Designing More Informative Clinical Trials for Off-Label Uses of Oncology Drugs

Executive Summary

Substantial uncertainty exists about the benefits and harms of many off-label uses of oncology drugs, creating an important challenge for clinical and health policy decision makers. The Center for Medical Technology Policy (CMTP) will conduct a six-month initiative with the overarching goal of developing recommendations on methods and strategies to improve the validity, relevance and consistency of clinical research designed to assess the comparative effectiveness and value of oncology drugs used for off-label indications. As part of this initiative, CMTP will convene a one-day multi-stakeholder Off-Label Oncology Think Tank to improve the systematic generation of evidence about the effectiveness of off-label uses of oncology drugs, providing a neutral ground to establish the steps necessary for improved evidence for drug therapy in cancer. Ultimately, this will address the unmet medical needs of oncology patients by establishing the value of off-label uses of oncology drugs. To accomplish the goal, there is a need to reach consensus among experts and stakeholders on better ways to more frequently and consistently design, fund, and implement prospective clinical studies of off-label therapies in oncology that will be more informative to:

- Patients making decisions to enter, continue, or switch treatment
- Physicians making treatment recommendations
- Investigators designing clinical trials to improve treatment
- Professional societies developing clinical guidelines
- Producers of compendia drug information
- Expert panels making decisions about compendia listing
- Payers making coverage and reimbursement decisions

The main deliverable of the initiative will be a document that provides an evidentiary framework for clinical trial design for off-label uses of approved oncology drugs. The need for this initiative emerges from the current approaches to research on off-label uses of cancer drugs that frequently do not incorporate the type and/or quality of evidence requested by post-regulatory decision-makers. As a result, there are large evidence gaps that impair decision making at the individual and population levels, resulting in inconsistency in how off-label prescribing occurs across prescribers and patient groups. Simultaneously, coverage for off-label use is similarly inconsistent. There are a variety of contemporary policy debates on how to address off-label prescribing and reimbursement decisions in the absence of the desired evidence of effectiveness. Through informed discussions, the Off-Label Oncology Think Tank will produce a framework of the issues to address in a methodological guidance surrounding post-approval study design that will support an evidence-based approach to determining the value of off-label use of oncology drugs. Participants will include a broad range of experts, stakeholders, and decision makers. In the succeeding months, CMTP will work with invited members of an expert working group to complete a draft methodological guidance document. The broader stakeholder group will then reconvene to provide input and comments on a second draft. The project will culminate in the public release of a guidance document for off-label oncology clinical trial design for broader comment.

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Background and Significance

Pervasiveness of Off-Label Use in Oncology

The Government Accountability Office (GAO) reported that one-third of anticancer medication prescribing represented off-label use in 1991.[1] 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.[2] The widespread use of off-label oncology drugs underscores one reason why oncology appears as an outlier and warrants a specific focus for research. In 2009, off-label use accounts for about 20% of all prescriptions and over 50% of expensive chemotherapy drugs.[3]

Limitations of Current Evidence

Since the Omnibus Budget Reconciliation Act of 1993, which approved Medicare reimbursement for off-label use of cancer drugs and biologics,[4] Congress has, perhaps unintentionally, encouraged off-label use of oncology therapeutics. Despite the prevalence of off-label use of oncology drugs and related services, the health outcomes and value of expenditures on these products and services are not well understood. Multiple stakeholders are affected, including patients, clinicians, professional societies such as The American Society of Clinical Oncology (ASCO), payers, pharmaceutical companies, and private organizations that produce or evaluate evidence on off-label uses in oncology.

CMS and other payers rely on compendia, which provide recommendations on the scientific evidence for cancer drugs, aggregated from peer-reviewed original literature on off-label use from the medical literature.[5] For more details, see the description of compendia review process and criteria in *Appendix A*. Currently, there are four accepted compendia approved for use by Medicare and many post-regulatory decision makers turn to these compendia for guidance.[6, 7] Many patients, oncologists and other clinicians, payers and policy makers are dependent on these compendia, yet compendia often are viewed as being "too lenient" in terms of the quality of evidence required for compendia listing. Some studies have raised questions about the rigor and consistency of the compendium process. A 2006 analysis of 14 off-label indications concluded that current compendia "lack transparency, cite little current evidence, and lack a systematic method to review and update generated evidence".[8] Authors from the Annals of Internal Medicine noted the "lack of standard and ambiguity" among existing compendia.[3,9,10] Furthermore, concerns have been raised about the speed with which the remaining compendia review the available evidence and issue conclusions about off-label drugs.[11] Arguably, if there were more valid and reliable evidence available for review and if compendia were up-to-date, consistent and standardized, this model might serve as an optimal method for determining whether anticancer drugs were safe, effective and useable outside of the FDA drug label. However, the documented concerns with the current compendia process reinforce the need for improvements in the framework for evaluating off-label uses for oncology drugs.

The Need for Better Evidence

The lack of evidence on the effectiveness of off-label use of oncology drugs presents multiple challenges faced by all stakeholders involved. When a physician prescribes off-label, he or she must take on the burden of determining the evidence of effectiveness, most of which is not readily available.[12] For pharmaceutical companies and other health care technology producers, effective drug therapies are not utilized optimally in the market, due to constraints in evidence generation and dissemination, lack of education and knowledge by users and, in some instances, misaligned reimbursement incentives. For payers, rising health expenses call for a more efficient and cost-effective alternatives for cancer care. For patients, there is a vital need to have access to the most promising cancer care available. It is

important to bridge these evidence gaps and provide a framework for addressing these challenges in an optimal manner.

Comparative Effectiveness Research

One approach to bridging these evidence gaps would be the application of prospective comparative effectiveness research (CER) methodologies. CER is defined by the Institute of Medicine as "...the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist patients, consumers, clinicians, purchasers and policy makers in making informed decisions that will improve health care at both the individual and population levels."[13] The evidence produced from traditional randomized, clinical trials (RCTs) used for regulatory approval purposes often does not answer the question "which treatment strategies work best in routine clinical practice?" CER not only addresses the broad scope of clinical effectiveness in "the real world" but also the related issues of relative value of treatment options.[14] In essence, the Think Tank, by convening multiple stakeholders, could provide a framework for utilizing CER applied to off-label use of oncology drugs. This approach is most important in order to establish an informed, multidisciplinary framework that addresses the needs of all decision makers involved.

CER applied to Off-Label Oncology

CER related to the off-label use of oncology drugs is particularly challenging because of the widespread "evidence gaps" in this therapeutic area. An important first step in CER when applied to oncology drugs involves identifying the most pervasive off-label uses by tumor type, line of therapy, and patient population. The next step involves selecting the appropriate clinically relevant alternatives early on in the process, chosen based on the most common decision-making scenarios. Traditional RCTs do not include relevant comparators, leaving decision makers to make comparisons across trials, where assumptions, research methods, patient populations, and other crucial characteristics may be different.

CER should select clinically-relevant outcomes that are intended to address the primary issues and concerns of patients, clinicians, payers, and policy makers. Many RCTs include outcomes that are of primary interest to regulators and often examine intermediate outcomes or prognostic factors associated with survival. Too often, they pay less attention to the evidence requested by post-regulatory decision makers that will also use those studies to guide their choices. These clinically-relevant outcomes may include more quality-of-life information and may involve longer follow-up periods than are typical for traditional clinical trials. Importantly, the selection of the most useful and relevant outcomes requires direct consultation with decision makers during study protocol development.

Finally, to be maximally informative, off-label oncology CERs should be designed to be generalizable in that they include sociodemographic diverse patient populations as well as patients with common co-morbidities that exist among cancer patients and/or are positively or negatively associated with the use of oncology drugs.

Realigning Incentives to Promote Better Evidence

There are a number of mechanisms for generating better evidence of effectiveness of off-label use of oncology therapies, which include pragmatic clinical trials (PCTs), registries, and coverage with evidence development. Historically, there has been little incentive for pragmatic studies to be conducted after FDA approval during the drug launch and post-marketing phases, which coincides with when decision makers are in greatest need of evidence. However, increasingly payers are requesting evidence that is

in alignment with the national initiatives for more informative information about the relative value of medicines from CER, not only in oncology, but across other medical domains.

Often, in response to requests for more "real-world evidence," alternatives to traditional RCTs are mistakenly viewed as being limited to retrospective analysis of existing data. That approach provides usable information but often loses too much internal validity in order to credibly inform coverage and policy decisions. The aim of the Off-Label Oncology Think Tank will be to identify alternatives to traditional efficacy trials and ascertain optimal strategies to retain internal validity, improve generalizability, and produce faster and more efficient studies. One such alternative involves PCTs.[15] PCTs are prospective studies designed specifically with the objective of producing information that will assist patients, clinicians and payers in making informed decisions about alternative drug therapies.

Proposed Solution: Initiative, Project Objectives and Phases

CMTP will convene a multi-stakeholder group for a one-day think tank to address the barriers to systematic generation of effectiveness for off-label uses in oncology, providing a neutral forum to establish the steps to improved quality cancer care. The overarching goal of the meeting is to develop strategies that will improve validity and relevance of clinical research designed to assess the comparative effectiveness and value of oncology drugs that are used for off-label indications.

We propose to develop a conceptual framework that reflects closer alignment between study design elements intended for regulatory approval and study design elements targeted to clinical and health policy decision makers. This Think Tank and the work before and after the meeting will involve a process that allows for multi-stakeholder input to address:

- How evidence gaps drive off-label uses for oncology drugs
- Methodological guidance for study design issues regarding off-label uses in oncology
- Data collection and monitoring
- The role of oncology clinicians in informing treatment comparators
- Reimbursement and coverage with evidence development considerations
- Funding and infrastructure for CER in off-label uses of oncology drugs
- Key Stakeholder groups required for effectiveness guidance and implementation

Our approach is intended to gain consensus and explicit guidance for identifying and discussing feasible strategies to improve: (1) the quality of evidence available to evaluate the incremental clinical benefit of oncology drugs used in off-label indications and (2) the efficiency of the process to develop that evidence. Much like FDA guidance, these standards have the potential to become a major driver of clinical research design, and should therefore be an important lever through which the comparative effectiveness evidence needed by decision makers is reliably and consistently generated for off-label use in oncology. Please refer to *Appendix B* for a preliminary list of questions related to this initiative.

The project will be conducted in the following phases:

Pre-Think Tank

Prior to the Think Tank, we are conducting background research in order to clearly characterize the perceived deficiencies in the current evidence base for off-label use of oncology drugs. Initial background work would focus on a systematic description of the common methodological limitation of studies of off-label use of oncology drugs. This information will be derived from appraisal of systematic reviews, clinical guidelines, compendia documents, coverage policies and other summaries of evidence related to off-label use of oncology drugs. Based on this information, we would then conduct semi-structured interviews with key experts and stakeholders concerning their concerns with current evidence and proposed improvements. We also would ask them to identify the key issues that should be addressed during the Think Tank relating to how to design prospective studies for off-label drugs uses that would be more informative to decision makers. In addition, prior to the Think Tank, we will use reports from AHRQ or other sources that highlight "evidence gaps" and talk with payers about specific oncology drug examples where additional trials are highly desired. The Think Tank will then address these issues and case studies with the eventual aim of drafting an "Effectiveness Guidance Document." Per the standard CMTP process, the EGD would be developed in collaboration with a multi-disciplinary workgroup and refined through broad distribution, comment and revisions.

Think Tank

During the Think Tank, short presentations will describe the findings of the pre-meeting reviews and themes that emerged from key informant interviews. Participants will be asked to provide feedback and discuss prior reports related to study designs for trials of off-label drug uses in oncology. Reports from the AHRQ, FDA, and the CMTP PCT workshop will be included along with participants' own experiences. Participants will then actively engage in a series of round table and small group activities aimed at outlining areas of consensus and debate. In particular, participants will be asked to highlight types of information that are currently missing from clinical trials but are necessary for informing oncology treatment selection and coverage decisions as they relate to off-label use. Case studies will be used to discuss "real world" examples and work through pragmatic approaches and solutions.

Post-Think Tank

After the Think Tank, CMTP staff will synthesize the results of the meeting and incorporate recommendations and themes into a Meeting Summary, which will be distributed to Think tank participants for review and revision. In addition, a manuscript in the form of a commentary or systematic review, highlighting "lessons learned" will be produced. Finally, it is anticipated that the Think Tank may motivate the production of a series of Effectiveness Guidance Documents (EGDs) for specific topics within oncology. These EGDs would be separate from the one for this initiative that will provide an evidentiary framework for clinical trial design for off-label uses of approved oncology drugs.

Key Stakeholders / Institutions:

- Agency for Healthcare Research and Quality (AHRQ)
- American Cancer Society (ACS)
- American Society of Clinical Oncology (ASCO)
- AMIA
- Angiogenesis Foundation
- Association of American Cancer Institutes
- Avalere Health
- Centers for Medicare & Medicate Services (CMS)
- Clinical Researchers
- Compendia Representatives
- Consumers and Patient Representatives
- Eastern Cooperative Oncology Group (ECOG)
- Food and Drug Administration (FDA)
- Imaging Companies
- National Cancer Institute (NCI)
- National Coalition for Cancer Survivorship (NCCS)
- National Institute for Health and Clinical Excellence (NICE)
- National Pharmaceutical Council (NPC)
- Payers
- PBAC
- Pharmaceutical Manufacturers
- Radiation Therapy Oncology Group (RTOG)
- Researchers
- Universities
- US Oncology
- Veterans Affairs

APPENDIX A

Compendia Review and Process Criteria

	AHFS-DI	Clinical Pharmacology	DRUGDEX	NCCN
Updating Interval	Max: 3-5 years Min: 4-6 weeks	Max: 2 years Min: 1 week	Max: None Min: 6 weeks	Max: 1 year Min: 4-8 weeks
Methods to search for evidence	Continuous surveillance of multiple evidence sources	Continuous surveillance of multiple evidence sources	- Weekly automated searches of medical literature - Daily review of key med journal TOCs and alerts from FDA, NIH, CDC, etc.	Literature searches done yearly by staff; supplemented by suggested citations of 19 member inst. plus Clinical Practice Guideline panel members
Sources	- Drug and medical information databases - Relevant medical journals - Government, professional association and industry reports - Routine monitoring of major peer-reviewed medical journals and bibliographic databases	- Official FDA- approved drug label - Primary medical and pharma journals - Abstracting services - Reference texts - - Pharmacology texts - Herbal and Alt Medicine texts - Medical texts -Drug interaction texts -Nutrition and IV therapy texts	- Drug and medical information databases e.g., PubMed, Toxline, www.cancer.gov, www.guidelines.gov, The Cochrane Library, MedWatch) - Relevant medical journals	- Primary evidence: Ovid/PubMed, journals, professional association meeting abstracts - Secondary and tertiary: textbooks, websites
Criteria for selecting evidence	Emphasis placed on well-designed, controlled studies, published meta-analyses and systematic reviews, cost-effectiveness analyses	Phase III or IV clinical investigation in the U.S.; lower level evidence at discretion of editorial staff	Designed to be broad; emphasis placed on well-designed, controlled studies, but may include case reports	Per NCCN Clinical Practice Guideline panels
Criteria for weighing evidence	1: High strength/quality (good RCT or meta-analysis, or overwhelming observational evidence) 2: Moderate strength/ quality (RCT with methodologic limitations, inconsistent or indirect evidence, meta-analysis of heterogeneous RCTs, strong observational evidence) 3: Low strength/quality (observational, case reports, case series, seriously deficient RCTs) 4-Opinion/experience NB – strength of endpoint added at each level for cancer uses	No criteria currently used NB – a system is under development; based on AHRQ publications	A: Meta-analysis of RCTs with homogeneity, or multiple, well-done RCTs involving large numbers of patients B: Meta-analysis of RCTs with heterogeneity, RCTs with small numbers of patients or with methodological flaws, or nonrandomized studies C: Expert opinion or consensus, case reports or case series No Evidence	High (RCTs or meta-analysis) Lower (Phase II trials or large cohort studies, ranging to individual practitioner experience)

APPENDIX B

A preliminary list of questions related to this initiative includes but is not limited to:

- What are the common deficiencies in the existing evidence base?
- How does one decide which potential off-label indications are most important to study?
- What important primary and secondary outcomes are missing from trials, and how can this data be efficiently generated?
- What is the relative value of the following endpoints and which are most impactful?
  - Cancer-specific mortality
  - Overall mortality/survival
  - Progression-free survival (PFS)
  - Health-Related Quality-of-Life (HRQoL)
  - Toxicities
- What are examples of high quality studies of off-label indications?
- What is the role for pragmatic clinical trials in addressing off-label use in oncology?
- What other methods might be useful in improving off-label studies in oncology?
  - Bayesian methods
  - Adaptive designs
  - Cluster RCTs
  - Delayed-design trials
- How can studies be implemented in real world practice settings?
- How should improvements in technology and changes in clinical practice patterns be incorporated into study design?
- Where are we headed with personalized medicine and molecularly-defined medicine in oncology treatment?
- How and when should design of these trials address the increasingly common use of biomarkers, which will increasingly be desirable to identify subgroups of patients who respond differently to the oncology drugs?
- What would be the roles of registries and electronic medical records in generating the desired evidence?
- What role might coverage with evidence development play in supporting these studies?
- How do the above vary by tumor site/stage?

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