilities. The TWG will be responsible for reviewing the preliminary draft of the EGD and providing the primary author with feedback and comments to help expend and amend this draft.

While the first draft of the document is being revised by the primary authors, CMTP will assemble a 20-25 person multi-stakeholder workgroup (called the Expert Stakeholder Advisory Workgroup, or ESAW) to provide nuanced feedback from each of the distinct perspectives they represent. ESAWs are composed of representatives of the following constituencies: payers, product developers, researchers, clinicians, patients, professional societies, and federal (and/or state) governmental agency observers. Representative organizations are selected based upon their interest and experience in the topic. After the first draft of the document is completed, the ESAW will convene for a half-day to discuss the EGD and provide feedback to the primary author. Themes from this meeting will be used by the primary authors to expand and revise the EGD. Once the next draft of the EGD is complete, TWG and ESAW participants will have a chance to provide a second round of comments via the Internet.

Finally, CMTP will open up the document to the larger public in order to collect a further round of feedback. This will be done in two ways: 1) the document will be posted on the CMTP website along with a link to a survey to collect comments, and 2) CMTP will hold an open public forum to present the final recommendations and allow stakeholders to respond to the guidelines. The feedback presented by different stakeholders will be considered by the primary author and CMTP in revising the EGD. Once the document is finalized, it will be posted on the CMTP website and widely distributed.
## APPENDIX B: MEETING PARTICIPANTS

<table>
<thead>
<tr>
<th>Last Name</th>
<th>First Name</th>
<th>Title</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abernethy</td>
<td>Amy</td>
<td>Program Director, Duke Cancer Care Research Program</td>
<td>Duke University</td>
</tr>
<tr>
<td>Allen</td>
<td>Jeff</td>
<td>Executive Director</td>
<td>Friends of Cancer Research</td>
</tr>
<tr>
<td>Bach</td>
<td>Peter</td>
<td>Associate Attending Physician</td>
<td>Memorial Sloan-Kettering</td>
</tr>
<tr>
<td>Bargout</td>
<td>Victoria</td>
<td>Director, Oncology US HEOR</td>
<td>Bayer</td>
</tr>
<tr>
<td>Basch</td>
<td>Ethan</td>
<td>Assistant Attending Physician</td>
<td>Memorial Sloan-Kettering; ASCO</td>
</tr>
<tr>
<td>Benner</td>
<td>Joshua S.</td>
<td>Research Director, Engelberg Center for Health Care Reform</td>
<td>The Brookings Institution</td>
</tr>
<tr>
<td>Blayney</td>
<td>Douglas</td>
<td>President/Medical Director of ASCO; Professor of Internal Medicine; University of Michigan Comprehensive Cancer Center</td>
<td>ASCO</td>
</tr>
<tr>
<td>Bruinooge</td>
<td>Suanna Steebby</td>
<td>Director, Research Policy Division; Cancer Policy and Clinical Affairs Department</td>
<td>American Society of Clinical Oncology</td>
</tr>
<tr>
<td>Cannon</td>
<td>Eric</td>
<td>Chief of Pharmacy, Director of Health and Wellness</td>
<td>SelectHealth</td>
</tr>
<tr>
<td>Cox</td>
<td>Emily</td>
<td>Senior Director, Research</td>
<td>ExpressScripts</td>
</tr>
<tr>
<td>Cullen</td>
<td>Kevin</td>
<td>Director</td>
<td>University of Maryland Marlene and Stewart Greenebaum Cancer Center</td>
</tr>
<tr>
<td>Cupit</td>
<td>Lisa</td>
<td>Medical Director</td>
<td>Bayer</td>
</tr>
<tr>
<td>Dawson</td>
<td>Nancy</td>
<td>Professor of Medicine and Oncology; Director of GU Medical Oncology</td>
<td>Georgetown University</td>
</tr>
<tr>
<td>Dias</td>
<td>Anthony</td>
<td>Managing Director, Blue Health Intelligence</td>
<td>Blue Cross Blue Shield Association</td>
</tr>
<tr>
<td>Downs</td>
<td>Christian</td>
<td>Executive Director</td>
<td>ACCC</td>
</tr>
<tr>
<td>Dy</td>
<td>Sydney</td>
<td>Associate Professor</td>
<td>Johns Hopkins University</td>
</tr>
<tr>
<td>Edwards</td>
<td>Mike</td>
<td>Chief, Hem-Onc Pharmacy</td>
<td>U.S. Army</td>
</tr>
<tr>
<td>Engstrom</td>
<td>Paul</td>
<td>Senior Vice President for Extramural Research Programs</td>
<td>Fox Chase Cancer Center</td>
</tr>
<tr>
<td>Farrell</td>
<td>Ann</td>
<td>Deputy Division Director, Division of Drug Oncology Products</td>
<td>FDA</td>
</tr>
<tr>
<td>Garner</td>
<td>Sarah</td>
<td>Associate Director for R&amp;D</td>
<td>NICE</td>
</tr>
<tr>
<td>Name</td>
<td>Title/Degree</td>
<td>Affiliation</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>--------------</td>
<td>------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Geraci</td>
<td>Clinical Pharmacy Specialist</td>
<td>Veterans Health Administration, Pharmacy Benefits Management Services</td>
<td></td>
</tr>
<tr>
<td>Giffin</td>
<td>Director, Forum on Drug Discovery, Development and Translation</td>
<td>Institute of Medicine</td>
<td></td>
</tr>
<tr>
<td>Goodman</td>
<td>Senior Vice President</td>
<td>The Lewin Group</td>
<td></td>
</tr>
<tr>
<td>Gorman</td>
<td>Director of Survivorship Policy</td>
<td>National Coalition for Cancer Survivorship (NCCS)</td>
<td></td>
</tr>
<tr>
<td>Hunsberger</td>
<td>Senior Program Statistician</td>
<td>National Cancer Institute</td>
<td></td>
</tr>
<tr>
<td>Husereau</td>
<td>Director, Project Development, HTA</td>
<td>Canadian Agency for Drugs and Technologies in Health</td>
<td></td>
</tr>
<tr>
<td>Hussain</td>
<td>Professor</td>
<td>University of Maryland</td>
<td></td>
</tr>
<tr>
<td>Kessler</td>
<td>Professor and Chair</td>
<td>University of Washington</td>
<td></td>
</tr>
<tr>
<td>Lau</td>
<td>Director, Tufts Evidence-based Practice Center</td>
<td>Tufts Medical University</td>
<td></td>
</tr>
<tr>
<td>Lehner</td>
<td>Global Chief Medical Office</td>
<td>Sanofi-Aventis</td>
<td></td>
</tr>
<tr>
<td>Li</td>
<td>President and Medical Director</td>
<td>The Angiogenesis Foundation</td>
<td></td>
</tr>
<tr>
<td>Lind</td>
<td>Senior Policy Advisor</td>
<td>AARP Public Policy Institute</td>
<td></td>
</tr>
<tr>
<td>Lipscomb</td>
<td>Professor of Public Health and Georgia Cancer Coalition Distinguished Cancer Scholar</td>
<td>Emory University</td>
<td></td>
</tr>
<tr>
<td>Lyerly</td>
<td>Associate Director for Population Sciences</td>
<td>Duke University</td>
<td></td>
</tr>
<tr>
<td>Martinez</td>
<td>PhD student in health services research</td>
<td>Johns Hopkins University</td>
<td></td>
</tr>
<tr>
<td>Matuszewski</td>
<td>Editor-in-Chief</td>
<td>Gold Standard/Elsevier</td>
<td></td>
</tr>
<tr>
<td>McEvoy</td>
<td>Assistant Vice President of Drug Information</td>
<td>ASHP</td>
<td></td>
</tr>
<tr>
<td>McGivney</td>
<td>Chief Executive Office</td>
<td>NCCN</td>
<td></td>
</tr>
<tr>
<td>Michaelson</td>
<td>Scientific Director, Laboratory for Quantitative Medicine</td>
<td>Massachusetts General Hospital/Harvard Univ</td>
<td></td>
</tr>
<tr>
<td>Montgomery</td>
<td>Project Manager</td>
<td>CMTP</td>
<td></td>
</tr>
<tr>
<td>Mooney</td>
<td>Chief, Clinical Investigations Branch</td>
<td>CTEP/NCI/DCTD</td>
<td></td>
</tr>
<tr>
<td>Mullins</td>
<td>Visiting Scholar</td>
<td>CMTP</td>
<td></td>
</tr>
<tr>
<td>Neuman</td>
<td>Senior Analyst</td>
<td>Medicare Payment Advisory Commission (MedPAC)</td>
<td></td>
</tr>
<tr>
<td>Paserchia</td>
<td>Lead Medical Officer</td>
<td>Coverage and Analysis Group, CMS</td>
<td></td>
</tr>
<tr>
<td>Paul</td>
<td>Vice President, Clinical Scientific Affairs</td>
<td>National Pharmaceutical</td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td>Title</td>
<td>Organization</td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>--------------------------------------------</td>
<td>-----------------------------------</td>
<td></td>
</tr>
<tr>
<td>Pazdur</td>
<td>Richard</td>
<td>Director, Office of Oncology Drugs</td>
<td>FDA</td>
</tr>
<tr>
<td>Platona</td>
<td>Adriana</td>
<td>Director, Pharmaceutical Evaluation Branch</td>
<td>Australia PBAC</td>
</tr>
<tr>
<td>Ramsey</td>
<td>Scott</td>
<td>Professor</td>
<td>Fred Hutchinson Cancer Research Center</td>
</tr>
<tr>
<td>Rangarao</td>
<td>Sneha</td>
<td>Research Associate</td>
<td>CMTP</td>
</tr>
<tr>
<td>Robinson</td>
<td>Karen</td>
<td>Co-Director, Evidence-Based Practice Center</td>
<td>Johns Hopkins University</td>
</tr>
<tr>
<td>Rossi</td>
<td>Gregory</td>
<td>Vice President of Global Pricing and Payer Strategy</td>
<td>Genentech</td>
</tr>
<tr>
<td>Seal</td>
<td>Brian</td>
<td>Senior Director, Health Services Research</td>
<td>Sanofi-Aventis</td>
</tr>
<tr>
<td>Seidenfeld</td>
<td>Justine</td>
<td>Research Associate</td>
<td>CMTP</td>
</tr>
<tr>
<td>Sonnad</td>
<td>Seema</td>
<td>Project Director</td>
<td>CMTP</td>
</tr>
<tr>
<td>Tam</td>
<td>Iris</td>
<td>Director</td>
<td>Genentech</td>
</tr>
<tr>
<td>Tunis</td>
<td>Sean</td>
<td>Director</td>
<td>CMTP</td>
</tr>
<tr>
<td>Yee</td>
<td>Don</td>
<td>Clinical Pharmacy Supervisor</td>
<td>Kaiser Permanente, MAS</td>
</tr>
<tr>
<td>Zagari</td>
<td>Martin</td>
<td>Executive Director</td>
<td>Amgen</td>
</tr>
<tr>
<td>Zetlaouii</td>
<td>Jean</td>
<td>VP, Portfolio Value Development</td>
<td>Sanofi-Aventis R&amp;D</td>
</tr>
</tbody>
</table>