# HOW CAN ADVERSE EVENTS INFORMATION BE USED TO MORE EFFECTIVELY INFORM CANCER PATIENT CARE?

Syril Pettit

A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Public Health in the Department of Health Policy and Management in the Gillings School of Global Public Health.

Chapel Hill
2019

Approved by:

Ethan Basch

Pam Silberman

Kristen Hassmiller-Lich

Steven Lipshultz

Rebecca Kirch

## ABSTRACT

Syril Pettit: How Can Adverse Events Information Be Used
to More Effectively Inform Cancer Patient Care?
(Under the direction of Ethan Basch)

Due to advances in screening and therapy design, cancer patients are living longer while on or following therapy. Therapy-related adverse events (AEs) are an unintended, but not infrequent, outcome of these treatments. AEs can impact quality of life, adherence to therapy, economic status, and treatment decision-making. This novel qualitative study is the first to undertake a multi-stakeholder evaluation of the impact of AE information on informing cancer patient care in the context of extended survival. The evaluation focuses on a growing subset of cancer patients – those receiving adjuvant therapy.

Adjuvant therapies, used to manage many common cancers, lower the risk that the cancer will return. In this setting, mediating the impact of potential acute or delayed adjuvant treatment-related AEs relative to an uncertain potential for tumor recurrence presents important challenges in balancing risks versus benefits.

Stakeholder perspectives on generating, disseminating, and/or adjuvant treatment-related AE information were elicited via key informant interviews with patient advocacy, clinical care, regulatory, drug development, and healthcare payer representatives. The stakeholders identified future needs in four key areas: 1) information resources, 2) information integration and implementation, 3) value systems and culture, and 4) alignment and ownership of collective efforts to improve the use of AE information in the adjuvant setting.

This study revealed the following novel insights: 1) there is cross-stakeholder agreement that change is needed to improve the use of AE information in the adjuvant setting to improve patient outcome, 2) the directionality of needed changes are similar across stakeholders, although specific priorities varied, and 3) the potential to realize broad systemic progress in the use of adjuvant-related AE information is a challenge that lacks clear ownership. This lack of ownership has adversely impacted resourcing, efficiency, and collective progress and is likely to be a progress-limiting factor in realizing transformational change.

To address the system-limiting challenges identified in this research, a proposed approach to incentivize and support stakeholders in forward action is offered. The proposal offers an infrastructure to promote collaborative and independent efforts in fulfillment of the many scientific, economic, communication, social, and implementation challenges identified in this research study.

## ACKNOWLEDGMENTS

There isn't enough space to thank my family and friends for supporting me through this journey. Your constant encouragement, humor, and company kept me going and have given me added incentive to finish—to allow more time with you! I am so fortunate to have had all of you by my side.

Special thanks to my husband, Tim, for never doubting and always being a fan.

Special thanks to my kids, Mara and Torin, for letting me revel (and gripe) about being a student right alongside them.

Thanks to my parents for instilling a life-long love of—and respect for—learning.

Thanks to all those friends from Team Lava for patiently, and supportively, listening to me prattle on for all those miles on the running trails—and for your great advice on data analysis and implementation. No end to your talents, ladies!

Thank you to my committee members for their expert guidance and enthusiasm. Your passion for your own work in this area has made all the difference.

Thank you to my colleagues at HESI for supporting my personal and professional growth—and for being such good friends and mentors.

And finally, I extend thanks to an incredible cohort, C12. You inspire me in so many ways with your commitment to public health and to doing good for the world.

**TABLE OF CONTENTS**

## LIST OF TABLES

## LIST OF FIGURES

## LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| ABLe | Above and Below the Line (Change Framework) |
| ASCO | American Society for Clinical Oncology |
| CMS | U.S. Centers for Medicare and Medicaid Services |
| CTC | Consensus Toxicity Criteria |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CTEP | Cancer Therapy Evaluation Program |
| DFS | Disease-free survival |
| EHR | Electronic health record |
| ESMO | European Society for Medical Oncology |
| FDA | U.S. Food and Drug Administration |
| HCUP | Healthcare Cost and Utilization Project |
| HTA | Health technology assessment |
| ICD | International Classification of Diseases |
| ICER | Institute for Clinical and Economic Review |
| KII | Key informant interview |
| LHS | Learning healthcare system |
| MCBS | Magnitude of Clinical Benefit Scale |
| MSKCC | Memorial Sloan Kettering Cancer Center |
| NCCN | National Comprehensive Cancer Network |

| | |
|---|---|
| NCI | National Cancer Institute |
| NHB | Net health benefit |
| OCM | Medicare Oncology Care Model |
| PCDD | Patient Center Drug Development |
| PCMH | Patient-Centered Medical Home |
| PCORI | Patient-Centered Outcomes Research Initiative |
| PFLY | Progression-free life-year |
| PFS | Progression-free survival |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| PRO | Patient-reported outcome |
| PRO-CTCAE | Patient-Reported Outcome Common Terminology Criteria for Adverse Events |
| QALY | Quality-adjusted life-year |
| QoL | Quality of life |
| RCT | Randomized controlled trial |
| RWE | Real-world evidence |
| TTO | Time trade-off |

# CHAPTER 1: BACKGROUND AND SIGNIFICANCE

Life with cancer and its treatment—whether as a patient, survivor, or supporter—is an almost universal experience. Per the U.S. National Cancer Institute (NCI), 40% of the population will be diagnosed with cancer in their lifetime and many others are friends or family members of cancer patients (Howlader et al., 2016). Fortunately, the last decade has seen tremendous advances in cancer therapy design and delivery and thus an increase in survival rates for many cancer types (Edwards et al., 2014). This increasing efficacy means that patients are living longer while on therapy or following their primary course of therapy.

Unfortunately, therapy-related adverse health events are an unintended, but not infrequent, outcome of these life-saving therapies (Berridge, Pettit, & Sarazan, 2014; Cleeland et al., 2012; Pettit et al., 2016). At their most severe or persistent, cancer treatment-related adverse events (AEs) can be lethal (e.g., cardiac failure or severe immune response) (Armstrong et al., 2014; Emens, Butterfield, Hodi, Marincola, & Kaufman, 2016). They can also inhibit the curative value of the therapy if the side effects impede a patient's ability to continue therapy (Castellanos, Chen, Drexler, & Horn, 2015). Oncologic therapies may also cause less dire but still debilitating systemic events, including fatigue, gastrointestinal issues, skin inflammation, and neuropathy (Bennett et al., 2016; de Golian, Kwong, Swetter, & Pugliese, 2016; Kumar et al., 2017; Macdonald et al., 2015; Ocean & Vahdat, 2004; Santoni et al., 2014; Speck et al., 2013). These events may occur acutely during treatment or may be delayed and/or persist months or years after a therapy is complete.

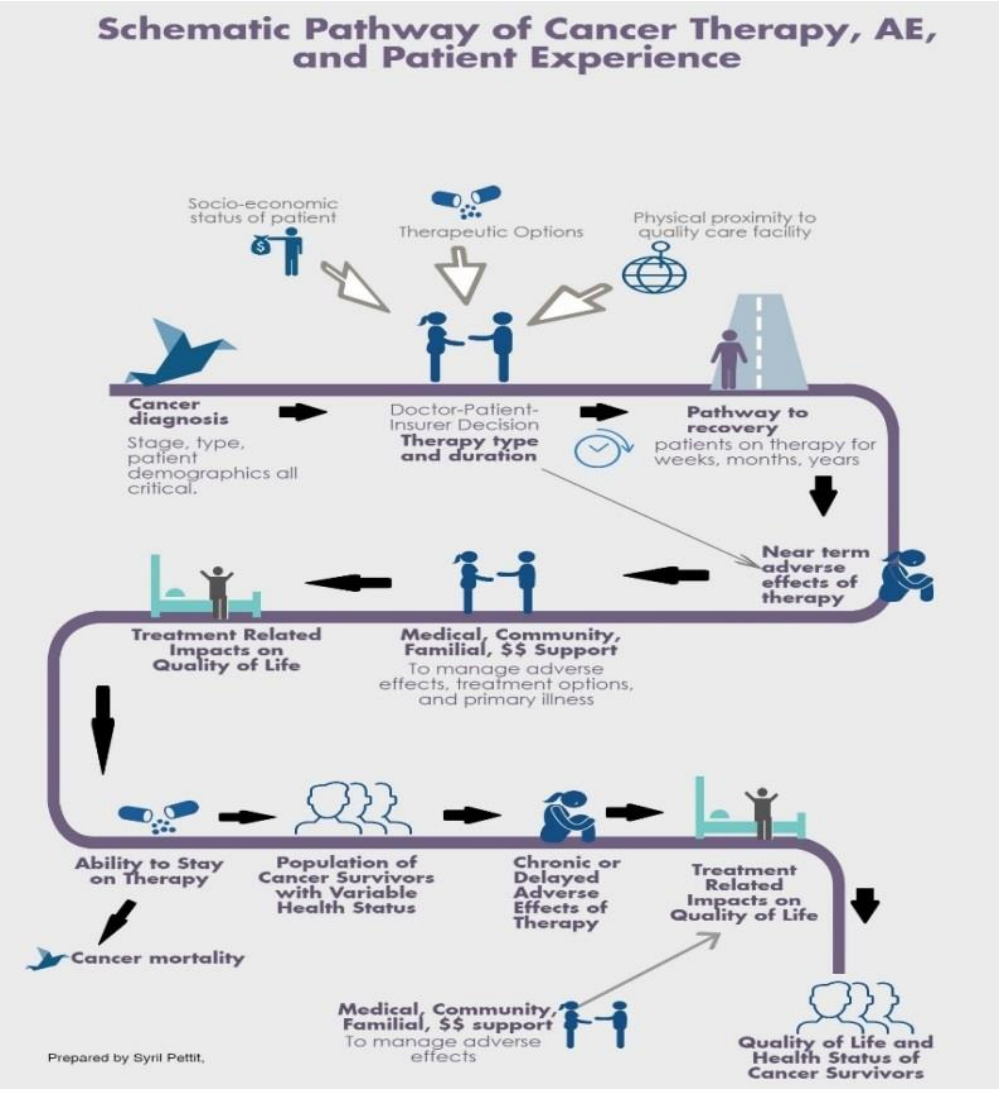
Before an oncology drug moves into clinical practice in the United States, the balance between acceptable AEs (risk) and efficacy (benefit) is influenced and assessed by pharmacologic drug design, nonclinical testing, clinical trials, and regulatory review, all of which are major investments spread across the private and public sectors. The average cost of development of a drug has been estimated at approximately $2.5 billion (Dimasi, Hansen, & Grabowski, 2003). During this process, the risk:benefit ratio for the therapy is calibrated (by the drug developer and regulatory reviewers) against the lethality of the target cancer (Kuderer & Wolff, 2014). Broadly speaking, these approaches provide an accepted and protective means of balancing anticipated AEs with efficacy in the patient population (Eichler, Pignatti, Flamion, Leufkens, & Breckenridge, 2008). In practice, the significant effort and investment in nonclinical oncology safety studies and clinical trials generates data that are more highly focused on and predictive of some outcomes (e.g., acute organ toxicities) than others (e.g., chronic pain or delayed-onset events) (Dambach et al., 2016; Woolf, 2010). Interindividual variability in response to treatment, heterogenous tumor types, and limited study durations remain challenges in the generation of highly nuanced predictions of population-level biological outcomes (Mak, Evaniew, & Ghert, 2014). However, investment in enhancing preclinical predictivity is a significant area of growth. The biomedical research community is pursuing the adoption of novel preclinical experimental platforms, innovative preclinical and clinical trial designs, the use of comparative effectiveness methods, and enhanced collection of patient-reported AE data to enhance the predictive relevance of premarket safety and efficacy data (Basch et al., 2016; Dambach et al., 2016; Fiore & Lavori, 2016; Redig & Jänne, 2015; Woodcock et al., 2016). Because of these public-private development and evaluation efforts, the oncologic therapy options currently available in the United States are more varied and effective than ever before (Buffery, 2016).

The practical impacts of treatment-related AEs and their associated supportive care requirements may not be fully characterized until the oncology drug is in broad clinical use (Pettit et al., 2016). These impacts can include a broad range of direct financial costs as well as emotional, social, logistical, and physical tolls. Observational studies and health record analyses demonstrate that cancer treatment-related events can degrade patients' or survivors' overall health status, cause financial strain, and limit their ability to meet family obligations, work, or pursue fitness or hobbies (Cleeland et al., 2012; Fitzner, Oteng-Mensah, Donley, & Heckinger, 2017). Modulatory factors such as variable treatment adherence rates, drug-drug interactions, access to care, and patient comorbidities result in a range of patient experiences and healthcare system demands (Fitzner et al., 2017). For the purposes of this analysis, this will be referred to as the "postmarket" setting. Supportive care to ameliorate AEs may require patients to procure a broad range of pharmacologic treatments, undergo monitoring and testing, change diet and exercise practices, or pursue "alternative" approaches like acupuncture (Kottschade et al., 2016; Lee et al., 2017; Wallner, Köck-Hódi, Booze, White, & Mayer, 2016). Even for a specific treatment-related AE (e.g., aromatase inhibitor–induced chronic pain), the nature of the supportive approaches that are adopted may vary considerably from site to site (Yang et al., 2017). Collectively, the cost of purchasing and administering therapy, monitoring health while on therapy or after, and managing AE detection and care represents a major societal investment—as much as $120 billion and growing annually (Fitzner et al., 2017; Yabroff, Lund, Kepka, & Mariotto, 2011).

Despite this investment, one notable mode of evaluation that is not routinely applied in the U.S. drug approval process is cost-effectiveness. The U.S. Food and Drug Administration (FDA) is not mandated to consider financial impacts when making regulatory approval decisions for

oncologics and thus does not consider cost factors in its decision making (McKee, Farrell, Pazdur, & Woodcock, 2010; Siddiqui & Rajkumar, 2012). Even if costs are not directly considered in drug design or approval, there can be no question that economic considerations (among other factors) materialize once the drug moves into clinical practice. As illustrated in Figure 1, a range of influences (e.g., cost of drug, access to clinical facilities, quality of life [QoL] impacts of treatment and disease, impact on familial support systems, etc.) affect overall patient experience and outcome.

**FIGURE 1: Schematic pathway linking cancer treatment, survivorship, adverse events, and quality of life**

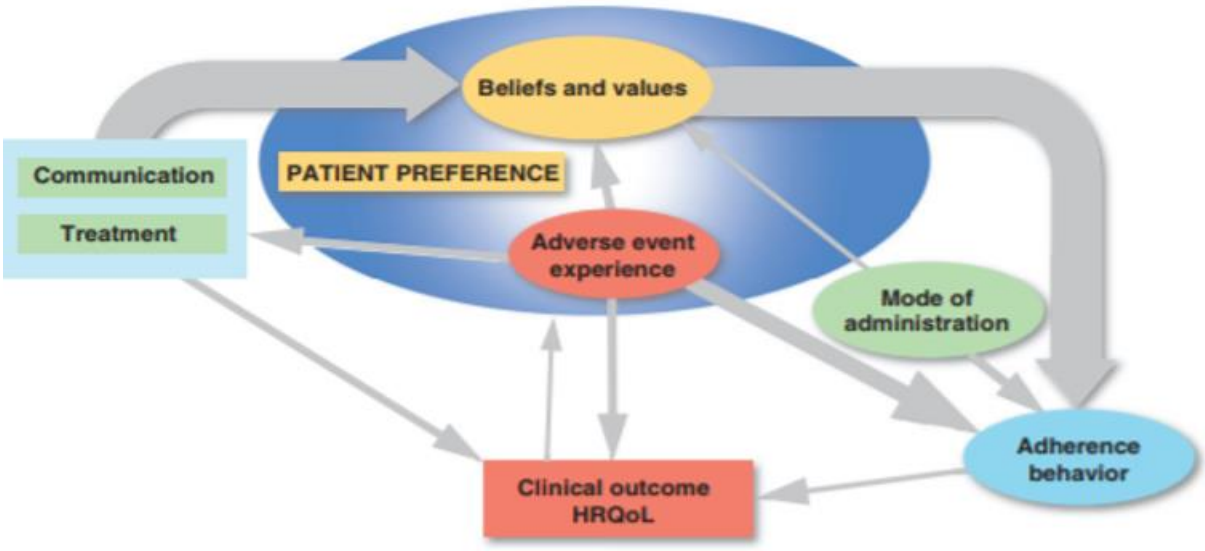


## Adverse Events, Patient-Centered Care, and Patient Preferences

Given the potential impact of AEs on patient outcome (health, QoL, and financial), the relevance of AE data as inputs to inform decision making by patients and clinicians seems evident. Foundational documents such as the World Health Organization (2003) report on adherence to long-term therapies and the movement toward "patient-centered care" and "shared decision making" clearly establish the need for patient access to understandable information about the benefits, risks, costs, and logistics of their treatment (Advisory Board Company, 2015; Atherton et al., 2013; Barry & Edgman-Levitan, 2012; Hare et al., 2017; National Institute for Health and Care Excellence, 2009; Zucca, Sanson-Fisher, Waller, & Carey, 2014). Patient-centered care, introduced in 1988 by the Picker Institute and later adopted by the Institute of Medicine report *Crossing the Quality Chasm*, promotes the following: consideration of physical comfort; emotional support; respect for patients' preferences and values; care integration and coordination; involvement of family and friends; and the provision of information, communication, and education that supports patients' ability to make informed decisions about their care (Institute of Medicine, 2001; Zucca et al., 2014). Although the concept of patient-centered care is widely embraced, the way in which these elements are pragmatically incorporated into practical care decisions or data generation incentives remains fluid (Barry & Edgman-Levitan, 2012). Not unexpectedly, preferences for balance of QoL versus length of life vary from patient to patient (and can vary during the course of therapy) (Meropol et al., 2008; Singh, Butow, Charles, & Tattersall, 2010). Further, the measurable impact of new patient-centered interventions is an area of active study with regard to the impact of patient satisfaction on therapeutic adherence and health outcome (Hoerger et al., 2013; Shingler et al., 2014).

Similarly, patient preference also plays an important role in understanding how AE or QoL information is incorporated into treatment and decision making. A 2014 in-depth literature analysis explored the published correlations between cancer treatment preferences (e.g., preference for a specific balance of toxicity, QoL, potential for "progression-free survival," logistics, cost, etc.) and potential adherence to therapy and patient outcome (Shingler et al., 2014). "Progression-free survival" is defined by the NCI (2018) as "The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse." Although no quantitative relationships could be established, the study recommends a "greater focus on the importance of patient preference in improving adherence levels to medication" and asserts that in oncology, "patient preference is a driver of adherence" (Shingler et al., 2014). As illustrated in Figure 2 below, Shingler et al. propose a range of influencing factors that may impact such adherence.

**FIGURE 2: Conceptual model for relationships between quality of life, adverse events, and adherence from Shingler et al.**



As summarized below, the authors specify three categories of factors (*external*, *cognitive*, and *behavioral*) that are theorized to influence adherence and are closely related to the patient experience of AEs.

*External Factors Influencing Adherence to Therapy*

- "Information (spoken/written/other) that the patient has with their healthcare provider, friend or relatives regarding likely treatment benefits, side effects and related burden."
- "Characteristics (of the treatment regimen) such as possible symptoms control etc. that patients may or may not perceive as a burden."

*Cognitive Factors Influencing Adherence to Therapy*

- "Beliefs regarding their disease and prognosis which they arrive with… the value they place on maintaining QoL versus perhaps maximizing their chance of survival…"

*Behavioral Factors Influencing Adherence to Therapy*

- "…[The] views or values that patients have regarding what they want from their treatment… e.g., wanting to maximize their survival… or …not wishing to undergo further rounds of chemotherapy."

Given the many levels at which AE information is anticipated to influence patient preference in this model, the incorporation (or absence) of a particular AE data type is again highlighted as a critical element with influence on clinical care and patient outcome.

**Value Frameworks: New Tools for Cancer Care Decision Making**

Although patient-centered care is not a new concept, the means of implementing this approach in a way that supports improved patient outcomes and knowledge generation, with regard to oncology treatment-related AEs and QoL impacts, has remained challenging. Over the

last 10 years, quantitative efforts to capture the *impact* of treatment-related AEs have often taken the form of economic studies and quality-adjusted life-year (QALY) models and projections (Pearce, Haas, & Viney, 2013). These efforts are largely aimed at economic, regulatory, and/or policy audiences. Beginning in 2016, the field took a significant conceptual step forward with the release of five major "value frameworks." These approaches are intended to inform policy decisions as well as pragmatic therapy choices *by clinicians and patients*. Value frameworks seek to fulfill some of the patient-centered care objectives by providing a means to integrate data on efficacy, safety (AEs), patient QoL, and, in some cases, cost for specific therapeutic modalities (ESMO, 2017; ICER, 2017; MSKCC, 2017; NCCN, 2017b; Schnipper et al., 2016).

The 2016 frameworks and their self-proclaimed objectives are as follows:

- *American Society of Clinical Oncology (ASCO) Value Framework*: "A framework that would enable a physician and patient to assess the value of a particular cancer treatment regimen given the patient's individual preferences and circumstances" (Schnipper et al., 2016).
- *European Society for Medical Oncology's (ESMO) Magnitude of Clinical Benefit Scale (MCBS)*: "The ESMO-MCBS is an important first step to the critical public policy issue of value in cancer care, helping to frame the appropriate use of limited public and personal resources to deliver cost effective and affordable cancer care" (ESMO, 2017).
- *Institute for Clinical and Economic Review (ICER) Value Assessment Framework*: "Ultimately, the purpose of the value framework is to form the backbone of rigorous, transparent evidence reports that, within a broader mechanism of stakeholder and public engagement, will help the United States evolve toward a health care system

that provides sustainable access to high-value care for all patients" (ICER, 2017).

- *Memorial Sloan Kettering Cancer Center's (MSKCC) DrugAbacus*: "DrugAbacus provides a way of thinking about how to price drugs. This interactive tool takes more than 50 cancer drugs and lets you compare the company's price to one based on value" (MSKCC, 2017).
- *National Comprehensive Cancer Center Network (NCCN) Evidence Blocks*: "The goal is to provide the health care provider and the patient information to make informed choices when selecting systemic therapies based upon measures related to treatment, supporting data, and cost" (NCCN, 2017a).

The construct of these five frameworks and their inputs, outputs, weighting, and intended audiences all vary considerably. However, all speak to a movement toward a more nuanced and inclusive evaluation of the impacts of therapeutic choice in the cancer care arena. The relative constructs of these five frameworks have been qualitatively compared and contrasted in the literature (Allen, Stewart, Roberts, & Sigal, 2017; Basch, 2016; Chandra, Shafrin, & Dhawan, 2016; Schnipper & Bastian, 2016; Subramanian & Schorr, 2016) and thus a comprehensive structural comparison will not be repeated here.

A synthesis of key elements of these frameworks with respect to incorporation of AE and QoL evaluation follows in Table 1. Note that some of the frameworks differentiate between adjuvant therapy (defined by the NCI as "treatment given after the primary treatment to lower the risk that the cancer will come back") and therapies given as primary treatment (NCI, 2017a). As highlighted in Table 1, AE/toxicity data (typically from published clinical trial data) are incorporated in all of the frameworks as a means of characterizing this key aspect of treatment choice.

**TABLE 1: Comparison of five major value frameworks regarding the use of toxicity and adverse event approaches[1]**

| Framework | Objective | Efficacy and safety data sources | Scoring/output | Efficacy/safety-related input data |
|---|---|---|---|---|
| ASCO | Inform joint decision making by patients and clinicians | Clinical trials | • Generates a single composite scored called the NHB<br>• Uses different algorithms for advanced disease vs. adjuvant setting | • Uses AE data drawn from clinical trials<br>• Can incorporate adjustments for QoL, treatment-free interval, improvement in cancer symptoms<br>• Can score for DFS (cure) or PFS |
| ESMO | Inform public policy, clinical guidelines, and direct clinical care | Clinical trials | • Semiquantitative process results in assignment of letter score (A–C) for adjuvant setting<br>• Semiquantitative process results in assignment of number score (1−5) for advanced disease | • Can score for DFS (cure) or PFS<br>• "Toxicity" and QoL rating incorporated |
| NCCN | Inform joint decision making by patients and clinicians | Clinical trial and expert opinion | • Assigns a series of Evidence Block Scores (5-point high score, 1-point low score) for categories such as toxicity, efficacy, cost, etc. | • Incorporates a range of both qualitative and quantitative inputs that are qualitatively synthesized via expert panels |

[1]Table 1 was modified from tables previously published in Chandra et al. (2016), Cohen, Anderson, & Neumann (2017), and Schnipper & Bastian (2016). AE, adverse event; ASCO, American Society of Clinical Oncology; DFS, disease-free survival; ESMO, European Society for Medical Oncology; FDA, U.S. Food and Drug Administration; ICER, Institute for Clinical and Economic Review; NCCN, National Comprehensive Cancer Network; NHB, net health benefit; PFS, progression-free survival; QALY, quality-adjusted life-year; QoL, quality of life; R&D, research and development. See Appendix F for an explanation of terms.

| | | | | |
|---|---|---|---|---|
| ICER | Provide synthesis for use by policymakers and payers/ formularies | Clinical trials, econometric studies | • Compares standard intervention and new treatment relative to short-term costs and longer-term healthcare system burdens and benefits | • Includes QALY scoring factors<br>• Serious AEs are factored into scoring<br>• Ability to work while on therapy factored into scoring |
| DrugAbacus | Provide pricing data for use by policymakers and payers | Drug safety/ efficacy data as provided to FDA | • Factors benefits and burdens of treatment into a new "price" based on the Abacus algorithm relative to industry-specified price | • Scores improved survival rate<br>• Serious AEs (e.g., grade 3 or greater) incorporated into scoring<br>• The probability that a patient discontinues treatment because of toxicity is considered in scoring<br>• Treatment novelty, R&D cost, health burden, and treatment duration |

**The Development of Patient-Relevant Data**

Novel opportunities to synthesize information from patient experience with a marketed drug, clinical trials, medical surveillance studies, electronic health records, and/or clinician expertise are the focus of recent calls to enhance the use of "real-world evidence" (RWE) to promote a "learning healthcare system" (LHS) in the United States (Califf et al., 2016; Sherman et al., 2016; Sherman, Davies, Robb, Hunter, & Califf, 2017). RWE is defined as "information on health care that is derived from multiple sources outside typical clinical research settings, including electronic health records (EHRs), claims and billing data, product and disease registries, and data gathered through personal devices and health applications" (Sherman et al., 2016). The concept of an LHS initiated from a series of workshops on healthcare improvement

as convened by the Institute of Medicine in the early 2000s. The LHS concept promotes the generation of "the best evidence and to apply that evidence to the healthcare choices that each patient and provider make in collaboration; to drive the process of discovery as a natural outgrowth of patient care; and to ensure innovation, quality, safety, and value in health care" (Institute of Medicine, 2007). Not surprisingly, the elements incorporated into the value frameworks above closely parallel the tenets of the LHS model. The generation of more RWE has been proposed as a means of realizing a more iterative and interconnected healthcare system.

The feasibility of RWE as a complement to regulatory safety evaluation via randomized controlled trials (RCTs) and/or as a means of generating novel efficacy, safety, or use information for marketed drugs is under active consideration but remains uncertain (Califf et al., 2016; Sherman et al., 2016, 2017). Novel clinical trial designs and settings (e.g., the National Institutes of Health Collaboratory), large-scale health record analysis (e.g., Million Veterans Program), and new patient-engaged networks (e.g., PCORnet) have been cited as potential opportunities to generate RWE (PCORnet, 2017; U.S. Department of Veterans Affairs, 2017; Weinfurt et al., 2017). As these are all relatively new programs (less than 3 years), their impacts are not yet defined. Ultimately, the success and novelty of any RWE approach to informing healthcare will rely upon the generation of *credible*, *fit for purpose*, and *otherwise unavailable* information as well as viable channels to *disseminate and use* this information. Sherman et al. (2017) cite the potential for RWE (e.g., postmarket surveillance or postmarket trials) to help refine dose-setting, subpopulation identification, and long-term safety considerations for novel cancer therapeutics that receive expedited initial approval. The model they describe, however, does not truly expand the traditional approach to drug evaluation and retains the longstanding emphasis on standard safety/efficacy endpoint collection and regulator-mediated evaluation and

decision making. If indeed RWE is intended to enhance the value of health data (AE-driven or otherwise) to a range of stakeholders, it seems clear that more nuanced and diverse evaluation of stakeholder need must be clarified.

Real-world patient experience is also being pursued via efforts to enhance patient engagement in regulatory approval considerations. In 2012, the U.S. Congress approved the Food and Drug Administration Safety and Innovation Act, which requires the FDA "to develop and implement strategies to solicit the views of patients during the medical product development process and consider the perspectives of patients during regulatory discussions." This directive, in combination with resources and programs defined via the Prescription Drug User Fee Act reauthorizations, led to the launch of the FDA's Patient Center Drug Development (PCDD) initiative. A primary outcome of the PCDD has been disease-focused meetings, convened by the FDA, that actively involve patients in providing perspective on risk:benefit considerations of relevance for the specific disease and associated therapies. Although these meetings have been an important step forward in integrating patient perspectives in selected settings, their impact on the overall approach to evaluating and conveying information on a therapy's impact on patient QoL and outcome is still evolving.

**An Unmet Need for Systems-Level Evaluation**

This introduction provides an overview of the plethora of AE data sources (e.g., drug safety and drug development, medical surveillance and patient reporting, clinical studies and clinician experience, RWE efforts, and regulatory science and trials) and AE-related decision frameworks (e.g., value frameworks, cost frameworks, patient-centered care frameworks, LHS models) inhabiting the cancer care landscape. On the one hand, this breadth can be viewed as a signal of the public health and cancer care communities' commitment to and investment in these issues.

On the other hand, the continued development and reinvention of these approaches suggests that the complement of current efforts may not be adequately synergistic or fit for purpose.

A systems-level assessment of whether the biomedical and public health communities are generating AE-related information and frameworks that are suited to the needs of contemporary cancer treatment decision makers is lacking. This study will address the question of whether the existing "puzzle pieces" fit together to provide the types of information most needed by patients and other key stakeholder groups to make informed decisions around cancer treatment (see Figure 3). By evaluating relevant information networks and network interactions, this study will develop new insights toward the goal of understanding the following question: How can AE information be used to more effectively inform cancer patient care?

**FIGURE 3: Data sources and approaches intended to "inform" cancer patient care and decision making**

# CHAPTER 2: LITERATURE REVIEW

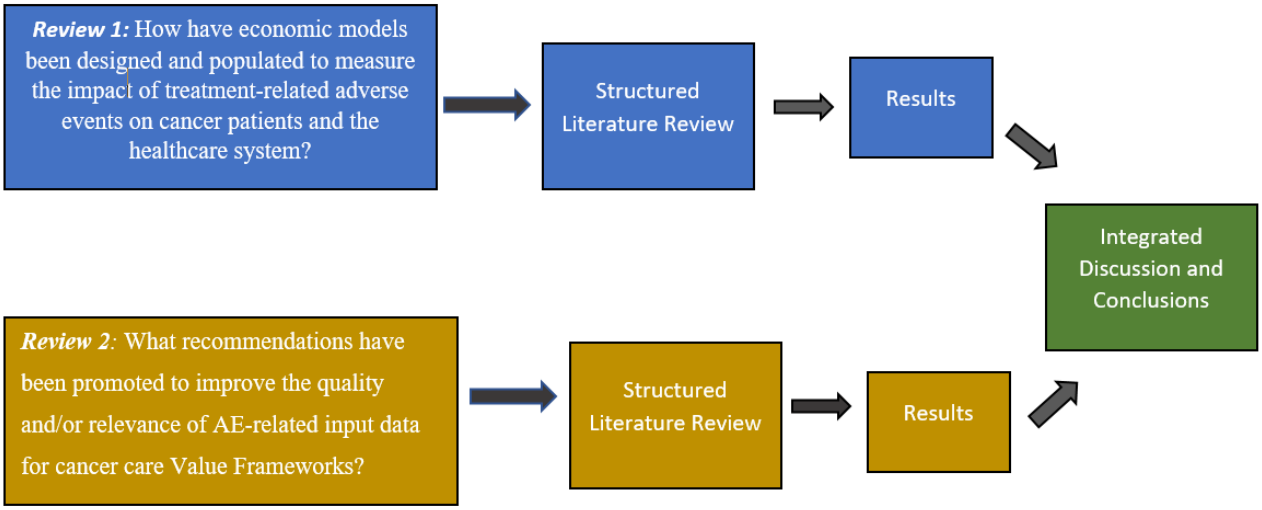
As a first step in addressing the question of how AE information can be used to more effectively inform patient care, it is necessary to first define how AE information has been used historically, how it is being used currently, and how it has been proposed for future use. Comprehensive literature reviews were conducted using published, peer-reviewed manuscripts as the informational bases for this evaluation. Specifically, two foundational questions were evaluated:

- Review 1: How have economic models been designed and populated to measure the impact of treatment-related AEs on cancer patients and the healthcare system?
- Review 2: What recommendations have been promoted to improve the quality and/or relevance of AE-related input data for cancer care value frameworks?

The first review focuses on economic impact models of treatment-related AEs in cancer patients and the healthcare system. A review of economic modeling approaches was deemed critical, as these methods were the primary format for "valuation" of treatment-related AEs prior to the publication of integrated value frameworks in 2016. The second literature review builds forward by defining the ways in which 2016/2017 integrative value frameworks have (or have not) modulated these prior approaches. Specific attention was given to published recommendations on the use of AE data to inform value framework–driven decision making. Two distinct literature search strategies (described below) were conducted, although the results are integrated here to define common approaches, key strengths and limitations, and consensus

recommendations for future needs. The methodological flow of this parallel approach is diagramed below in Figure 4.

**FIGURE 4: Multistage process for structured literature reviews**




## Literature Review Part 1: Cost Models and Valuation of Adverse Events

An informal review of the literature reveals multiple recent publications that calculate the costs/burdens of managing a broad range of cancer treatment-related toxicities. To date, there has not been a structured evaluation of the variance in these methodologies with a specific emphasis on their underlying assumptions and data sources, the diversity of AEs and costs evaluated, and/or the range of populations studied. A 2013 review covered some of these topics as they related to studies between 1999 and 2009 with a primary focus on whether QoL, multiple dose administration, and multiple AEs were considered in the cost assessment (Pearce et al., 2013). This review builds on prior evaluations by incorporating material from the years 2007–2017, enhancing the focus on the source of AE data and AE terminology (ontology), characterizing the target patient population to whom the cost/risk predictions apply, and exploring assumptions around the cost of AEs and related supportive services. Specifically, this review addresses the

following question: How have economic models been designed to measure the impact of treatment-related AEs on cancer patients and the healthcare system?

A structured search was conducted using the following databases: PubMed, Web of Science, CINAHL Plus with Full Text, and EconLit. The selection of biomedical, nursing/allied healthcare, and economics databases for inclusion in this review reflects the multidisciplinary nature of the issues and stakeholders under study. Additional studies were identified through a manual search of references in relevant articles (snowballing) and evaluation of resources from leading organizations in the cancer care arena in the United States (e.g., ASCO). The search terms used in this effort are described below (Table 2). Because the databases that were searched span multiple disciplines, the subset of terms utilized for that database varied slightly from database to database.

**TABLE 2: Search terms for literature review**

| **Date limitations: 2007 to present** | |
|---|---|
| **Concept** | **Key words, search terms** |
| Cancer focus | “cancer” or “oncology” |
| AND | |
| Treatment | “therapy” or “treatment” or “therapies” or “drugs” or “medication” |
| | AND |
| Adverse effects from therapy | “safety” or “toxicity” or “adverse effect” or “adverse event” or “toxicities” or “harm” |
| | AND |
| Cost and/or burden evaluation | “value of treatment” or “cost of toxicity” or “cost of toxicities” or “cost of adverse effects” or “burden of toxicity” or “burden of toxicities” or “burden of adverse effect” or "toxicity management" or “cost-effectiveness” or “pharmacoeconomics” |

### *Inclusion and Exclusion Criteria*

The focus of this research is on those studies that specifically seek to characterize the costs (economic, social, logistical) of managing and treating adverse effects of oncologic therapy. To ensure the contemporary relevance of the methodologies and underlying economic, healthcare, and treatment assumptions, only those studies published in the last 10 years were reviewed. The term "comparative effectiveness" is intentionally excluded in order to exclude the "comparative effectiveness research" literature. Although these studies do sometimes include cost estimates of AEs, their focus is exclusively on the differential/comparator between two similar therapies, and thus the total cost of AEs (the focus of this review) is rarely measured (Pearce et al., 2013). Prior systematic reviews of AE effect cost assessments have noted this limitation in the use of comparative effectiveness studies and thus they were excluded from this search. Radiological or surgical interventions were excluded, as the focus of this research is drug-induced AEs, not those initiated by radiotherapy or surgical intervention. Proposed inclusion and exclusion criteria are included in Table 3.

**TABLE 3: Inclusion and exclusion criteria**

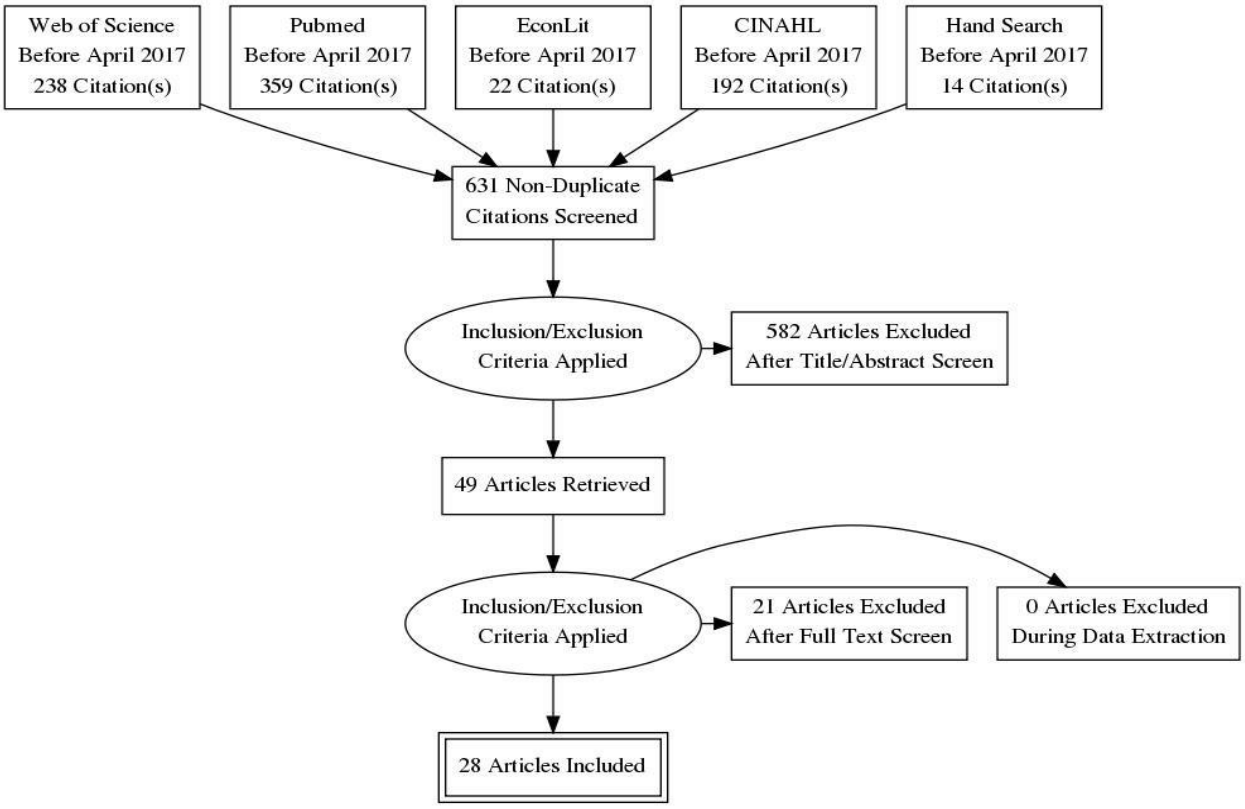
| Inclusion criteria | Exclusion criteria |
|---|---|
| • Qualitative and quantitative studies | • Focus of study is exclusively or primarily on healthcare delivery outside of the United States |
| • Descriptive and analytical studies | • Studies that do not substantively evaluate cost or treatment burdens associated with adverse consequences of cancer treatment |
| • Methodological and meta-analyses that employ primary analysis of data | • Article is older than 2007 |
| • Focused primarily on the U.S. healthcare system. Studies that included non-U.S. system evaluation were also included as long as U.S. healthcare evaluation was also incorporated | • Studies focused on the cost of "best supportive care" defined as provision of palliative care in the absence of an antineoplastic regimen (Zafar, Currow, & Abernethy, 2008) |
| • Studies that measure adverse events associated with a prescribed pharmacologic intervention to treat cancer | • Studies not in English |
| | • Chemoprevention or homeopathic studies |
| | • Studies for which the intervention is surgical or radiological |
| | • Summary reports or reviews unless they include novel analyses |

The proposed search strategy was as follows: a) search databases as specified above; b) include all references identified in direct as well as snowballing search into reference manager and remove duplicates; c) review all manuscript abstracts and date of publications against inclusion/exclusion criteria and restrict reference list accordingly; d) conduct a full text review of all remaining manuscripts; and e) for those manuscripts meeting all inclusion criteria, populate the extraction table accordingly. The articles remaining after all exclusion criteria had been applied were reviewed in full. This literature evaluation and data collection allows for comparison approaches for estimating the cost of AEs with a unique emphasis on the source of the AE data, cost data, population assumptions, and the ontologies used to describe them. Uniquely, this review will focus on U.S.-based assessments, whereas prior reviews have been

heavily weighted to evaluations outside of the United States. This study is limited to the United States, as other countries have different means for setting reimbursement levels and may have differential access to drugs and therapies. As such, cost estimation values and approaches are not meaningful across national boundaries.

The structured literature search yielded 631 unique citations after deduplication. Following a review of the abstracts of all 631articles, 49 were deemed eligible for full text review. After full text review, an additional 21 studies were excluded for failing to meet the study search criteria. A total of 28 studies were then utilized in the final review. The flow chart of study selection (Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] diagram) is included here as Figure 5.

**FIGURE 5: PRISMA diagram demonstrating the part I literature evaluation and exclusion process**



### *Study Characteristics*

The results of this structured review (2007–2017) provide insight into both the procedural means and situational assumptions driving estimation of the costs of AEs associated with oncologic therapy. The studies reviewed here employed one of two general approaches: estimation of the total cost of a therapeutic regime (drug costs, clinical visit costs, adverse effect costs, etc.) or assessment of the cost of one or more specific AEs associated with a designated cancer therapy. These studies used a variety of approaches to calculate costs, including probabilistic models representing transition between different treatment/health states, retrospective cost estimations, and/or prospective data collection and cost estimation. The studies covered a broad range of therapeutic drug classes, cancer types, and patient populations. Per the inclusion criteria, all studies included cost estimates and assumptions that were designed to be reflective of a U.S.-based patient population and U.S. medical and insurance practices. This review will not compare the absolute value of reported costs across studies because of the variable drugs, study designs, timescales, and patient populations assessed.

With the exception of one prospective cohort study (Haiderali, Menditto, Good, Teitelbaum, & Wegner, 2011), all studies reviewed here relied upon previously published clinical trials/published reports or EHR data as sources of information on cancer patient experience with oncologic therapy. Despite the varied nature of these studies, their many shared approaches provide valuable insight into the utility and limitations of efforts to quantify the impact of treatment-related AEs on cancer patients and the healthcare system. Three key areas were identified for cross-study comparison purposes: 1) assumptions around the cost of AEs and related supportive services, 2) source of AE data and impact of AE terminology usage, and 3) characterization of the target patient population to whom the cost/risk predictions apply. A

synthesis of the treatment of these issues across the literature follows below and in Tables 4A–4E. Collectively, these three data elements create a picture of their approaches to assessing the economic impact of cancer treatment-related AEs.

### *Cost Assessment Methodologies and Data Sources*

A review of the cost assessment methodologies and data sources is included here as Table 4A. Although all articles included in this review incorporated cost assessment of treatment-related AEs, the primary objective of the studies varied. Some sought to model or predict the total cost burden associated with a specific oncologic therapy, while others focused primarily on characterizing the frequency and cost of one or more treatment-related AEs. There was an almost even split (43%/46%) between the 26 articles that employed mathematical modeling approaches, primarily Markov models, and those that conducted retrospective total cost estimations based on published data from clinical trials and the literature. Markov models are stochastic or probabilistic models that characterize relationships between different states (e.g., disease state 1, disease state 2, disease free, dead) based on the probability of moving from one state to another. Of the remaining 2 of 28 papers, one employed a prospective cost assessment involving real-time data on incidence and costs and the other was a meta-analysis of published cost studies (Haiderali et al., 2011; Niraula et al., 2014).

**TABLE 4A: Cost assessment methodologies**

| Topic | Number of articles | References |
|---|---|---|
| Studies utilizing Markov models to estimate cost<br>(*Note:* Markov models are widely used for health economic analyses to evaluate potential outcomes of a disease process. The model reflects movement across different health states that are predefined by the modeler.) | 12 (43%) | Ayvaci, Shi, Alagoz, & Lubner, 2013; Burudpakdee et al., 2012; Chu, Schulman, Zelt, & Song, 2009; Dalton et al., 2012; Goulart & Ramsey, 2011; Havrilesky, Secord, Kulasingam, & Myers, 2007; Hess et al., 2015; Kurian et al., 2007; Twelves et al., 2006; Usmani et al., 2016; Y. N. Wong et al., 2009; Xie, Diener, Sorg, Wu, & Namjoshi, 2012 |
| Studies conducting retrospective cost estimation based on analysis of published data from trials or other sources | 13 (46%) | Ayvaci et al., 2013; Burudpakdee et al., 2012; Chu et al., 2009; Dalton et al., 2012; Goulart & Ramsey, 2011; Havrilesky et al., 2007; Hess et al., 2015; Kurian et al., 2007; Niraula et al., 2014; Twelves et al., 2006; Usmani et al., 2016; Wong et al., 2009; Xie et al., 2012 |
| Studies conducting prospective data collection and cost estimation | 1 (3%) | Haiderali et al., 2011 |
| Meta-analyses across published cost studies | 1 (3%) | Niraula et al., 2014 |

The data used to inform these cost studies varied in both source and content (Table 4B). More than a third of the articles (39%, n=11) utilized cost estimates from the U.S. Centers for Medicare and Medicaid Services (CMS) as their sole source of data on the cost of treating AEs associated with therapy. The CMS database includes data on Medicare-insured patients aged 65 years and older, people younger than 65 with certain disabilities, and those with end-stage renal disease (CMS, 2014). Another 25% of the articles (n=6) drew data from commercial, regional, or proprietary healthcare databases and another 15% (n=4) from the public Healthcare Cost and Utilization Project (HCUP). HCUP is a compilation of databases that include encounter-level hospital data drawn from Medicare, Medicaid, private insurance, and the uninsured but does not include outpatient data. Among these, a few articles highlighted the distinction between the fees

recorded in the HCUP database and the actual cost to the hospital or physician (and in one case, discounted to reflect the differential between the cost to the hospital and the amount billed to the insurer) (Havrilesky et al., 2007). The remaining seven articles (26%) drew data on cost from other published studies. The underlying source of data in these cited studies was not assessed for purposes of this review but is anticipated to have come from the sources above.

**TABLE 4B: Defining costs**

| Topic | Number of articles | References |
|---|---|---|
| Studies incorporating "indirect" costs such as time off work, caregiver costs, or lost employment potential | 6 (25%) | Ayvaci et al., 2013; Bristow et al., 2007; Haiderali et al., 2011; Kurian et al., 2007; Sorensen et al., 2012; Tina Shih, Xu, & Elting, 2007; |
| Studies utilizing Medicare as a proxy for cost data for drugs and services required to treat an adverse event | 11 (41%) | Ayvaci et al., 2013; Bajaj, Veenstra, Goertz, & Carlson, 2014; Bilir et al., 2016; Goldstein et al., 2014, 2016; Goulart & Ramsey, 2011; Haiderali et al., 2011; Hess et al., 2015; Rajan, Carpenter, Stearns, & Lyman, 2013; Wong et al., 2009; Xie et al., 2012 |
| Studies utilizing prior peer-reviewed studies as a proxy for cost data for drugs and services required to treat an adverse event | 6 (22%) | Dalton et al., 2012; Kurian et al., 2007; Niraula et al., 2014; Ting et al., 2015; Twelves et al., 2006; Usmani et al., 2016 |
| Studies utilizing private healthcare or state healthcare costs to estimate fees regarding adverse events | 7 (26%) | Bristow et al., 2007; Burke, Wisniewski, & Ernst, 2011; Chu et al., 2009; Craver et al., 2011; Sorensen et al., 2012; Stopeck et al., 2012; Tina Shih et al., 2007 |
| Studies using the Healthcare Cost and Utilization Project to estimate costs associated with adverse events | 4 (15%) | Burudpakdee et al., 2012; Delea, Amdahl, Diaz, Nakhaipour, & Hackshaw, 2015; Havrilesky, Chino, & Myers, 2013; Kowal-Podmore, Munakata, Tencer, & Smith, 2008 |

The majority of studies (~75%, n=21) identified in this review incorporated only direct costs (defined as cost of a hospital visit associated with an AE and/or cost of a physician visit) into

their modeled or cumulative cost assessments. Ninety-five percent of these studies (20 of 21) also included the cost of prescribed drugs (to treat the AE) in their estimation and/or the cost of over-the-counter drugs. Only one of these 21 studies (~5%) limited their analysis to direct hospital/physician fees (Burke et al., 2011). A significantly smaller percentage of the studies (25%, n=6) also included a valuation of "indirect" costs such as lost wages for time off work, caregiver costs, lost future employment potential, and so forth. The assumptions around the impact of the AE on lost worktime were variable but hourly wage rates and compensation data were consistently drawn from the U.S. Bureau of Labor Statistics.

The representation of the cost assessment varied across the studies and included calculation of additional QALYs relative to total treatment cost, incremental cost to avoid a particular AE, total accumulated costs during a given treatment period (primary treatment costs and AE-related costs), total accumulated costs to treat AE only, and costs per progression-free life-year (PFLY).

### *Defining and Quantifying Adverse Events*

In the context of clinical trials reported in the United States (and Europe), AEs are typically described with a grading system developed in the 1980s by the Cancer Therapy Evaluation Program (CTEP) of the NCI. This system, called the Consensus Toxicity Criteria (CTC), includes a standardized list of outcomes and symptoms in oncology trials and also includes a severity grading scale associated with these effects (Thanarajasingam, Hubbard, Sloan, & Grothey, 2015). Grade 1 is the least severe and can include outcomes like fatigue. Grade 4 indicates very severe toxicities (like liver failure), and grade 5 denotes death associated with an adverse treatment effect. The source and nature of AE data included in the reviewed studies is summarized in Table 4C.

**TABLE 4C: Nature/frequency of treatment-related adverse events**

| Topic | Number of articles | References |
|---|---|---|
| Studies using postmarket databases to support adverse event type and incidence**;** includes electronic health records, surveillance studies, cohort studies, etc. | 5 (18%) | Burke et al., 2011; Chu et al., 2009; Craver et al., 2011; Rajan et al., 2013; Tina Shih et al., 2007 |
| Studies citing other sources of data on adverse event type and incidence | 2 (7%) | • Direct patient survey and case reports: Haiderali et al., 2011<br>• Drug label data: Sorensen et al., 2012 |
| Studies referencing Common Terminology Criteria for Adverse Events (CTCAE) or other formal adverse event reporting standards | 1 (3%) | Ayvaci et al., 2013 |

RCTs from Phase II, III, and/or IV were the predominant source of data (75%, n=21) on the frequency and nature of the AEs incorporated into these cost evaluation studies. Of those studies utilizing clinical trials, 76% (n=21) incorporated only those AEs that were reported as a grade 3 or grade 4. Only 1 of 29 studies identified in this review made any direct reference to the specific ontological criteria used to define the grading in their studies (e.g., Common Terminology Criteria for Adverse Effects [CTCAE]) (Ayvaci, Shi, Alagoz, & Lubner, 2013). The CTCAE was initially developed by the NCI CTEP in 1983 and has been continually updated to include additional AE ontologies and severity grades (Chen & Setser, 2008). The remaining studies that referenced RCTs either did not fully specify the AE inclusion criteria or incorporated all reported AEs.

A significantly smaller percentage of the studies (18%, n=5) utilized "postmarket" databases (e.g., Premier Perspective Database with data from 600 U.S. hospitals) as a resource to identify the frequency and nature of AEs requiring clinical care. These data sources used International Classification of Diseases (ICD) codes to delineate patient symptoms and treatment. (*Note:* Outside of the clinical trial setting, clinicians do not routinely utilize the CTCAE to delineate

AEs in clinical practice.) ICD codes were also used to classify adverse effects in the one study that collected prospective data for the evaluation of treatment-related AEs via direct reporting from participating clinicians and patient surveys (Haiderali et al., 2011). One study utilized treatment label data as the source of information for adverse effect frequency and type (Sorensen et al., 2012). In addition to incorporation of AEs as measured by CTCAE or ICD reports, the impact of treatment-related AEs on patient QoL may also be considered in the risk:benefit assessment of therapeutic approaches. The evaluation of QoL impacts can be a complicated and subjective process. Existing and rapidly evolving survey tools include Patient-Reported Outcome Common Terminology Criteria for Adverse Events (PRO-CTCAE) and EuroQol-5D surveys (EuroQol, 2017; NCI, 2017b). These tools seek to incorporate patient perspective on the impact of therapy on endpoints such as pain, self-care, mobility, and so forth. Per Table 4D, only one of the 28 studies identified in this review incorporated direct measures of QoL into the cost assessment (Haiderali et al., 2011) via surveys of participating patients. However, 39% of the studies (n=11) included "utility factors" in their Markov models. These utility factors incorporate QoL-related adjustments relative to the different health conditions in the models. These adjustment factors appear to have been based primarily on EuroQol 5D surveys and time trade-off (TTO) surveys conducted in prior clinical trials—most of which were conducted in the early 2000s. Specific discussion of the assumptions or relevance of the utility factors selected was minimal to absent.

**TABLE 4D: Incorporation of "quality of life"**

| Topic | Number of articles | References |
|---|---|---|
| Studies incorporating quality of life via the use of "utility factors" derived from prior literature | 11 (33%) | Ayvaci et al., 2013; Bristow et al., 2007; Delea et al., 2015; Goldstein et al., 2014; Goulart & Ramsey, 2011; Havrilesky et al., 2007; Kurian et al., 2007; Manolio et al., 2013; Stopeck et al., 2012; Ting et al., 2015; Usmani et al., 2016 |
| Studies incorporating measures of quality of life based on de novo measures by investigator | 1 (3%) | Haiderali et al., 2011 |

***Defining Patient Populations***

The utility of the study predictions to inform future treatment decisions requires a clear definition of not only the cancer type and therapy but also the patient population demographics. In the reviewed studies, 21% (n=6) focused their cost and AE predictions on populations older than age 60 years, 46% reported results of relevance to patients older than age 18, and 32% did not specify the age demographic of the study predictions (Table 4E).

**TABLE 4E: Defining the population**

| Topic | Number of articles | References |
|---|---|---|
| Defines target population of the model/analysis as a patients age 60 or older | 6 (21%) | Ayvaci et al., 2013; Chu et al., 2009; Goulart & Ramsey, 2011; Havrilesky et al., 2007; Rajan et al., 2013; Ting et al., 2015 |
| Studies modeling/describing patient populations of various ages | 13 (46%) | Bajaj et al., 2014; Bilir et al., 2016; Burke et al., 2011; Craver et al., 2011; Goldstein et al., 2014, 2016; Haiderali et al., 2011; Hess et al., 2015; Kurian et al., 2007; Niraula et al., 2014; Sorensen et al., 2012; Tina Shih et al., 2007; Twelves et al., 2006 |
| Studies in which study population/relevant population ages are not described | 9 (32%) | Bristow et al., 2007; Burudpakdee et al., 2012; Dalton et al., 2012; Delea et al., 2015; Kowal-Podmore et al., 2008; Stopeck et al., 2012; Usmani et al., 2016; Wong et al., 2013; Xie et al., 2012 |

### *Limitations of This Review*

This review has a number of limitations. Because this review sought to assess impact in a U.S. healthcare context, economically based health technology assessments (HTAs) as required in Europe and several other regions to assess the cost-benefit of novel therapies were not incorporated. HTA studies are numerous and relatively standardized in their approaches and assumptions. Although HTAs relate only to single-payer healthcare systems that do not match the current U.S. multipayer profile, they could provide potentially useful sources for methodological comparisons. Because selected HTAs also include QoL (QALY) assessment in their economic evaluation of the cost-benefit of the therapy, they can also provide a resource in this regard for financial valuation-focused queries. The breadth of U.S.-based studies in this review provides an opportunity to characterize a diverse range of methods, but it also means that comparison across studies at a granular level is limited. Future studies might focus on a single drug class or cost assessment approach to allow for more focused cross-study comparison of input data and conclusions. Additionally, more comprehensive insights into methodological and data input assumptions across these studies could be gleaned by review of key underlying studies cited by the studies reviewed here. Finally, the use of cost as a means of capturing the totality of treatment-related AEs on patients is an approach subject to considerable debate in economic, clinical, patient, and medical ethics communities (Danis, 2017; Kumar & Moy, 2013). Beyond the technical challenges of obtaining relevant data (as described above), the distillation of a broad range of physical, emotional, financial, and logistical challenges into a “dollar” figure is distasteful and dismissive to some. This review is offered without judgement on this point, but with recognition that the exercise of estimating cost allows for thoughtful examination of a range of clinical, lifestyle, financial, social, and temporal elements that extend well beyond the scope

of the typical U.S.-based drug safety assessment. Further discussion of the linkages between economic-driven AE value approaches and integrative value frameworks for informing cancer care will follow in the discussion section below.

## Literature Review 2: Current Practice in and Expert Perspectives on the Use of Adverse Events in Value Frameworks

Since the publication of the ASCO Value Framework, the ESMO Magnitude of Clinical Benefit Scale, the ICER Value Assessment Framework, the MSKCC DrugAbacus, and the NCCN Evidence Blocks (ESMO, 2017; ICER, 2017; MSKCC, 2017; NCCN, 2017b; Schnipper et al., 2016), multiple organizations and experts have published commentaries on or critiques of the frameworks. These comparisons have focused primarily on a) the construct of the framework, b) the ease of use of the framework, and/or c) the utility and relevance of the output. This review builds on prior evaluations with a collective synthesis of recommendations for future improvement of the frameworks as they relate to sourcing and interpreting framework input data—particularly AE and/or patient-reported outcome (PRO) data. This review addresses the following question: What recommendations have been promoted to improve the quality and/or relevance of AE-related input data for value frameworks?

A structured literature search was conducted using the following databases: PubMed, Web of Science, and CINAHL Plus with Full Text. The selection of biomedical and nursing/allied healthcare databases included in this review reflects the broad base of stakeholders involved in evaluating value to patients during cancer care. Additional studies were identified through a manual search of references in relevant articles (snowballing). The proposed search terms used in this effort are described below (Table 5).

**TABLE 5: Search strategy**

| **No date limitations: search conducted July 2, 2017** | |
|---|---|
| **Concept** | **Key words, search terms** |
| Cancer focus | "Cancer" or "oncology" |
| AND | |
| Value frameworks | "value framework" |
| | AND |
| Adverse effects from therapy | "safety" or "toxicity" or "adverse effect" or "adverse event" or "toxicities" |

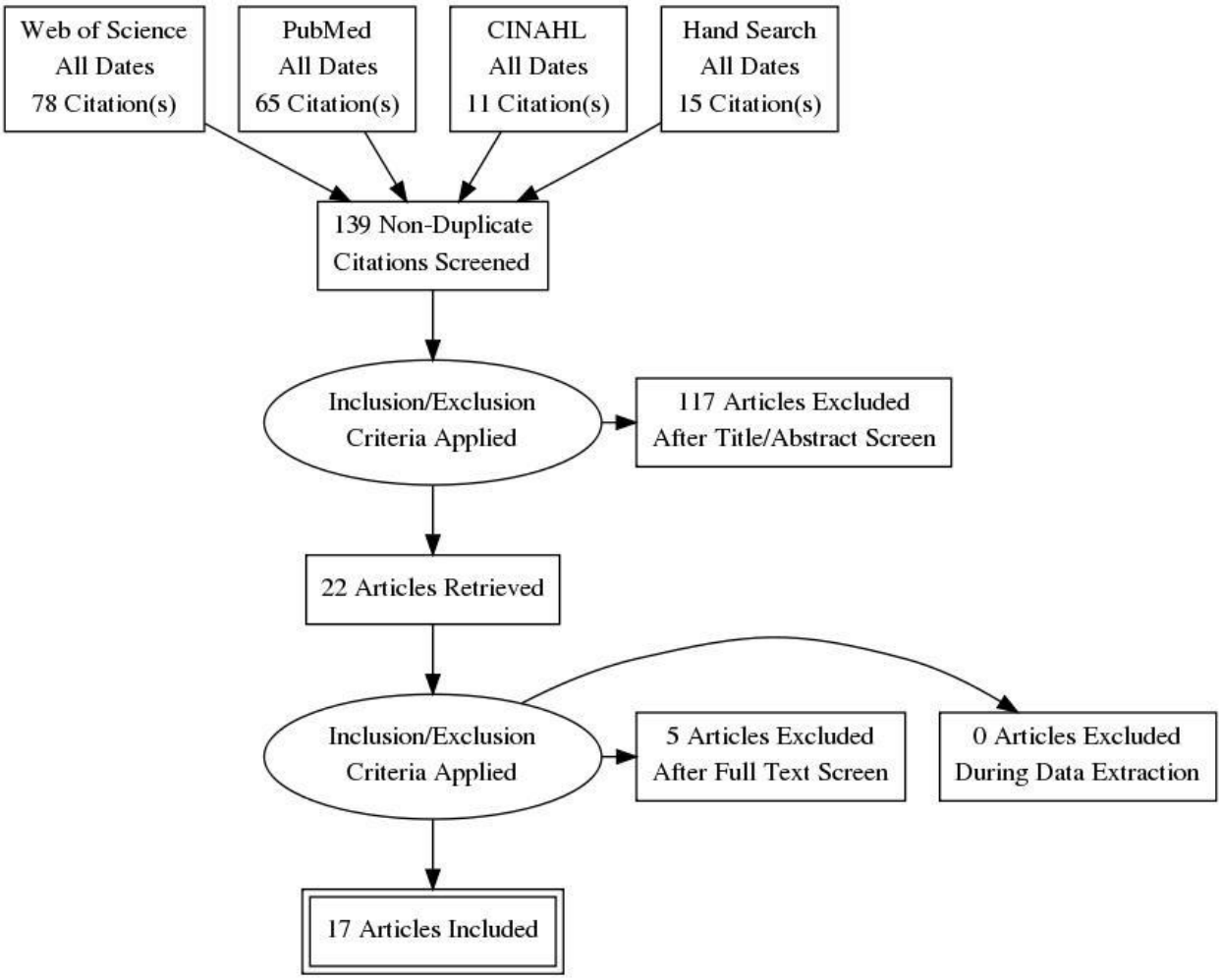
The inclusion and exclusion criteria are described in Table 6. The search strategy parallels that of the prior review.

**TABLE 6: Inclusion/exclusion criteria**

| **Inclusion criteria** | **Exclusion criteria** |
|---|---|
| • Studies that provide analysis or assessment of one or more comprehensive "value framework(s)" or an equivalent approach to integrate adverse event evaluation into an overall pharmacologic intervention to treat cancer | • Primary/seminal framework references were excluded |
| • Qualitative and quantitative studies | • Studies not using adverse event and/or safety data to assess cancer treatment interventions and decision making |
| • Descriptive and analytical studies | • Article is older than 2012 |
| • Peer-reviewed studies | • Studies not in English |
| | • Studies relating to frameworks for assessing risk to environmental carcinogens or exposures |
| | • Meeting reports and non–peer-reviewed studies |

The results of this literature search are summarized in the PRISMA diagram in Figure 6.

**FIGURE 6: PRISMA diagram demonstrating the part II literature evaluation and exclusion process**




This review captures recommendations and perspectives from a total of 17 peer-reviewed publications. The reviewed studies were almost evenly split between those including a narrative/qualitative comparison of different frameworks and those incorporating case study/quantitative comparisons across different value frameworks. As detailed in Table 7, 47% (n=8) included a narrative comparison across two or more different frameworks and 35% (n=6) conducted quantitative or semiquantitative case study comparisons across two or more frameworks. Of those conducting quantitative comparisons, three of six studies prospectively applied the frameworks using either novel data sets or by challenging a novel expert group to

reapply the data and rerun the framework (Cohen, Anderson, & Neumann, 2017; Del Paggio, 2017; Shah-Manek, Galanto, Nguyen, & Ignoffo, 2017). The remaining four publications addressed either a single framework or a single element of the frameworks (e.g., use of toxicity data) (Jim & McLeod, 2017; Miller et al., 2017; Waldeck, Botteman, White, & van Hout, 2017; Yu, 2016). With limited exceptions, all studies provided perspectives on opportunities to improve either the construct of the framework or some aspect of the input data. The most common identified areas for improvement, in relation to the nature and quality of input data used to populate these frameworks, fell into eight categories described in Table 8.

**TABLE 7: Study designs**

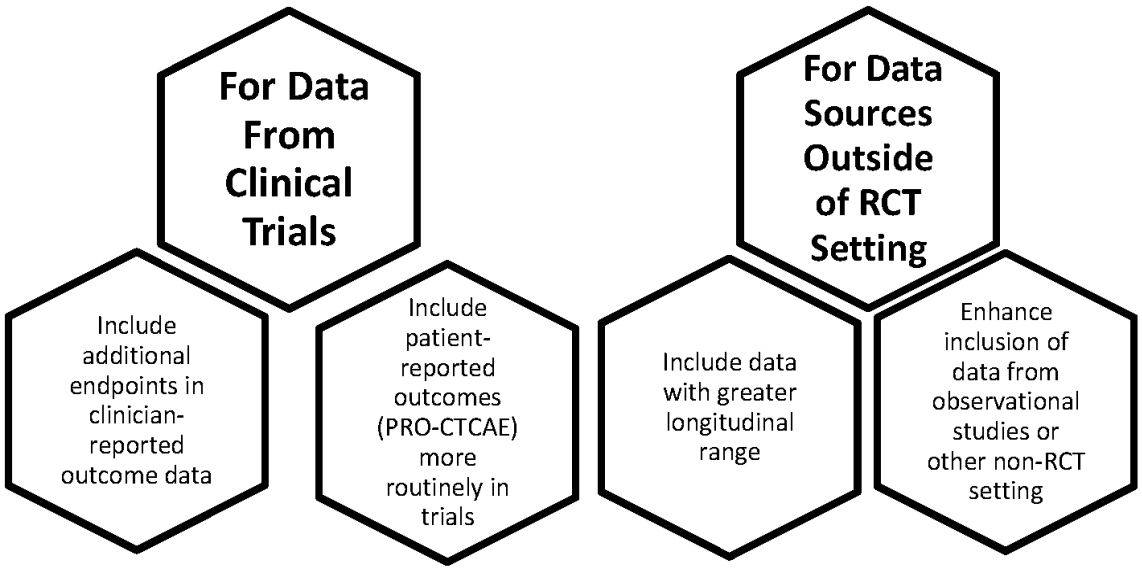
| Study design | Number of articles | References |
|---|---|---|
| Publications with narrative comparisons of different frameworks | 8 of 17 (47%) | Allen et al., 2017; Basch, 2016; Chandra et al., 2016; Evans, Cheung, & Chan, 2017; Mandelblatt, Ramsey, Lieu, & Phelps, 2017; Neugut et al., 2016; Schnipper & Bastian, 2016; Subramanian & Schorr, 2016 |
| Publications with case study-based quantitative comparisons across different frameworks | 6 of 17 (35%) | Bentley et al., 2017; Booth & Del Paggio, 2017; Cohen et al., 2017; Del Paggio, 2017; Shah-Manek et al., 2017; Westrich, Buelt, & Dubois, 2017 |
| Studies that reran analyses prospectively using published data to populate value frameworks | 3 of 6 (50%) | Cohen et al., 2017; Del Paggio, 2017; Shah-Manek et al., 2017 |
| Studies that addressed either a single framework or a single element of framework inputs | 4 of 17 (18%) | Jim & McLeod, 2017; Miller & Aplenc, 2017; Waldeck et al., 2017; Yu, 2016 |

**TABLE 8: Proposals for improvement of inputs to existing framework**

| Suggested improvement | Number of articles | References |
|---|---|---|
| Need improvements to clinical trial design to obtain more patient-relevant data | 5 of 17 | Allen et al., 2017; Bentley et al., 2017; Booth & Del Paggio, 2017; Del Paggio et al., 2017; Jim & McLeod, 2017 |
| Need cost data that reflect full cost of care/treatment (not just drug costs) | 5 of 17 | Chandra et al., 2016; Del Paggio, 2017; Mandelblatt et al., 2017; Miller & Aplenc, 2017; Waldeck et al., 2017 |
| Frameworks should incorporate patient-reported outcome data (via inclusion of patient-reported outcomes in clinical trials) | 4 of 17 | Basch, 2016; Bentley et al., 2017; Del Paggio, 2017; Jim & McLeod, 2017 |
| Frameworks should incorporate data from sources other than clinical trials (e.g., observational studies) | 3 | Allen et al., 2017; Basch, 2016; Chandra et al., 2016 |
| Frameworks should incorporate more robust and/or detailed safety and/or toxicity data | 6 | Basch, 2016; Chandra et al., 2016; Del Paggio, 2017; Jim & McLeod, 2017; Mandelblatt et al., 2017; Miller & Aplenc, 2017 |
| Frameworks should use integrated quality of life measures in lieu of safety data | 1 | Waldeck et al., 2017 |
| Frameworks should incorporate more longitudinal data | 2 | Allen et al., 2017; Basch, 2016 |
| Frameworks should engage patients in the data evaluation and input process | 3 | Allen et al., 2017; Basch, 2016; Booth & Del Paggio, 2017 |

As clarified in Table 8, no one recommendation or modification to improve the relevance of the frameworks for informing patient QoL was cited by all the publications. The need for more robust and/or detailed safety and toxicity data inclusion in frameworks was, however, the most common recommendation identified. This recommendation manifests in two general directions, as illustrated in Figure 7.

**FIGURE 7: Summary of recommendations from literature review for improving adverse event data relevance in value frameworks**




Additionally, several studies called for more overarching changes to clinical trial design with regard to patient inclusion criteria, duration, outcomes measures, and so forth (Allen et al., 2017; Bentley et al., 2017; Booth & Del Paggio, 2017; Del Paggio et al., 2017; Jim & McLeod, 2017). The details of such modifications were not thoroughly addressed in these publications and are the subject of much discussion elsewhere, but they could have significant impact on the type of AE data generated in the future (Bhatt & Mehta, 2016).

Although not the focus of this review, it is important to note that many of the publications also called for broad-based improvements in the design or use of the frameworks themselves. Specifically, enhanced clarity and transparency as to the intended audience for the framework outputs (Basch, 2016; Booth & Del Paggio, 2017; Chandra et al., 2016; Cohen et al., 2017; Waldeck et al., 2017) and improved guidance to enhance reproducibility were common recommendations (Bentley et al., 2017; Cohen et al., 2017; Evans et al., 2017; Mandelblatt et al., 2017; Shah-Manek et al., 2017; Westrich et al., 2017).

### *Synthesis of Results of Literature Evaluations*

Characterizing the risk:benefit profile of an antineoplastic therapy requires integration of a complex and heterogenous mix of pharmacologic, economic, actuarial, ethical, and sociologic factors. The complementary literature searches described here illustrate progress toward this integration. However, with respect to use and integration of AE information, several common themes and areas for improvement were identified. These areas of commonality are discussed in detail below and will be used to inform the subsequent research aims of this study.

#### *Challenges in Use of Clinician-Reported Adverse Event Data Derived From Randomized Controlled Trials*

In both the purely economic and integrated value framework approaches reviewed here, Phase II–III RCTs serve as the primary source of data on the incidence of treatment-related adverse effects. Almost 80% of the cost studies and/or value framework approaches currently rely heavily or exclusively on RCT data to inform toxicity/safety. RCTs are accepted, well-controlled studies with defined inclusion criteria and dosing and monitoring strategies. However, many of the studies reviewed here noted the limitations of RCTs for purposes of providing pragmatic patient decision support (i.e., high internal validity but low external validity). These limitations include the following:

- Populations engaged in RCTs tend to be "healthier" and with fewer comorbidities than the average patient population on the therapy (Martin et al., 2004). The frequency and severity of AEs in the clinical trial population may be under-representative of AE incidence and severity in the broader patient population and may thus lead to an underestimation of overall cost burden (Mitchell et al., 2014).

- The type of AEs recorded in Phase II/III trials specifically have been reported to skew toward a focus on only high-grade (grade 3 or 4) toxicities, pool toxicities of varying severity, include both quantitative and qualitative evaluations, and/or misgrade toxicities (Peron, Maillet, Gan, Chen, & You, 2013; Zhang et al., 2016b). Thus, it is possible that a significant pool of AE data could have been systematically excluded from these evaluations. Even when lower-grade toxicities are reported in RCTs, this review demonstrates an almost exclusive (~80%) use of the high-grade AE data for purposes of cost modeling or in value frameworks. The ASCO framework was recently revised to allow for incorporation of grade 1 and 2 AEs if they occur at sufficient frequency (Lowell E Schnipper et al., 2016). Given the tendency to under-report low-grade AEs in trials and published concerns about "unclear reporting of lower-grade toxicities," the potential for these endpoints to usefully inform patient/clinician choice via integrative tools is limited at present (Miller et al., 2016; Shah-Manek et al., 2017; Zhang et al., 2016a).
- The timeframe of study in an RCT provides a limited window (months to ~4 years) for capture of treatment-related effects. Some AEs do not manifest for many years after the closure of therapy and/or persist for many years after therapy has been completed. As such, RCTs may provide an incomplete picture of impact.
- The evolving nature of the CTCAE ontology used to record and grade creates a "moving target." The number of terms has expanded by a factor of 4 in the last 20 years. Thus, the version of CTCAE (or other ontology) can have a significant impact on the nature, naming, and overall reported incidence of AEs used in cost evaluation studies. Several clinical specialty areas that address common antineoplastic treatment-

related AEs (e.g., rheumatology) have developed their own AE ontologies and grades to reflect the more nuanced perspective of a specialist (Calabrese, Kirchner, Kontzias, Velcheti, & Calabrese, 2017). Future AE incidence burden evaluations would benefit from a thorough characterization of the ontological and inclusion/exclusion framework that guided the capture of their core input data and its potential impact on outcomes.

- RCTs are designed for evaluation by regulatory scientists for purposes of drug approval decision making. These studies have not been designed to generate information to be used by clinicians or patients with regard to individual therapeutic or supportive care pathways.

*Alternatives to the Use of Clinician-Reported Adverse Event Data Derived From Randomized Controlled Trials*

Although of many of the studies reviewed here identified one or more shortcomings of RCT-derived AE data, only three (17%) of the reviewed publications on value frameworks proposed the future incorporation of data from sources outside of an RCT setting (Allen et al., 2017; Basch, 2016; Chandra et al., 2016). Similarly, only 18% of the cost models used data sources outside of RCTs for AEs (Burke et al., 2011; Chu et al., 2009; Craver et al., 2011; Rajan et al., 2013; Tina Shih et al., 2007). This trend points to a simple fact: while it is relatively easy to identify weaknesses in the RCT as a data source for informing patient value-choices, the identification of viable alternatives or complements is quite challenging.

As described in Figure 7, recommended alternatives fell into two general and not mutually exclusive categories: 1) increased use of PRO measures and 2) increased use of observational/surveillance/EHR data sets.

### *Patient-Reported Outcomes and Quality of Life Metrics*

As patients and clinicians seek both enhanced progression-free survival as well as positive QoL, the inclusion of PRO data and/or QoL metrics into the valuation (economic or otherwise) of antineoplastic therapy regimes has gained prominence in recent years. The sources of data on QoL in the studies in this review included Markov model-based utility factors derived from EuroQol 5-D surveys, direct patient surveys that collected data on quality metrics, and clinician judgement on impact of patient QoL. The ICER and ESMO frameworks include QoL through incorporation of a QALY metric. ASCO uses palliation of symptoms and treatment-free intervals as a proxy for QoL measures. The quality of these input data are uncertain, as some of the QoL adjustment factors used in these economic evaluations were derived from assessments conducted as many as 20 years ago and some included undocumented "value judgements" based on clinician experience (Delea et al., 2015; Havrilesky et al., 2009; NCCN, 2017b; Stopeck et al., 2012). Additionally, the way in which these data were integrated into the value assessments described in this review varied from probabilistic modeling approaches to awarding of ad hoc "bonus points." It is beyond the scope of this review to assess the relative strengths and weaknesses of each of these approaches. However, this review does reveal that the practice of including PRO or QoL metrics into integrated value assessments relating AEs and treatment choice is neither systematic nor standardized.

Undoubtedly, this is a challenging space. The tools and perspectives on the extent to which QoL or PROs can or should be leveraged routinely in trials or clinical practice are evolving rapidly (NCI, n.d.). The disparity between patient and clinical perspectives on AE burden is well established (Basch et al., 2015). Thus, the future use of tools to assess AEs from the perspective of the patient may provide novel insights into the overall physical, logistical, and financial

burden of antineoplastic therapy. This is likely to hold true in both the clinical trial and the standard clinical setting.

*Increased Use of Observational/Surveillance/Electronic Health Record Data Sets*

Collectively, the publications reviewed here offered very limited recommendations for or examples of incorporating AE data from sources other than RCTs. The few prospective or patient database–driven economic evaluation studies in this review appear to provide a clearer picture of the frequency and nature of AEs, although the less controlled setting can make an estimation of treatment-attributable costs more challenging (Burke et al., 2011; Chu et al., 2009; Craver et al., 2011; Rajan et al., 2013; Tina Shih et al., 2007). None of the value frameworks utilize such data at this time. This phenomenon reflects the "gold standard" status of RCTs for driving drug safety and efficacy decisions and lack of standards for use of other data sources. Increasingly, the potential for observational studies and large-scale healthcare databases to provide reliable data on a broad range of patient adherence practices, outcomes measures, and polypharmacy/comorbidity situations has been recognized (Balicer & Afek, 2017; Fiore et al., 2017; Mahajan, 2015). Future developments in this arena will require a thoughtful confrontation of the tension between uncontrolled data derived directly from patient care settings and the value of nuanced and realistic representation of patient experiences.

*The Costs*

A detailed discussion of cost estimation models is not the focus of this review. However, the link between value decisions, cost calculations, and AE-related impacts is an important component of this discussion. Some economic evaluation studies reviewed here attempted to include all treatment-related costs that the author could identify (drug cost, hospital cost, doctor visits, monitoring and testing, over-the-counter drugs, administration fees, lost work cost,

caregiver costs, future employment potential costs, etc.; e.g., Sorensen et al., 2012), whereas others addressed only the primary cost of treating the AE in a hospital setting (Burke et al., 2011). Exact cost metrics used within the current value framework structures were equally variable but are largely restricted to cost of the drug and/or primary treatment visits. Many of the analyses reviewed here specifically recommended that future iterations of the model should incorporate the full cost of care including AEs (Chandra et al., 2016; Del Paggio, 2017; Mandelblatt et al., 2017; Miller et al., 2017; Waldeck et al., 2017) This recommendation, while sound on its face, begs the questions of what constitutes the burden of antineoplastic therapy-related AEs, who carries these burdens, and thus how broadly should costs be captured? It also speaks to the importance of transparent discussion regarding the stakeholders to whom the value assessment is intended to apply.

*The Patients*

At the core of all of the value discussions and treatment choices described here are the patients. Somewhat surprisingly, nearly a third of the economic valuation studies reviewed here failed to provide clear demographic information on either the patient population that constituted their input data or the patient population to whom their model/valuation was intended to characterize or both (Bristow et al., 2007; Burudpakdee et al., 2012; Dalton et al., 2012; Delea et al., 2015; Kowal-Podmore et al., 2008; Stopeck et al., 2012; Usmani et al., 2016; Wong et al., 2013; Xie et al., 2012). In fact, none of the primary value frameworks described in Table 1 or any of the publications about these frameworks (as reviewed here) included a discussion of patient demographics *other* than a focus on patients with a specific disease. Even for those studies where the patient population was clearly defined, there were sometimes disconnects between the target population and the patient group that served as primary data on AEs, QoL

metrics, and/or cost estimations. For example, ~40% of the studies reviewed here utilized cost data from Medicare, although only ~20% characterized their study population as older than age 60. Such disconnects may be inevitable given the limited availability of data in this space. However, the relevance of frameworks for information on patient choice and treatment decisions could be enhanced with greater clarity around these limitations and their potential impacts on the way in which AE-related impacts are synthesized and subsequently interpreted.

## Summary of Opportunities to Improve the Use of Adverse Events to Inform Care Decisions[2]

Patients, payers, clinicians, regulators, and drug developers all have a vested interest in the development of approaches that allow for informed choice around the use of antineoplastic therapies that enhance progression-free survival with minimal impact on overall QoL. Recent efforts to characterize the impact of AEs associated with antineoplastic therapy reveal that many therapeutic classes are associated with significant financial, logistical, and health burdens for the patients who receive these treatments. However, the review above illustrates that our current means to assess and synthesize the scale and impact of this burden on patients and the system at large are insufficient. Much of the input data used in current efforts to describe AE incidence and severity may be of limited relevance for a diverse and comorbid patient population. Personal experience and preferences are challenging topics to integrate into a standardized decision framework, but this review clarifies that incorporation of PROs, QoL, and patient preference is a significant deficit. Similarly, presentation of the overall impact of AE on patient experience can be challenged by uncertainty around the extent (chronological as well as functional) of the costs

[2]*Note:* The literature reviews conducted for Chapters 1−3 served as the basis for a publication in August 2018 in *Cardio-Oncology* (Pettit & Kirch, 2018).

and attributes that should be incorporated into these assessments. In summary, the collective literature review and analyses conducted here support the following:

- Future initiatives seeking to provide integrated information to patients and clinicians relating to therapeutic choice in cancer settings would benefit from incorporation of AE data of greater relevance to the "real-world" patient experience (i.e., "more patient-relevant information");
- There is a need for enhanced transparency around the strengths and limitations (i.e., fitness for purpose) of different AE data types to be used to inform cancer care and therapy development/support decisions; and
- There is an overall lack of clarity around how to best use AE data to inform cancer patient care and cancer therapy safety assessment.

# CHAPTER 3: RESEARCH AIM AND METHODS

As evidenced by the literature evaluation conducted in Chapters 1 and 2, there are significant challenges associated with contemporary processes and incentives for AE and QoL data *generation*, *dissemination*, and *use* for cancer care decision making. However, "cancer care" is an incredibly broad and heterogenous arena. We know that the specific timescales, networks, and incentives for developing or using therapy-related AE or QoL information can vary significantly depending on a patient's overall prognosis (e.g., metastatic versus adjuvant) and anticipated duration of therapy (Allen et al., 2017). Patient preferences, clinician recommendations, and regulatory requirements for information around trade-offs between length of life and QoL also vary in different cancer treatment settings (Meropol et al., 2008). An evaluation of systemic opportunities for improved AE data utilization must both acknowledge critical contextual distinctions and recognize that some elements of systemic change could benefit a broad range of settings.

This study recognizes the importance of context by conducting a focused exploration of the roles, expectations, and information flows across stakeholders involved in the *adjuvant therapy setting*. Adjuvant therapies are defined by the NCI as "treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy" and is used in managing many of the most common cancer types, including breast, lung, and prostate cancer (NCI, 2017a). Adjuvants may be administered over extended time periods, often when the patient is putatively "cancer free" and there is a significant likelihood of extended patient survival. In this setting, mediating the impact of potential acute or delayed adjuvant treatment-

related AEs relative to an uncertain potential for tumor recurrence can be extremely challenging. Information about adjuvant-related AE frequency, scope, control, and support options can be reasonably expected to have a real impact on outcomes such as the decision to initiate or maintain adjuvant treatment, therapeutic adherence, patient health, QoL, and/or ability to fulfill tasks during daily living (Meropol et al., 2008). Because of these important impacts, a study of the incentives and barriers to generating and using AE information linked to adjuvant therapy was selected as the focus for this research. This study does not specifically explore differences between different cancer types treated with adjuvant therapy, or different therapeutic classes of adjuvants. For purposes of this exploratory study, perspectives on the integration of evidence around treatment benefits and risks that are common across the adjuvant setting at large are informative. As discussed in Chapter 5 ("Cross-Stakeholder Results and Discussion"), some observations from this study of the adjuvant arena also have relevance in the acute treatment setting and the long-term survivorship arena.

Specifically, this study explored the following aims:

- **Primary aim:** Utilize qualitative interviews to understand and integrate key stakeholder perspectives on current and future roles as developers and/or users of adjuvant therapy-related AE information for cancer care decision making.
    - ***Sub-aim 1:*** Understand the perceived roles that therapy developers, regulators, clinicians (oncologists and non-oncologists), patient advocates, and payers ("the stakeholders") play in adjuvant therapy-related data generation, dissemination, and use, and how these stakeholders are affected by incentives and available resources.
    - ***Sub-aim 2:*** Learn what the stakeholders feel is most important for them to be

better supported in their role as generators, disseminators, or users of adjuvant therapy-related AE information and why they have identified these needs.

- ***Sub-aim 3:*** Evaluate systemwide alignment across the stakeholders with respect to roles, incentives, and barriers that impact their generation or use of AE information to inform cancer care via adjuvant therapy.
- ***Sub-aim 4:*** Identify systemic gaps that could be leveraged into opportunities for improving the use of AE information to improve cancer care for patients on adjuvant therapy.

## Methods

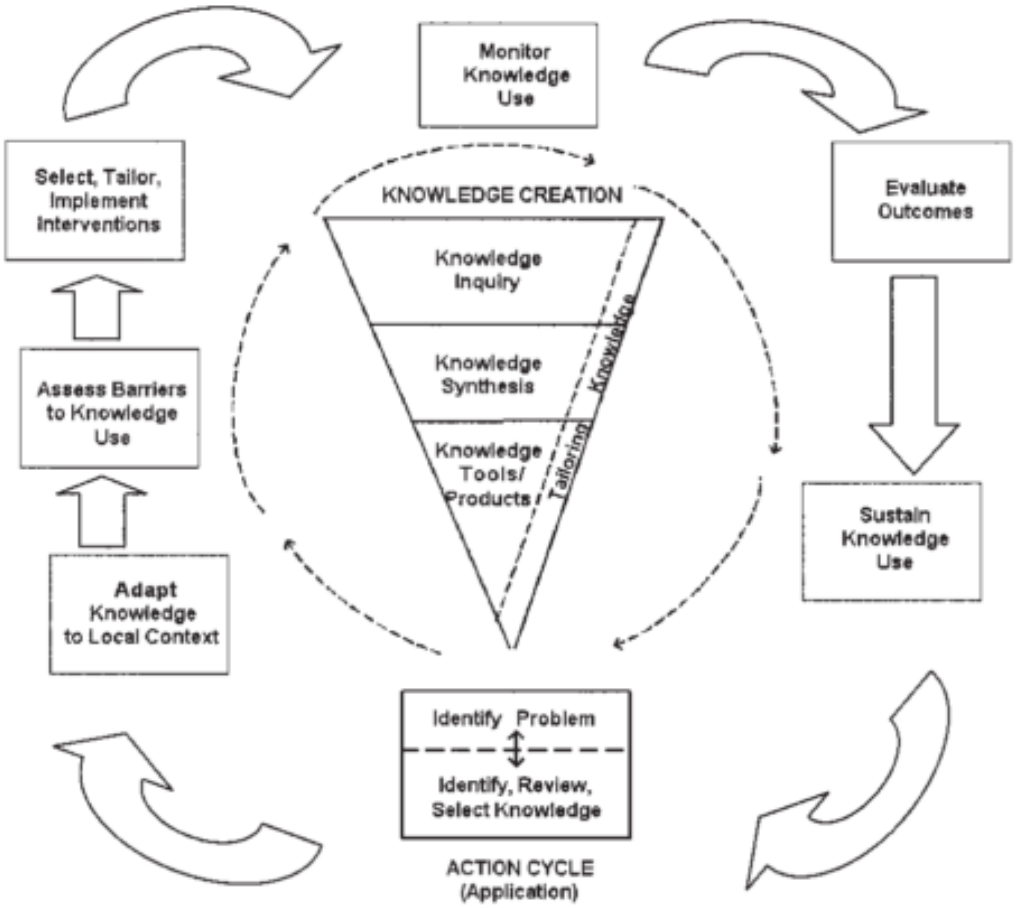
Semistructured key informant interviews (KIIs) were identified as the preferred means to elicit qualitative information from critical stakeholders that serve as the basis for this study. KIIs are an established approach for eliciting nuanced and in-depth stakeholder input from established experts. Such interviews are recognized means to elicit perspectives relative to programmatic, social, and cultural issues as well as insights around stakeholder motivations and behaviors (Creswell, 2014; University of Washington, n.d.; USAID, 1996). The validity of the KII approach for this specific study is further supported by prior research in which KIIs were used as a key data source for similar healthcare-focused studies. For example, KIIs have been used to elucidate challenges and opportunities in collaboration across different clinical communities seeking to collectively improve patient care and to characterize the potential to adapt clinical care guidelines to facilitate shared decision making across clinicians and patients (Barker, Bosco, & Oandasan, 2005; Van Der Weijden et al., 2013).

The structure and focus of the KIIs for this study was guided by an implementation science–derived conceptual model. Implementation science frameworks have been used previously to characterize inter-relationships between stakeholders and health/program outcomes in complex healthcare ecosystems, including cancer care (Burke et al., 2015; Chambers, Feero, & Khoury, 2016; Hassmiller Lich, Urban, Frerichs, & Dave, 2017; Mitchell & Chambers, 2017; Price, 2016). For this study, an existing implementation framework was modified to generate a novel conceptual model with enhanced relevance to the adjuvant therapy-related AE setting (see below).

**Development of the Conceptual Model Guiding the Interview Design**

Process models are employed in implementation science studies to provide "practical guidance in the planning and execution of implementation endeavors and/or implementation strategies" (Nilsen, 2015). The process model known as the Knowledge to Action Framework (Figure 8) describes an idealized process for the movement of information to action across stakeholders (Graham et al., 2006). This model was developed based on Graham's review of dozens of process of change models and has remained a highly cited framework since its publication (Burke et al., 2015). Although the Knowledge to Action Framework does not specify cancer care or oncologic research, the knowledge generation and usage pathways it describes are directly relevant to the systems and issues identified as central in the literature review for this study (see Chapters 1 and 2). The Knowledge to Action Framework was thus selected as a seminal resource from which to build a more tailored conceptual model for this investigation.

**FIGURE 8: Graham's Knowledge to Action Framework[3]**




The Graham framework provides a sound foundation against which to anchor the following general themes that are central to the primary and supporting aims of this study:

- Which party (or parties) is responsible for problem formulation and thus directing related knowledge creation? How is this initiated, sustained, and/or realigned?
- Which party (or parties) is responsible for adapting knowledge to the local context and evaluating barriers to access or use? How is this initiated, sustained, and/or realigned?

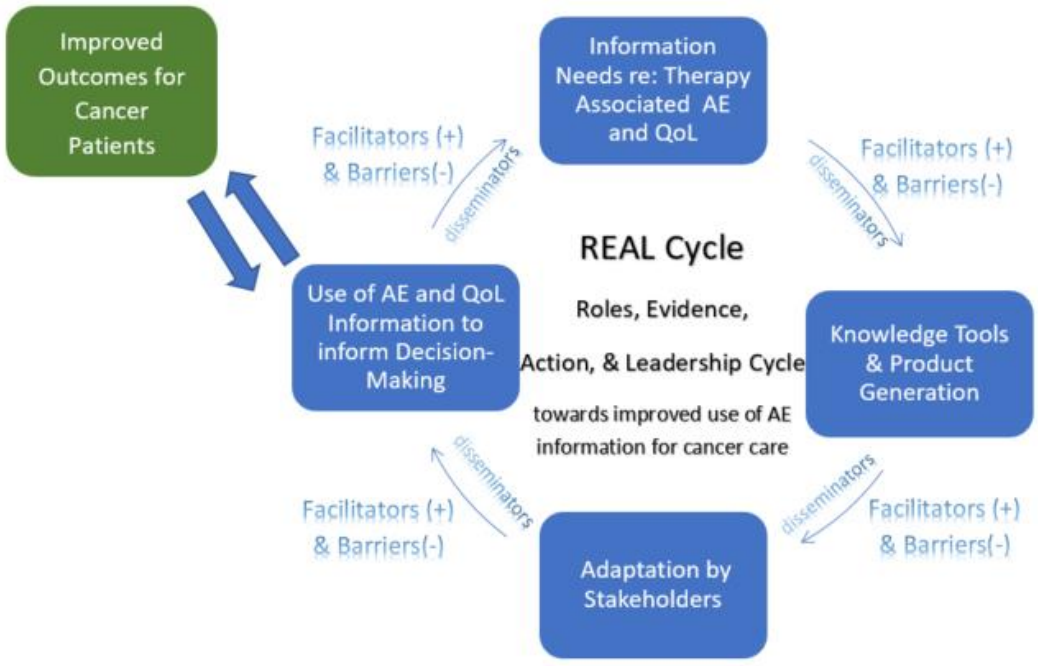
[3]*Source:* Graham et al. (2006).

- Which party (or parties) is responsible for evaluating whether the information is achieving its desired outcomes/reaching its intended user base? How is this initiated, sustained, and/or realigned?

Based on the literature review and the investigator's professional knowledge, the Graham model was modified to enhance its direct relevance to the therapy-related AE and QoL knowledge generation and usage setting (Figure 9). This new conceptual model, named the "**R**oles, **E**vidence, **A**ction, and **L**eadership Cycle" (**REAL** Cycle), traces the movement of AE and QoL information needs to information generation to information adaptation to information use for cancer care decision making and back to information needs. The REAL Cycle provides a frame for integrating diverse stakeholders' self-perceived roles (and their perceptions of the role of others) with respect to AE-related data for cancer treatment and care decision making. The flow of information in this model is shown to be modulated by facilitating and inhibiting factors as well as the presence of information disseminators. This study utilized the REAL Cycle to build a line of inquiry and data collection in support of the study aims.

The REAL model anticipates that when AE and QoL information is used to meaningfully inform cancer patient care in the adjuvant setting, it can lead to improved outcomes for cancer patients (green box in Figure 9). Per Chapters 1 and 2, these outcomes could take the form of enhanced adherence to and efficacy of therapy, enhanced awareness or use of supportive care options, reduced therapy-related AEs, greater patient understanding about the impacts of their therapy, and so forth. However, a direct assessment of the link between AE and QoL information and specific patient outcomes was beyond the scope of this study.

**FIGURE 9: REAL Cycle: Roles, Evidence, Action, and Leadership toward improved use of adverse events information in cancer care[4]**




## Translating the Conceptual Model Into Qualitative Research Plans

The translation of the REAL Cycle into a qualitative research plan per the primary aim comprised two elements: a) definition of critical stakeholder groups and b) design of qualitative KIIs. A discussion of the methods for each approach follows below.

### *Definition of Key Stakeholders for Study*

This study sought to build understanding of systems-level interactions within and across stakeholders who are engaged in generating, disseminating, using, and/or requesting adjuvant treatment-related AE information of relevance to cancer patient care. The stakeholder categories were defined per evaluation of the literature (Chapters 1 and 2) and professional experience. The

[4]This is an original conceptual model generated by the investigator.

specific stakeholder categories and number of stakeholders interviewed for this study were as follows:

- *Patient advocacy.* Representatives interviewed from this category are organizational leaders of patient advocacy organizations. The representatives interviewed for this study are employed by organizations that are focused on cancer exclusively or have dedicated patient-focused programs in the cancer arena. All of the patient advocates who were interviewed had some direct involvement with patients receiving adjuvant therapy. Although individual patient interviews could also provide important perspectives, they were excluded as a primary data source for this study, as the research was focused on the interactions between structured or semistructured elements of the cancer care information network. However, all patient advocates interviewed for this study were also cancer survivors themselves and thus provided both personal and organizational perspectives. Four of the five individuals interviewed are the senior operating officer/executive director/founder of the nonprofit patient advocacy group that they represent. A total of four interviews in this category were completed and evaluated, at which point saturation of themes was reached.
- *Clinical care.* Representatives interviewed from this category are MD-level clinicians working in major academic and private medical centers in the United States. All interviewees are involved in the care of cancer patients undergoing active cancer therapy or as part of post-therapy supportive care. Specifically, this study included oncologists with experience in adjuvant therapy delivery as well as rheumatologists and cardiologists involved in monitoring and treating adjuvant therapy-related AEs. A

total of five interviews in this category were completed and evaluated, at which point saturation of themes was reached.

- *Regulatory science.* Representatives interviewed from this category are U.S. or European[5] government-employed regulatory scientists and regulatory policy makers who hold a PhD (n=3) or MD (n=2). All regulators interviewed for this study are directly or indirectly involved in the evaluation of nonclinical and/or clinical drug safety information associated with the regulatory approval and ongoing safety monitoring processes for adjuvant and other cancer therapies. All of the regulators interviewed are also actively engaged in the development of new and revised regulatory standards and practices for cancer therapy evaluation at the national and international level. A total of five interviews in this category were completed and evaluated, at which point saturation of themes was reached.[6]
- *Cancer therapy research and development.* Representatives interviewed from this category are business-sector pharmaceutical scientists who are involved with the development of nonclinical and/or clinical data and methods associated with the safety and efficacy assessment of new or existing cancer therapies. Each of the five interviewees is employed by a different pharmaceutical company and all of the companies operate as multinationals. All of the individuals are senior leaders in their organizations (80% with more than 25 years of experience in the field) and are

[5]Although the recommendations from this research will be primarily U.S. based, both U.S. and E.U. regulators work under a set of guidelines for pharmaceutical safety assessment through the International Council on Harmonization. As such, perspectives from both U.S. and European regulators were engaged to provide a greater breadth of perspective on current approaches and opportunities.

[6]Saturation was assessed by the investigator as the point at which no new major themes, insights, or properties were revealed during the interview process (Creswell, 2014).

responsible for scientific, managerial, and strategic oversight over their domain of expertise (e.g., nonclinical safety, translational safety, clinical trials, PROs, etc.). A total of five interviews in this category were completed and evaluated, at which point saturation of themes was reached.

- *Healthcare plans.* Representatives interviewed from this category are employed by a U.S. public payer (CMS) or by a private-sector healthcare insurer. All representatives were personally familiar with treatment and supportive care coverage policies and programs for cancer patients receiving adjuvant therapy. Four of the interviewees' job roles included senior leadership and program design responsibilities for their employer and one was responsible primarily for program evaluation of novel payment and coverage models for his employer. A total of five interviews in this category were completed and evaluated, at which point saturation of themes was reached (three private payers and two government payers, although one respondent had worked in both sectors and some insights in both aspects).

### *Stakeholder Recruitment*

Specific interviewees were selected based on their anticipated fulfillment of five criteria for key informant interviewees as delineated by Tremblay (1957): role, knowledge, willingness, communicability, and impartiality. Individuals in these categories were deemed to be either generators, disseminators, and/or utilizers of therapy-related AE information for cancer treatment decisions. Sampling blended an informant sample emphasis (those selected for their specific expertise) with a maximum variation sample emphasis (those selected to represent diverse experience) (Marshall, 1996). As breadth was a necessary component of the sampling design, the investigator used a purposeful sampling technique for selection of interviewees.

An informational e-mail was used to recruit potential interviewees and explain the study rationale, time expectations, and voluntary nature of their participation and to request feedback on participation interest. A one-page project description was also provided (Appendix E). Sample recruitment scripts for e-mail and phone outreach are included as Appendix A. All interviews were conducted via telephone or web-based audio conference.

Once an interviewee agreed to participate, a formal communication was sent via e-mail to confirm the objectives for the interview, to provide the institutional review board (IRB) approval number, data recording policy, and phone number/web link for connecting to the interview session, and to thank the individual in advance for his or her voluntary involvement. Consent to interview and consent to record were both confirmed via verbal agreement at the start of the interview and as part of the digitally recorded and subsequently transcribed interview (see Appendix B). Details on data confidentiality and storage follow below.

Telephone interviews (n=24) were conducted between August 1, 2018 and October 31, 2018.

**Design and Focus of Qualitative Key Informant Interview Questions**

The REAL Cycle was used to develop question themes and subthemes for the KIIs. The interview guide is included here as Appendix C and reflects the final guide after initial modification following conduct of two cognitive interviews prior to the formal launch of the study. A mapping of each KII question to the overall study aims is included in Table 9 below.

**TABLE 9: Relationship between key informant interview questions and study aims**

*Note:* See the Key Informant Interview Guide (Appendix C) for detailed probes that were also be used by the Interviewer.

| KII question | Information elicited via prompts during discussion | Relationship between KII response and study aims |
|---|---|---|
| **1. INTRODUCTORY QUESTION:** "Please tell me about your organization and its mission with regard to cancer therapy and cancer care. What is your role in this organization?" | • General contextual information | Provides context as to the roles and responsibilities of the respondents and informs the alignment of and relationship between stakeholders ***(Sub-aim 1)*** |
| **2. ROLE:** "Please describe your role in balancing the beneficial and negative effects associated with the provision of adjuvant therapy to cancer patients." | • Scope of a stakeholder's role as characterized from their own perspective<br>• Input on facilitators and barriers to fulfilling stakeholder's role | Provides insight to key facilitators and barriers to the roles identified by each stakeholder ***(Sub-aim 2)*** |
| **3. RESOURCES:**<br>**3A.** "In the context of the roles you have described, can you tell me about the resources you rely upon to support these roles (e.g., data, experts, studies, funding, medical records, invoices, etc.)?"<br>**3B.** "Do these resources meet your needs? Why or why not?" | • The nature of specific information and resource flows within the system<br>• Perceptions of the quality, relevance, and ease of access of AE information and resources cited by the stakeholders<br>• Perspective on what it would take for stakeholders to be better supported in their roles | Elicits information on specific resources, accessibility and implementation, and systemic strengths and weaknesses ***(Sub-aims 2, 3, and 4)*** |

| | | |
|---|---|---|
| **4. FUTURE NEEDS: SELF**<br>"Are there other types or sources of information or resources that you wish your organization had to help with respect to helping patients balance the beneficial and negative effects of adjuvant therapy?" | • Barriers to current roles that are revealed upon suggestion of why something new/different needed<br>• Potential future directions of value to stakeholder respondent<br>• Barriers or facilitators to procuring the additional information or resourcing identified by the respondents<br>• Perspectives on how new/different information would change or improve the stakeholder's ability to fulfill their role (or support others in theirs) | Elicits stakeholder recommendations on gaps in the system and opportunities for improved support in their role<br>***(Sub-aims 2 and 4)*** |
| **5. FUTURE NEEDS: SYSTEM** "Moving forward, is there anything you would you like to see change (either in your own organization or others) to improve our *overall approach* to balancing treatment-related risks and benefits related to adjuvant therapy?" | • Stakeholder perspectives on how they might better relate to or inform other stakeholders in the future<br>• Perspectives on what other stakeholders could or should do to improve this system Facilitators and barriers associated with the change they recommend | Elicits stakeholder recommendations on gaps in the system and opportunities for improved systemic functionality<br>***(Sub-aims 3 and 4)*** |
| **6. OPEN:** "Are there additional comments or thoughts you'd like to offer?" | • Opportunity for stakeholder to address concerns or issues not raised above | ***Variable*** |

### *Ethics*

Review of the study design was finalized by the University of North Carolina (UNC) IRB (IRB-17-2590) on February 20, 2018. At that time, it was determined to not be human subjects research and was thus exempt from IRB oversight requirements. Per personal communication from legal counsel at her employing institution, the investigator (Syril Pettit) did not require an IRB from her employer, as they do not issue IRBs. The research conducted was not a condition

of the investigator's professional employment and was exclusively part of her independent professional development as a student at the UNC Gillings School of Global Public Health. No data or human resources from her primary employer were used in the dissertation research. None of the individuals or organizations engaged via this research are or were employed by the investigator's employer or received any compensation for services from that employer, nor did they receive any compensation for their participation in this research.

### *Data Collection and Management*

With permission of the interviewee (obtained prior to the start of each interview), KIIs were recorded as digital audio files using GoToMeeting™ software and saved with an encoded file name on a password-protected network drive location. A digital file linking the interviewee name to the encoded file name was kept in a password-protected location accessible only to the principal investigator. The original audio files will be deleted following approval of this dissertation and completion of an associated publication.

All audio files were transcribed (again with a coded file name on a password-protected network drive location) from their audio format into a text document transcript format. Transcriptions were contracted to Rev.com, a professional fee-for-service transcription service. The investigator reviewed all text transcriptions for accuracy by comparison against the primary audio recording.

### *Data Analysis and Coding*

#### *Coding Software*

Text transcripts of all interviews were evaluated via the encrypted, password-protected, web-based qualitative evaluation tool, Dedoose version 8.0.42 (www.dedoose.com).

*Coding Support*

Dual coding on all interviews, and finalization of the code book, was achieved in collaboration with Mr. Randall Teal, Qualitative Research Specialist, UNC Communication for Health Applications and Interventions Core Center. Further details on the code book development and secondary coding and reconciliation processes are included in Table 10. In summary, after initial coding and reconciliation, Mr. Teal and the investigator reached 100% consensus on coding of all sections of all interviews conducted for this study. A copy of the final code book and coding guide is included as Appendix D.

**TABLE 10: Code book development and secondary coding process**

| Action | Participant(s) | Process/outcome |
|---|---|---|
| REAL framework used to deductively define key themes and codes | Principal investigator | Initial draft code book |
| Sample coding of two KIIs with initial draft code book | Principal investigator | Code book modified with the addition of novel inductive codes, to simplify and clarify other codes, to link codes to specific interview questions, and to provide descriptive text to guide coders in application of the codes. Production of revised draft code book |
| Coding of two KIIs with revised draft code book | Principal investigator and secondary coder | Meeting held to compare coding assignments between the primary and secondary coders. Minor modifications to code book to clarify application of different codes and to eliminate codes deemed unnecessary. Code book and key finalized (Appendix D). For those limited areas of disparity in code assignment, coders discussed variances and agreed on a final consensus code assignment for all segments of text |
| Coding of 11 KIIs with final code book | Principal investigator and secondary coder | Meeting held to compare coding assignments between the primary and secondary coders. For those limited areas of disparity in code assignment, coders discussed variances and agreed on a final consensus code assignment for all segments of text |
| Coding of final 11 KIIs with final code book | Principal investigator and secondary coder | Meeting held to compare coding assignments between primary and secondary coder. For those limited areas of disparity in code assignment, coders discussed variances and agreed on a final consensus code assignment for all segments of text |

## Limitations/Boundaries of Research

The major delimitations of this proposed study are as follows:

- *Scope.* This study's focus on adjuvant therapy was deemed appropriate in order to adequately delimit stakeholder feedback and provide a basis for cross-stakeholder

comparison. The focus on adjuvants was also deemed appropriate because of the unique risk:benefit questions that relate to that setting. However, future research efforts might add to this study by either narrowing the focus to a particular adjuvant class or patient subpopulation or by expanding to additional or alternative treatment settings.

- *Stakeholders.* The stakeholder base proposed for evaluation in this study is limited to stakeholders from the regulatory, clinical care, patient advocacy, drug research and development, and healthcare payer perspectives, as they are considered of primary relevance to the questions to be addressed relating to scientific information on AE type and frequency. However, future studies might incorporate perspectives from additional stakeholders that have been intentionally excluded from this study, such as legislators, individual patients, academic researchers, grantors, and so forth.
- *Depth versus breadth.* The study is delimited to a sampling of informants who can provide input from diverse sectors (e.g., patient advocacy, regulatory)—with recognition that they are unable to speak on behalf of their sector as a whole and that their personal and professional experiences shape their replies. In each sector included in this study, there are potentially many ways to subdivide that sector and thus elicit further granularity and specificity of replies. Although general saturation of themes was reached with five individuals per informant category, it is possible that subsequent studies could further subdivide the stakeholder groups and explore intra-stakeholder variance more extensively.
- *Geography.* This study is focused on multiple stakeholder groups in the cancer care arena but is primarily delimited to the United States. Although many of the

recommendations and comments will be relevant and applicable across geographic lines, it is recognized that the regulatory approval, cultural norms and expectations, and healthcare payment/access systems vary from country to country.

- *Qualitative focus.* This study is restricted to qualitative approaches and perspectives. With additional time and resources, this study could be augmented with quantitative survey data and/or quantitative case analyses relating the impact of specific AE information to specific patient health outcomes or other decision endpoints.

**Approach to Information Synthesis**

A synthesis of the stakeholder feedback was conducted by the primary investigator with scientific advice and support from her dissertation committee members and Mr. Randall Teal. A synthesis of *stakeholder-specific* perspectives on roles, challenges, and future opportunities for the use of information around adjuvant therapy-related AE information to improve cancer care decision making (Sub-aims 1 and 2) is included here as Chapter 4. An evaluation of *cross-stakeholder alignment* in perspectives on current status and future needs (Sub-aims 3 and 4) is addressed in Chapter 5. A proposed "Plan for Change" that translates the findings from Chapters 3 and 4 into actionable next steps is included as Chapter 6.

# CHAPTER 4: INTRA-STAKEHOLDER RESULTS AND DISCUSSION OF TRENDS

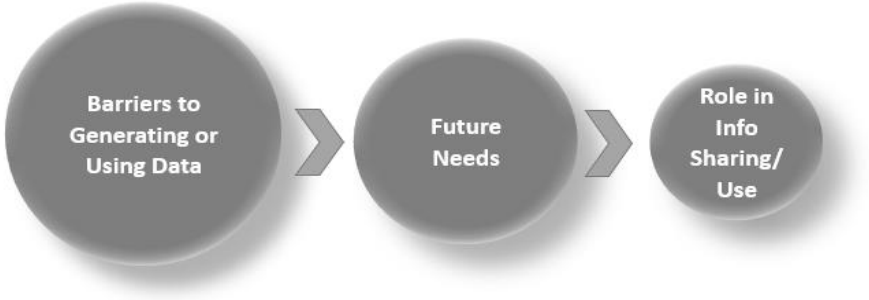
## Introduction

This chapter provides a synthesis and discussion of *intra-stakeholder group* perspectives on the use of adjuvant therapy-related AE information to improve cancer care patient care (Sub-aims 1 and 2). After dual coding of all interviews, the Dedoose qualitative analysis software was used to visualize major trends in code usage within and across stakeholders and to coalesce excerpts of text relevant to each of the codes as applied to the KIIs (see Chapter 3 for methodological details).

This chapter begins with a detailed synthesis of intra-stakeholder themes with respect to current roles, challenges, and future needs. A summary this feedback, along with a discussion of their perspectives on alignment and ownership of future efforts, is also included. The chapter concludes with a further exploration of differences in stakeholder roles and needs identified in this study as elucidated by trends in code application across stakeholders. Discussion of broad, inter-stakeholder themes stakeholder is reserved for Chapter 5.

Overall, the codes applied with the most significant frequency across all interviews were as follows (*scale is approximate*) (Figure 10):

**FIGURE 10: Visual Representation of Coding Frequency**




Those codes used with less frequency were as follows: "Participant Job and Personal Background," "Motivators to Generating or Using Data," "Roles in Data or Information Sharing," "Roles in Data or Information Generation," "Job Role Changes Over Time," "Specific Data Resources," and "Role in Adjuvant Therapy."[7] Because of the respondents' predominant focus on "roles," "barriers," and 'future needs," this chapter will provide a synthesis of responses for each stakeholder group in relation to these three general categories of feedback.

## Responses Summarized by Stakeholder Category

### *Drug Developers*

*Roles*

Although the specific job categories of the respondents in the drug development arena varied, all of the stakeholders interviewed in this category characterized their primary role as supporting the movement of safe and effective drugs into the marketplace so that those therapies can be available to patients. Specific roles included the development of data toward risk

[7]Although the majority of the interview content specifically addressed adjuvant therapy, the code "Roles in Adjuvant Therapy" was intentionally applied only for very specific comments about the participant's role in supporting adjuvant therapy *relative to other therapy types*. As such, the lack of frequency of the code application does not reflect a lack of overall focus on adjuvant therapy-related issues in the interviews.

(toxicity):benefit (efficacy) profiles for nonclinical drug development,[8] translational drug development,[9] clinical safety, and PRO evaluation. Respondents emphasized that a significant focus of their role is to develop data with the most robust possible translational relevance for predicting and optimizing likely outcomes (adverse and therapeutic) in the patient populations for whom the therapy is targeted.

> We are trying really hard with a lot of ambition to move towards chronic therapies or even curative therapies. So, having a side effect profile where we cure the cancer but get the individuals some other difficult to manage, potentially even life changing debilitation is not acceptable to us if we can avoid it.

This stakeholder group consistently characterized their role as data generators. When queried about the direct consumers of the information that they generate about a therapy's risk:benefit profile, the majority of those interviewed specified that their current job roles are heavily focused on generating information for one of two primary objectives:

- Generating data on a novel therapeutic's safety or efficacy to colleagues within their company to facilitate internal decision making; and/or
- Generating information necessary for fulfillment of regulatory requirements necessary to achieve approval.

*Roles in Adjuvant Therapy*

All of the interviewees noted that their direct experience in developing data for adjuvant therapies was less extensive than their experience with those designed for treatment of metastatic

---

[8]Nonclinical drug development includes the use of animal models, computer-based simulation and prediction models, and cellular or other in vitro systems to predict safety and efficacy in patients prior to entry into clinical trials.

[9]Translational drug development focuses on bridging information from nonclinical models and clinical experience to optimize efficacy via appropriate dosing and safety considerations.

cancer. Respondents noted that many of the therapies approved for adjuvant use were developed initially for primary therapeutic treatment and only later shifted to adjuvant settings. Therapies that receive secondary approval for use in adjuvant treatment, after primary approval for treatment in the metastatic setting, may require significant, minimal, or no novel data generation (as data on the safety of these are often derived from patient experience in the primary treatment setting) as directed by the regulatory authority (ICH, 2009).

*Current Challenges*

With respect to their role in informing adjuvant therapy development and use, the most commonly cited limitations were as follows.

**Difficult to replicate the timescale of treatment.** Many of the respondents cited challenges in replicating the timescale of treatment in the adjuvant setting. Specifically, they noted the difficulty in generating timely and relevant safety data that can meaningfully inform patients taking an adjuvant therapy for months to years in duration. These limitations were cited in both the nonclinical (animal/in vitro model) context and clinical context. In the nonclinical context, the primary concern was as follows:

> We can't do studies for 5 years. Not just because it's costly, but because, simply, the life span of either an in vitro model or an animal model is not going to allow for that type of work.

In the clinical arena, the feasibility and utility of conducting long-term clinical trials to define the balance of AEs relative to increases in overall survival for patients on extended adjuvant treatment was also cited as a limitation. Several respondents noted that as the time scale of dosing extends, in either a clinical trial setting or in a standard clinical setting, the number of variables impacting patient response to the therapy (both beneficial and adverse) are increased. Thus, this can make it difficult to meaningfully assess *causality* of potential AEs experienced by

patients on adjuvant therapy (e.g., whether those events are a result of the therapy, the disease, other medical or environmental conditions, etc.). Respondents expressed a variety of views as to whether existing postmarketing studies on patient experience in the adjuvant arena provide sufficient information to inform patients and clinicians about adjuvant treatment-related AEs. For example, some felt that such studies were adequately robust and met current needs, some felt their relevance for longer-term treatment was insufficient, and some were unable to comment on their level of rigor and relevance.

**Difficulties in measuring and/or detecting relevant safety endpoints.** Respondents in this category also placed significant emphasis on the challenge of predictively, reproducibly, and rigorously *measuring* AEs of relevance to patients who will be receiving adjuvant therapy. For safety evaluation via animal models, some toxicities or AEs may not manifest until after the study period (e.g., delayed cardiotoxicity) and thus would be missed by even an extended nonclinical study evaluation. Additionally, some of the most frequent AEs associated with adjuvant therapies (e.g., chronic pain, chronic fatigue, memory impairment, etc.) were cited as difficult if not impossible to reliably induce and/or measure in animal models. The majority of respondents also noted that with the increasing using of immunotherapies and other novel treatment modalities applied to adjuvant settings, the modeling challenges are likely to increase rather than decrease in the near term.

> One thing I think we're always a little bit on the back foot around is really understanding intrinsic toxicity concerns around new modalities.

Respondents also noted that predicting patient experience with a high degree of specificity, particularly within patient populations with variable comorbidities, polypharmacy, and so forth, is a significant challenge for the field in general (not just in the adjuvant or cancer therapy arena).

**New metrics on patient experience lack standardized use.** Those respondents most familiar with the use of PRO measures in clinical trials asserted that the tools for measuring patient experience in trials are robust and available. However, they lamented what they perceived to be a lack of routine uptake and utilization by regulators and the cancer research community at large.

> I think we need to align around analytic techniques and optimal vehicles for patient communication of these results, but I don't think we need new methods. I think we need alignment around the approaches we have now in a more systematic way.

These respondents felt that this lack of uptake has hindered their potential to benefit patient and clinician education.

**Regulatory data generation requirements focus on efficacy more than chronic safety for oncologic therapies.** Several participants noted that regulatory requirements for the approval of oncologic therapies for metastatic cancer appropriately focus on expeditiously (but safely) bringing new therapies to patients. These regulatory standards place significantly less emphasis on evaluation of the potential long-term (chronic) toxicity of the therapy. The guidelines for approval of oncologic therapies as developed by United States, European Union, and Japanese regulatory authorities state that

> In the development of anticancer drugs, clinical studies often involve cancer patients whose disease condition is progressive and fatal. In addition, the dose levels in these clinical studies often are close to or at the adverse effect dose levels. For these reasons, the type, timing, and flexibility called for in the design of nonclinical studies of anticancer pharmaceuticals can differ from those elements in nonclinical studies for other pharmaceuticals. (ICH, 2009)

Put simply, chronic toxicity studies (e.g., 2-year rodent carcinogenicity studies) and extended reproductive toxicity studies in animal models are typically not conducted for approval of an oncologic therapy used for metastatic cancer. Even when seeking approval for use of a therapy in

the adjuvant setting, the respondents noted that a regulatory incentive/requirement to conduct such studies is not always present. As clarified in a June 2018 "Question and Answer" document published by the FDA, the regulatory guidance used for metastatic cancer therapy data development should be used as a "starting point" for therapies intended for the adjuvant setting as well (FDA, 2018). The FDA notes that adjuvant therapy approvals may *in some cases* require the conduct of additional chronic nonclinical studies, reproductive or other toxicology studies, or clinical trials. However, the FDA (2018) further states that "When the anticancer pharmaceutical is shown to extend survival of patients, no additional general toxicology studies are usually warranted," and existing clinical data from the initial approved use in the metastatic setting is often considered most appropriate for informing a subsequent adjuvant approval (FDA, 2018). Many of the respondents linked their uncertainties around the biological relevance of longer-term studies on adjuvant-related AEs to a lack of regulatory incentive to conduct such evaluations. One respondent offered the following very pointed observation around when or whether pharmaceutical companies would conduct extensive nonclinical chronic safety studies:

> I think we won't do it until health authorities request that… it's expensive and I don't think that chronic is going to go there unless it has to.

*Future Needs*

The most common recommendations for future development were as follows.

**Increase connectivity between clinical and nonclinical research teams within a given pharmaceutical company.** All but one of the respondents noted that information collected on AEs in patients (during trials or postmarketing) was not routinely shared with nonclinical safety groups, unless that toxicity was robust enough to bring a regulatory safety stop to the therapy development program. Thus, they felt there was a missed opportunity to consider the nature,

prevalence, and patient perspective on specific AEs in future nonclinical or translational studies or monitoring approaches. Improved data sharing and collective analysis within a company was cited as an area ripe for improvement.

**Improve approaches to data generation and sharing around safety across companies and researchers.** The opportunity to promote/improve data sharing and collaborative data development across the pharmaceutical sector was also a common theme. Specifically, respondents cited opportunities to work together as a research community to develop better nonclinical models of and biomarkers for AEs. If realized, this could enhance understanding of the biological mechanisms associated with AEs nonclinically and improve clinical prediction or control of AEs. This recommendation was cited as a need in the adjuvant arena in general. However, it was cited as an increasingly pressing need, given the rise of immunotherapy and other novel treatment modalities that lack established nonclinical safety models or long-term clinical data. Respondents called for a new cadre of predictive safety testing approaches that are aligned for monitoring near and long-term AEs associated with novel mechanisms of therapeutic action. The use of pooled AE information from clinical surveillance studies was also identified as a potential future resource for improving both study designs and the patient relevance of information delivered via drug labels and patient education materials.

**Better engage the "patient perspective."** The respondents consistently noted that more should be done to engage the patient's viewpoint in drug development. Phrases such as "consider patient perspective," "integrate patient experience," and "consider patient stories" were used frequently. However, little was offered as to exactly how this information would or should be collected and integrated to achieve this objective. Overall the respondents seemed to envision a future in which patient tolerance for and experience of AEs more directly informs adjuvant drug

design, safety information development and delivery, and therapeutic dosing. However, their view of the path to achieve this objective was only vaguely defined.

**Promote and support a culture shift in drug development.** In both explicit and implicit ways, the respondents called for shifts in thinking around risk:benefit evaluation and patient experience in both adjuvant and general oncology drug development. As one respondent noted,

> We are trying to be more long term in our thinking… I'd love to tell you that we were there… where we are is [long-term effects are] a significant consideration as we advance development candidates… not necessarily that we can always fix it.

Within this stakeholder group, there were frequent calls for a future where drug development and evaluation programs increasingly and, with more precision, serve the needs of a growing population of long-term cancer survivors and patients on longer-term adjuvant therapy. Many of the participants noted specific examples of practice changes in their organizations aimed at moving toward this future state (e.g., novel conversations around optimal animal models, integration of PRO concepts into clinical tests and labels, etc.). However, many expressed uncertainties about how these smaller transitions would translate to consistent systemic changes in drug development practice. They noted a lack of clear drivers to support systemic change in drug development/safety evaluation practice and uncertainty around who would be responsible for leading such efforts.

**Link financial incentives to reduced AE profiles in adjuvants.** Some of the respondents who focused on needed culture changes also noted that building an economic argument to support investments around reducing AEs associated with a given adjuvant therapy was an unmet need. This was well summarized by one of the respondents as follows:

> So, if a drug company wants to make a drug that has as better safety profile, or even an adjuvant... I don't know who would take that on as a strategy and why. I'm not sure about the economic side of that… I think there needs to be more discussion about how the patient story can translate into the business case.

Participants who offered this feedback felt that organizational culture change (as described in the above comments) would only be sustainable if the financial return on investment for new practices was also defined.

*Summary of Roles and Accountability*

Overall, respondents in this category were highly focused on their regulatory-defined role in generating experimental data to support safe and efficacious use of therapy, but they highlighted many predictive testing/modeling challenges in this arena as they relate to the adjuvant application context. Participants observed a broadening treatment and survival horizon for cancer therapy in general. Many observed a growing societal focus on therapy-related AEs relative to patient QoL but noted that this has not yet translated into novel financial or regulatory drivers. With respect to accountability for implementing future change, these stakeholders identified roles their sector could play in developing novel data or novel therapies. However, they also described uncertainties around what groups or forces would drive both the positive and negative pressures necessary to generate new approaches for reducing the impact of AEs associated with adjuvant therapy.

***Regulators***

*Roles*

Broadly speaking, both the U.S. and European-based regulators interviewed for this study defined their primary role as evaluators of safety and efficacy data on novel therapeutics. They emphasized that their role in the oncology space is to balance the critical need for access to novel,

life-saving therapies with the reality that many of these therapies have expected and potential toxicities to the patient. A further discussion of current regulatory standards for oncologic therapy approvals and adjuvant approvals is included in the drug development sector discussion above.

The roles of the specific interviewees engaged for this study included nonclinical safety evaluation, clinical efficacy and safety data evaluation, national and international regulatory standard setting, and regulatory program coordination.

*Roles Related to Adjuvant Therapy*

With regard to adjuvants, not unlike the interviewees in the drug development sector, the respondents observed that regulatory review of novel adjuvants occurs with less frequency than for primary therapies. Also, as described above, regulators most involved with nonclinical data noted that such data are not often directly incorporated into adjuvant therapy approval considerations. However, they did provide perspectives on the translational relevance of nonclinical data for adjuvant products.

*Current Challenges*

With respect to their role in informing adjuvant therapy development and use, the most commonly cited limitations were as follows.

**The regulatory approval process for adjuvant cancer therapy requires a difficult balance of weighing future risks against future benefits.** All of the regulators interviewed noted that they must consistently strike a balance between evaluating the safety of the oncology products that they approve and ensuring that approvals are expeditiously delivered to patients.

> We don’t have the long-term data when we have to make decision on approval. And it’s often not reasonable to wait for that long to have very firm outcome data on long-term toxicity or overall survival, even if you have very good effect on progression-free survival...

While this was not offered as a challenge to be "overcome," the respondents observed that decision making in this context requires a fluid approach to evaluating trade-offs with often imperfect datasets. They noted that striking this balance for therapies to be used in an adjuvant setting requires yet another layer of calibration. In the case of an adjuvant, regulators must weigh risk:benefit where a patient is (putatively) cancer free and the trade-off becomes risk of potential toxicity versus risk of potential tumor recurrence.

> Often with the adjuvant therapies you're exposing many people who will never get the disease [i.e., recurrence of the tumor]… even if they hadn't had the therapy. You really have to look at the burden of treatment for the entire population versus benefit in perhaps the small group of people who will relapse with the disease.

While no alternative approaches were offered, the respondents consistently noted that decisions in the adjuvant space require a complex and expert-judgement–driven process that weighs available data against uncertain potential outcomes.

**Data to inform decisions are variable in their relevance and availability.** Per above, the respondents consistently noted that longer-term outcome studies on tumor recurrence and/or adverse effects following adjuvant therapy are sometimes limited in availability and utility. Specifically, the following limitations were cited by multiple respondents:

- *Rigor of PRO data.* Several respondents noted that they are encouraged by the increasing incorporation of PRO measures in clinical trials, as they feel it is an important step toward better engaging patient perspectives. However, there was general concern about the interpretability or maturity of these data for informing regulatory decisions. Specific comments included the following:

  > The quality of the data (PRO data) is much lower, usually it has been, which makes them less useful.

> I think the use of a lot of the patient quality of life information is relatively primitive in cancer in my opinion, compared to other fields.

Stated concerns around PRO data quality and data "maturity" primarily included uncertainties about how to rigorously and consistently incorporate PRO data into regulatory decisions, perceived variability in the consistency/accuracy of patient self-reporting, and concerns about a lack of consensus methodology for collecting and interpreting PRO data.

- *Durability of patient registries.* The value of patient registry data as a source of extended patient outcome on adjuvant therapy was viewed as questionable by some.

> The databases that are set up for surveillance are not adequate… the surveillance databases are good for about 2 to 3 years after product approval… they're not directed at long-term effects.

In this regard, respondents often cited difficulty in continuing to keep track of patients and/or their medical history and exposures over longer terms.

- *Uncertain causality of AEs*. More than half of the respondents emphasized the challenges of distinguishing adjuvant treatment-related AEs from other background morbidity in patient populations. They noted that effects that can be defined as treatment-related AEs (e.g., pain, fatigue) are also commonly reported ailments in control groups and populations at large. A regulatory decision as to causality can thus be confounded.
- *Relevance of animal model data.* Stakeholder feedback from the regulatory stakeholders interviewed varied on this point. Some seemed to feel that, for small

molecule therapies,[10] the current nonclinical animal database is sufficient to broadly predict long-term AEs.

> Overall, for small molecules, they [nonclinical models] have been predictive of effects in humans, and long-term effects are being addressed through carcinogenicity studies… carcinogenicity studies can detect toxicities that we are not seeing in 1-month or 3-month studies… I don't know what else we can do.

Others highlighted challenges in using traditional animal or in vitro models to generate longer-term toxicity data, data relevant to patients with multiple comorbidities and polypharmacy, and data on QoL-type endpoints like pain and nausea. All agreed that translatable animal models for evaluating AEs from novel immunotherapy (in adjuvant or metastatic settings) is a growing challenge.

*Future Needs*

All of the stakeholders in this category cited future opportunities to improve the development and/or or use of AE information in the adjuvant context. The most common recommendations were as follows:

**Improve/develop better metrics for assessing "burden of treatment."** The majority of respondents noted a desire for improved tools, data, and approaches to consistently capture and integrate the overall burden of treatment. They noted that they work very hard to rigorously apply available information against current regulatory standards. However, their efforts would be facilitated with new methods for systematically and rigorously defining and integrating a broader range of information on a patient population's anticipated experience (e.g., fatigue, pain, impact

[10]"Small molecules" refers to the therapeutic classes and structures of drugs traditionally developed and delivered for chemotherapy. This would not include new therapies such as immunotherapy.

on daily activities, long-term or delayed AEs associated with a therapy, etc.) into regulatory decisions/actions on adjuvants. One subject summed it cogently as follows:

> If you're talking about adjuvant therapy where you may take it for a long time, and you may take it when you're healthy and you're not at [immediate] risk of the disease, then it's more important to understand the actual burden of treatment to the patient, and their quality of life. And those instruments are, I think, not as readily available.

**Re-evaluate societal values regarding risk:benefit trade-offs in cancer therapy.** As the societally appointed arbiters of risk:benefit information for adjuvant therapies, more than half of the regulatory-sector respondents called for renewed discussion around the appropriate set points for such decisions.

> There is a societal need to talk about the risk:benefit for short-term versus long-term toxicity and efficacy.

Respondents generally viewed this societal discussion a critical step in incentivizing and guiding the design of future data, guidelines, communication tools, and patient support. Respondents broadly indicated that shifts in survival rates and increasing societal value for patient QoL considerations are drivers for these discussions. However, neither specific forums nor conveners for these conversations were specified by the respondents.

**Enhance public access to clinical data.** Although some aspects of trial reporting are already legislatively mandated, several of the respondents called for further enhanced public data sharing of clinical trial data. They offered that more rapid and complete access to all trials could better inform clinicians, healthcare agencies, academicians, and patients about anticipated outcomes and effects and could be mined for research.

**Improve communication to patients.** Several of the respondents noted that the regulatory arena could better serve patients if information around "quality of life" and AEs associated with

a therapy was conveyed in a more systematic, readily understandable, and patient-relevant format. One respondent noted,

> We've always hoped that information (on the label) could be translated by others or made into more accessible forms for others.

The accountability for achieving this goal was not clearly defined by the respondents but did not seem to be viewed as a regulatory role.

*Summary of Roles and Accountability*

Respondents highlighted their role as one of reviewing and evaluating information on adjuvant therapy to evaluate risk:benefit trade-offs. Limitations in long-term outcome data—and longer-term AE and QoL information—were acknowledged. However, the necessity of progressing approvals to support patient access to adjuvant therapy in the face of imperfect information was stressed. The potential to recalibrate societal expectations as to what is "acceptable" with respect to a burden of treatment for adjuvant therapy was posed as a critical future discussion point. These stakeholders offered few details as to who should be accountable for furthering such discussions, but they predicted that such discussions could translate into changes in regulatory practice at some future time.

***Clinicians***

*Roles*

Two subcategories of MD-level clinicians were interviewed for this research: oncologists and other specialists (cardiologists and rheumatologists) who support AEs that can be associated with some adjuvant therapies. For all respondents, their general role was characterized as providing advice and clinical therapy to patients to help promote their long-term survival and meet contemporary health challenges. Many of the clinicians interviewed discussed their role in

working with patients to understand their long-term treatment goals and to describe how available therapeutic options could impact those goals.

*Roles Related to Adjuvant Therapy*

All of those interviewed noted particular challenges in advising patients who are initiating or on adjuvant therapy. They observed that adjuvants can be viewed as "preventative therapy" and may follow a long and difficult course of curative therapy. Thus, the burden of novel treatment efforts and potential AEs at a time when the tumor burden is absent or negligible can be particularly stark for these patients.

> It is a more complicated decision process for them (patients considering adjuvant therapy) than those who are not getting it in an adjuvant setting. I think they can be more frustrated when they have adverse events in adjuvant settings rather than primary treatment settings.

The oncologists involved in this study emphasized that a key component of their role in counseling patients on the use of adjuvant therapy is helping them determine when and whether to initiate treatment. According to one respondent,

> Adjuvant therapy is insurance, more than anything else. But it does come with risks. And so, every single discussion should really be around weighing the risks and the benefits around this treatment.

The rheumatologists and cardiologists who were interviewed were very explicit in their defining themselves in a *supportive* role relative to cancer patients—and not the lead resource for the overall treatment strategy or decision making. They often used phrases such as "I facilitate the patient's ability to continue on cancer therapy" or "My role is mostly supportive." Roles for these physicians were primarily limited to helping to manage and/or monitor for possible treatment-related side effects to facilitate the patient's ability to stay on the therapy, increase the patient's symptom management, and to maintain overall health during and following the course

of adjuvant therapy. They noted that decisions about which adjuvant cancer therapy should be pursued are "deferred to the patient and their oncologist."

*Current Challenges*

With respect to their role in supporting patients on adjuvant therapy, the most commonly cited limitations across the clinicians interviewed for this study are those described below. The text below specifies whether these perspectives were shared or differed between oncologists and the specialists interviewed for this study.

**Insufficient information on some adjuvant-related AEs.** All of those interviewed cited concerns about the insufficiency of data for some adjuvant-related AEs. These limitations fell into three general categories: insufficient numbers of clinical studies on adjuvants, insufficient reporting of adjuvant-related AE data within published studies or in drug labels, and insufficient mechanistic understanding of the biological pathways underlying treatment-related AEs. As one respondent neatly summarized, "For prevention [i.e., adjuvant therapy], there are fewer trials." Participants also commented extensively on the disparities between published trials and their professional experience with respect to some AEs. They observed that, in some instances, the breadth and impact of AEs experienced by their patients receiving adjuvant therapy was not well reflected in published reports and labels. One went as far as to say, "For me, drug labels are pretty much useless for what I'm doing specifically." It is important to clarify that the clinicians interviewed here did not appear to feel that therapy delivery was unsafe but rather that documentation was not adequately nuanced.

The limitations referenced in these comments extended to both extensively used adjuvants as well as more recently approved adjuvants. For the oncologists interviewed, their most prominent concerns related to perceived deficiencies in the data around *nonlife-threatening AEs*. To

compensate for systematic deficiencies in the available data on adjuvant therapy-related AEs, most of the oncologists interviewed emphasized that they had to rely on their own professional experience as a resource.

> What is less obvious or clear from the evidence base, but that emerges with time is what patients are telling us about their experiences on these treatments… those things like gastrointestinal symptoms, muscle cramps, etc.… there is some level of signal of symptomatic adverse event that's needed to really bring that issue to attention, and otherwise, it largely comes from experience to understand what people are going through.

This sentiment was extended further by those respondents, typically specialists, addressing AEs associated with more recently adopted adjuvant therapeutic approaches. The following comment is emblematic of the challenges described by these respondents:

> We have a little network of people who ask each other questions ("Have you had this sort of situation?"), and try to pool our knowledge to give the patient the best information. But I think that's what you have to do in the early days of something when there's not a robust literature of prospective studies.

A third area of concern around data availability focused on a lack of understanding of the pathogenesis of particular adverse effects. Some of the respondents noted that the lack of clear understanding of the pharmacological mechanism of action driving these adverse effects is an impediment to providing treatment to reduce or eliminate their impact on patient health.

**Difficult to maintain currency with available information.** All of the respondents emphasized challenges in maintaining currency with evolving data and practice recommendations, particularly on more recently released therapies (e.g., immunotherapy). For the respondents in this study, all connected to major academic or research hospitals, logistical access to information via their own institutional library systems and personal attendance at scientific conferences was not in itself viewed as a hurdle. However, they observed that managing the volume of information and determining its quality and relevance for their

individual practices was a significant challenge. Respondents identified a lack of time to routinely review and compare/contrast new studies as a major limitation.

**Integrating information is complex.** Some of the most pervasive and prolific commentary from this stakeholder group focused on the challenges of effectively integrating information across clinical studies, published guidelines, and patient preferences into rigorous treatment recommendations. Existing "risk calculator" tools were acknowledged as a sometimes-helpful starting point, but none of the interviewees who addressed these tools felt that they were fully sufficient for facilitating treatment decision making.

> Ultimately, it's garbage in, garbage out… When I use things like [risk calculators], I do so understanding that it might not be completely updated. It might not have all the studies included in it that I might have hoped, and it is really more about getting a general sense of a where a patient may fall.

Comments about existing tools ranged from overall dismissal to general caution against asking more of the existing tools and data than they can provide.

**Changing medical practice requires tackling a daunting breadth of issues.** All of the clinicians interviewed envisioned a future in which an improved understanding of and support for adjuvant treatment-related AEs would result in improved patient experience and outcome. However, many were uncertain how to realize this future state given the number of stakeholders and systemic components (regulatory, technology, work flow, logistics, data availability, heterogenous patient populations) that could impede change. One clinician commented that it is a "pretty daunting task that would require sustained effort to generate something that would be reliable and useful." Several questioned what group or groups would have the accountability to address the limitations noted above.

*Future Needs*

The following recommendations and future opportunities were identified by this stakeholder group.

**Build evidence-based guidelines for managing AEs.** The specialists interviewed for this study were most adamant about the need for more consistent, evidence-driven guidelines to help them treat patients on adjuvant therapy in a way that alleviates symptoms but does not hinder the efficacy of the adjuvant therapy itself. While some clinicians felt that informal, peer-to-peer information exchange was both a necessity and valid, others expressed concern that such approaches lack consistency and would fail to systematically inform future treatment approaches. The most eloquent summation of this concept was as follows:

> There are dangers in creating practice without data, but there's nothing more dangerous than having no agreements and then everybody does whatever they want…

Physicians who echoed this sentiment called for efforts to better promote discussion around best practices and to actively share contemporary experiences to inform treatment.

**Enhance coordination between oncologists and other medical fields via raised awareness of shared issues.** Several respondents called more fluidity of care and interaction between oncologists and those treating therapy-related symptoms. They acknowledged that this occurs, in part, because "everybody has their checkboxes and neither of us is on each other's checkbox." Recommendations included development of clinical pathways that are more multidisciplinary and other less formal means of raising "awareness" of multidisciplinary treatment approaches. Highly specific means for improving cross-disciplinary coordination was not extensively described, but many suggested that this was an important objective that should be further pursued.

**Leverage standard-of-care settings to generate meaningful information on PROs and outcomes.** Many of those interviewed expressed frustration that more was not being done to collect and analyze patient experience in standard-of-care settings, and many felt that more progress should be made in this regard.

> We end up generalizing the decision for the patient based on what has been collected in clinical trials that might have been conducted 10 years ago on a different continent. But we treat patients every single day, but that data is not being put to good use for the patient that I have in the clinic.

> Everybody does a little bit on what they feel, but we are not collecting these data.

It was recognized, however, that the way data are currently collected and stored in EHRs is not fully conducive to research and decision making. Some noted that current data collection in EHRs in standard practice is designed for payment and insurance systems. They offered that future progress will require not only a commitment to collecting and interrogating these data, but possibly a restructuring of the data formats and content at the outset.

**Expedite access to data from clinical trials.** Several of the respondents were frustrated that access to clinical trial data can be very slow and challenging. They called for more rapid and complete data accessibility, but specific mechanisms were not described.

**Reduce the cost of care.** Some of the respondents noted that reducing the overall cost of care would benefit their patients who are receiving adjuvant therapy by decreasing financial barriers to the initiation or maintenance of treatment (or supportive services). A small subset of those interviewed were actively engaged in policy discussions around healthcare costs, but discussions around specific policy approaches were not explored in this study.

**Create robust tools to allow clinicians and their patients to better understand risk:benefit trade-offs.** One of the most common recommendations across the clinical

stakeholders interviewed was a call for understandable, visual, and reliable tools that would aid in shared doctor-patient decision making.

> We've often talked about how it'd be very helpful to have better evidence and probably graphical representations of patient experience factors related to symptoms, function, and quality of life or otherwise… those types of data and representations just really don't exist in ways that can be easily relied upon as reference materials.

A key subcomponent of this recommendation was the call for enhanced data of relevance for predicting the nature and frequency of treatment-related AEs for adjuvants.

*Summary of Roles and Accountability*

These stakeholders focused on their role in providing decisional and medical support to patients considering or pursuing adjuvant therapy. Challenges associated with tracking, integrating, and communicating complex data sources (sometimes containing too much information, sometimes not enough) were stressed. Disparities between clinician experience of AEs during adjuvant therapy and the published literature/drug labels were noted. Opportunities to engage data and experience from standard-of-care settings were promoted, although the resources, incentives, and logistics for achieving this objective were elusive. This stakeholder group directly addressed the need for systemic change in the collection, use, and dissemination of AE information for adjuvant care. However, discussions around accountability for change resulted in lists of many stakeholder groups as well as concern around how such groups might be aligned and incentivized to work collaboratively.

### *Patient Advocates*

#### *Role*

The patient advocates interviewed for this study primarily described their roles as supporters of cancer patients and cancer survivors, in almost any nonmedical capacity they need. One advocate summed up the role as "enfranchising and articulating, midwifing, patient voice at the micro, meso, and macro level." Roles included serving as a resource for accessible information about treatments, sharing experiences with therapy, learning about economic and employment issues, mental health issues, and insurance coverage, and so forth. Advocates also described their role in "validating" patient experience by providing a central point for patients to share their experiences free of judgement and among their peers. They noted that more than 80% of cancer patients are treated at community hospitals and thus their support role is particularly acute in those settings.

#### *Role in Adjuvant Therapy*

Interestingly, some of the interviewees noted that their support roles can be even more pronounced in the adjuvant setting because the initial "warrior mode" associated with battling metastatic disease has passed for many patients, leaving fatigue and desire to focus on things other than treatment. According to several of the respondents, patients at this stage sometimes need even more significant support to manage diagnosis, treatment options, and self-care. The advocates interviewed frequently noted that their organizations serve as a resource for coalescing and sharing information generated by other sources. They cited a heavy reliance on published sources of information such as the NCCN, ASCO, NCI, PubMed, Cochrane Reviews, and so forth. Sometimes information from these sources was compiled into content delivered via websites, patient navigators (often with some scientific or medical training), or novel formats

that are language and culturally appropriate. Many referenced the role that patients play in sharing self-identified methods to manage both the effects of cancer and the effects of treatment-related AEs via chat rooms and other online or live patient forums. For example, one advocate described the development of Spanish-language content in a short pictorial story format that would be familiar and accessible to its intended audience.

In the patient advocacy arena (perhaps more than any of the other four stakeholder groups interviewed for this study), the discussion of limitations and future needs was almost inextricably intertwined.

*Current Challenges*

The following limitations and challenges were most commonly cited by the patient advocacy stakeholders interviewed for this study.

**Focus on treating symptoms and not the patient.** Many of the advocates described a consistent lack of clinical acknowledgment of the personal impact of nonlethal treatment-related side effects (e.g., pain, balance issues, weight gain, etc.) on patients. There was a clear sense of frustration that some clinicians do not appreciate the burden that these effects bring to their patient's ability to achieve daily tasks, engage with family, manage friendships and work, and so forth. They were careful not to implicate all clinicians but were also adamant about the scope of the problem. Advocates expressed frustration that a "there's a pill for that" attitude can result in additional layers of pharmaceutical burden without adequately focusing on solutions that both lessen adjuvant treatment-related AEs and accommodate other daily living requirements and limitations. There was no clear consensus from these stakeholders as to how clinicians should specifically support and address these symptoms.

**Insufficient therapeutic options.** This feedback was most prevalent from those advocates who worked frequently with patients with less treatable cancers but was echoed by all in one form or another. The advocates cited limitations of available therapeutic options for both primary and adjuvant treatment.

**Patients' unwillingness to take ownership of their own care.** Several of the advocates expressed frustration that patients do not often enough demand more information, service, options, and consideration from their clinicians and health providers. They noted that patients must recognize that "they are essentially the decision makers," and that they have a right and obligation to make their own treatment choices, to the extent feasible.

**Lack of accessible and understandable sources of information.** A concern about access to information included reference to both written content and verbal communications. One advocate described efforts to bridge this gap by development of materials about treatment, side effects, financing and insurance, and so forth in a variety of languages and formats to support patients who are not native to the United States. Others described the complexity and inaccessibility of many elements of the administrative elements of the treatment process, particularly the legalistic language within consent forms for clinical trials. The role of "patient navigators" in synthesizing information or facilitating access to information resources was cited repeatedly as a critical role, but one that was often under-resourced and underpopulated. The provision of information on "access to quality care" (i.e., types of services offered from specific providers; available medical, social, and economic support options and the logistics, financing, and eligibility associated with access to these services; the treatment options available and their implications for the patient, etc.) at early stages of treatment was stressed.

*Future Needs*

The following future needs were identified.

**Patients and clinicians should more openly confront issues around mortality.** Although this point was not noted by all the patient advocates that were interviewed, for those who raised it, it was clearly a point of significant passion: “We have to get as comfortable as can be with the prospect of our own death and dying.” It was noted that until there is more open acknowledgment that no therapy is ultimately truly preservative (e.g., all patients and their doctors will die), it will be impossible to candidly and honestly discuss trade-offs between quality and quantity of life.

**Clinician-patient relationships should be partnerships that reflect greater mutual understanding of options and preferences.** Many of the advocates called for greater balance in doctor-patient decisions around treatments. Interestingly, these discussions called almost equally on both doctors and patients to invest more of their time, judgement, and emotion in better meeting this challenge.

**The healthcare system in the United States should be more efficient and less expensive.** When asked about future needs, opportunities to improve the U.S. healthcare system were frequently cited. Advocates observed significant disparities between the amount of money flowing through the U.S. healthcare system and their sense of the overall quality of care delivered to patients. They expressed frustration that treatment decisions were overly administrative and insufficiently responsive to patient concerns.

**More research on long-term effects of treatment is needed.** The need for additional research on the long-term health impacts of adjuvant therapy was cited as an unmet opportunity. As one respondent noted,

> Too few people are studying what it means long term to live with the after-effects of treatment… that's the poor stepchild of survivorship. They don't care about that. You are lucky to be alive.

Per the above, some of the advocates reflected frustration that patient feedback on AEs or other QoL endpoints was at times undervalued and/or dismissed. Some advocates specifically called on drug developers to further develop information relating to AEs and/or to develop therapies with fewer AEs, whereas others failed to specify who might take on this role.

**More tailored information is needed in order to know what is relevant for specific patients.** Several respondents called for access to more tailored information such that individual patients could make decisions that are right for their disease, personal situation, finances, and so forth. To this end, all called for clinicians to engage more comprehensively with their patients to facilitate the application of tailored medical treatment. For example, one recommended the development of information "passports" that would accompany a patient and include details around their genetic profile, disease status, prior treatments, and so forth to ease these conversations and reduce the information retention burden on patients.

*Summary of Roles and Accountability*

The patient advocates engaged in this study emphasized their role in providing informational, emotional, and logistical support to patients on or considering adjuvant therapy. They cited more extended, frank, and collaborative discussions and decision making between clinicians (and other caregivers) and their patients as a key need. The challenge of supporting patients deciding to embark on "preventative" therapy (and balance the subsequent burdens against uncertain outcomes) were cited as an essential but demanding role. A need for increased focus on patient QoL and desire to address, and not just medicate, treatment-related morbidities was also stressed, although consensus around specific approaches was lacking. With respect to accountability,

some elements of desired change were assigned to groups such as patients, drug companies, clinicians, or patient navigators. However, resources or incentives to systematically support these future changes were typically described as highly limited.

### *Payers*

#### *Roles*

The payers interviewed for this study included those from both governmental and private insurance programs (see Chapter 3 for a more complete description). The roles described by these subjects fell primarily into three categories: 1) providing financial support to cover services and therapies required by those utilizing their insurance coverage, 2) providing case management and navigation services to those same individuals, and 3) developing and evaluating new models of care coverage. In the first category (payment), all of the subjects were adamant that they "don't tell a physician how to practice medicine" and provide coverage for that which is "reasonable and necessary." A further discussion of limitations in this role follows below.

With regard to providing case management and information-sharing services, most of the stakeholders described their role (or their organization's role) in providing support to patients on an assigned or on-demand basis. They noted that this information is often also available from clinicians, but *"*case managers are also another layer of support for them once they get home and are experiencing those side effects." Information provided via these individuals included "psychosocial" support, information about treatment side effects, information on therapeutic options, and so forth. One participant noted that this support role is particularly important in the adjuvant and postadjuvant setting because "a lot of time[s] a health plan will focus really on the patient as they're undergoing active treatment. And when they switch to nonactive treatment [adjuvant or maintenance therapy] …you're actually spending less time with them… we've

rolled out patient education programs that don't stop when treatment stops." Specific resources cited as a basis for both education and/or treatment approvals include published clinical trials, educational resources, and data/treatment synthesis reviews prepared by professional scientific societies such as ASCO, the American Cancer Society, community oncologist associations, and so forth. Some also noted that information was reviewed and evaluated by an internal physician advisory board that reviews evidence-based guidelines and best practices. These advisory boards serve as a resource to the case managers and inform treatment approval decisions by the payer.

*Role in Adjuvant Therapy*

In characterizing their roles in providing support to patients on adjuvant therapy specifically, many respondents chose to focus on recent payment models that they felt had the potential to improve quality of care for patients on adjuvant therapy. Specific analysis of these payment models and their strengths and weaknesses is beyond the scope of this study. However, a brief discussion of the roles that these systems may play in supporting patients on adjuvant therapy, as described by the study respondents, follows below. On the public side, subjects described the Medicare Oncology Care Model (OCM) as a novel opportunity to improve care delivery and enhance cost efficiency for cancer patients. The OCM was described by the subjects as an exploratory model that "doesn't have silos so you can look outside of classic care [model], so you can do the right thing." Respondents focused on the OCM's goal of incentivizing clinicians to look at the "total cost of care" and make choices that reduce overall costs to the system. As described by the participants, in this model, "wraparound services" such as transportation to routine doctor visits to address side effects from adjuvant therapy may be eligible for coverage if such expenditures are anticipated to reduce the likelihood and expense of a subsequent emergency room visit. With respect to evolving payment models on the private payer side, some

participants described the Patient-Centered Medical Home (PCMH) model. The PCMH is a payment model focused on providing comprehensive, quality care as coordinated at the primary care level. The respondents commented that the PCMH's focus on "quality of care" and access to patient navigation services makes it a robust model for supporting cancer patients on adjuvant therapy. Although the participants characterized the inclusion of navigation and wraparound services in the fee structure of these models as a positive for patients on adjuvant therapy, they acknowledged that these models are relatively new and evolving. The overall cost:benefit to the payers and impact on patient service utilization (and cost to patients) is yet to be fully determined.

Most participants observed that payers have no role or only a very limited role in generating public or systemically accessible learnings from their database of adjuvant therapy delivery/support approaches and patient outcomes. Some of the limitations in this regard are discussed below.

*Current Challenges*

The major themes with respect to challenges and limitations as cited by the payers interviewed for this study are described below.

**Healthcare plans are limited in their ability to be nimble and personalized.** While most of those interviewed stated a personal recognition of the value of offering a broad range of wraparound patient support services (e.g., transportation, massage therapy, counseling, etc.), they confirmed that the ability to offer such services in a customized and nimble manner is necessarily delimited. As one of the private payers noted,

> Health plans are under very strict monitoring for individual considerations… any types of one-offs that we approve without clear written criteria… and so there is a lot of hesitance in the payer space to provide wraparound service[s] because not everybody needs them… it's difficult to write a medical policy when not everybody needs something but it's something that maybe a couple of people might need based on their goals or based on their specific circumstances.

In addition to challenges in offering services that meet the needs of only selected participants in the plan, some payers also noted that coverage of a novel supportive service (at least in traditional payment models) is dependent upon a robust evidence base on its efficacy. However, as one respondent noted, "The evidence base is really lacking for these kinds of wraparound therapies." Specific opportunities to enhance this evidence base were not defined by the participants.

**The use of datasets held by payers to improve future care has significant limitations.** Many of the respondents noted significant limitations on the use of information collected by payers (e.g., treatment type, cost of care, patient characteristics and prior conditions, patient outcome, clinician location and characteristics, etc.). Many commented that, while entirely appropriate, data privacy limitations make it difficult/impossible to comprehensively evaluate and share information that might benefit the broader clinical community. Some also noted that payers' ability to efficiently collect, synthesize, and share information (even within their own network) can be problematic. As such, the ability to identify and adopt time-sensitive calibrations in payment coverage or recommendations regarding treatment can be stymied. The third limitation related to challenges in collecting and evaluating data in a statistically robust manner. It was noted that data about treatment outcomes and care delivery could be "lumped" to create a larger base for analysis and detection of trends. However, in those scenarios, the diversity of variables associated with care delivery, patient types, and so forth was often so significant that extraction of only very broad trends was possible. When data were "split" into smaller and more homogenous subunits to

promote more ready interpretation, the total "n" for analysis also decreased substantially and thus interpretation was challenged by inadequate sample sizes.

**Cost of drugs negatively impacts the patient's quality of care and adherence.** Both public and private payers commented on the impact of high drug prices on patient outcome. They cited cost of both adjuvant and nonadjuvant therapies (even with insurance coverage) as a hurdle to accessing the best possible therapies and/or to sticking to treatment schedules. Many respondents observed that the costs of cancer therapies are, in general, increasing and felt that this trend is becoming increasingly problematic.

**Patient awareness of the impact of nonadherence is inadequate.** A subset of the respondents noted that one of their challenges in realizing optimum outcomes for patients in their plan is a lack of compliance with proscribed treatment schedules.

> A lot of it breaks down to patient education and patients understanding that the schedules need to be followed very well in order to … have the most impactful treatment.

Providing additional education and outreach to patients was recommended as a remedy.

**Patients on adjuvant therapy are a distinct subcategory of cancer patients with unique and challenging needs.** A subset of the respondents observed that their programs provide less focused service delivery and decision support for patients in the adjuvant treatment phase relative to other treatment phases. One respondent noted, with some frustration, that "The majority of plans are really looking at a population of people who are at the end of life and not people who are going to enter into a maintenance phase." This same respondent also noted that the information support needs of patients considering adjuvant therapy present unique challenges relative to patients in the metastatic or palliative care phase: "There's a very open trade-off between quality of life and length of life… that makes this phase pretty difficult to sort through."

**Data relating to treatment options and care pathways are complex and rapidly changing.** All the participants confirmed that internal clinical advisory boards rely on available scientific/clinical data to inform plan coverage and provide information to participants. A range of views were expressed as to whether these teams are able to effectively review and integrate this information in a timely and robust manner. Challenges related to having the time to perform routine systematic reviews of novel studies and identifying data of relevance to a specific patient or patient population.

*Future Needs*

The following specific recommendations and future opportunities were offered by a majority of the stakeholders interviewed in the payer category.

**Improve support for chronic AEs associated with therapy.** Many respondents observed a trend in the payer sector toward greater recognition of patient QoL as a metric of quality care. They also anticipated increasing attention on the role that chronic toxicities/AEs play in QoL.

> There is an increased awareness in the long-term toxicities of therapies, both physical and emotional and socio-economic in terms of holding to a job and all those things… There's also an increased awareness that we aren't doing as well as we could … there's still work to be done.

Very specific recommendations for making improvements in this arena were not offered, but in response to questions in this regard, there were suggestions that new models such as the OCM and the PCMH model might help to address this in the future. In this vein, many also called for increased support for access to a diverse range of services that support QoL during and following adjuvant therapy. Although suggestions for the specific types of supportive services and plan coverage mechanics varied across the participants, there was general recognition that optimizing

outcomes and reducing side effects for patients receiving adjuvant therapy requires consideration of more than just traditional medical intervention.

**Adopt new payment models (such as the OCM and the PCMH model) as new standards.** The majority of the payers that were interviewed for this study promoted the further adoption and codification of novel payment models as a means to enhance care provision and reduce costs for patients on adjuvant therapy. It should be noted that the majority of those interviewed also hold professional roles in the development and evaluation of novel models such as the OCM and the PCMH model. However, even those not involved with these models specifically observed that current insurance models will require some type of innovation to better serve the needs of cancer patients on adjuvant therapy.

**Reduce the cost of drugs.** The majority of the respondents called for a decrease in oncology drug prices as a means to enhancing access to and coverage for quality oncologic care. However, most anticipated a continued rise in pricing.

**Enhance data sharing across plan participants and with insight from the clinical community.** The opportunity to use data sharing from within payers' databases and experience to improve outcomes for patients and enhance system performance was a commonly stated future goal.

> If there [were] more robust data sharing [and] more robust collaboration from an education standpoint, I would see that as a huge win for our patients and members… I think we all have a common goal but we're just not as integrated or as connected as we need to be.

However, as noted in the limitations section, many respondents cited the numerous and substantial barriers to this type of data sharing and use. Specific means to reducing these barriers and thus realizing this opportunity were not identified by the respondents.

**Enhance the systematic capture of patients' experience of QoL when evaluating quality measures associated with insurance coverage.** The majority of the payers interviewed called for more systematic means to capture and integrate QoL measures in payment plan evaluation efforts. They acknowledge a growing awareness of the importance of patient perception of QoL and its direct relevance in the adjuvant space. However, they noted the need for development of tools and methods that would allow for its routine integration into plan evaluation in the future.

**Provide more frequent access to clinical information (24/7) so that minor problems do not become major ones.** A subset of the stakeholders interviewed called for enhanced patient access to clinical advice. They postulated that by creating almost unlimited access for response to questions and concerns, they could significantly reduce more costly visits to emergency rooms and specialty care centers.

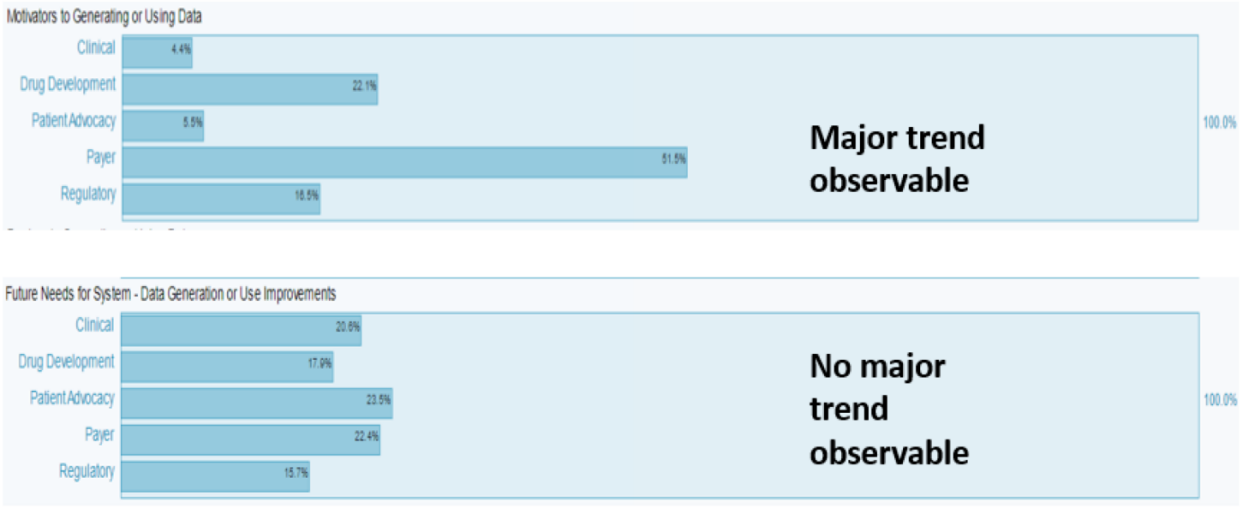
*Summary of Roles and Accountability*

These stakeholders described their roles in providing healthcare reimbursement/coverage as well as in developing and innovating healthcare payment models in general. They stressed the need to engage with patients on adjuvant therapy in an ongoing and interactive way (to benefit the patient and to avoid preventable costs due to deferral of care). Some stakeholders described challenges in aligning the provision of consistent, evidence-based coverage with variable patient needs. Opportunities to support an LHS were commended and pursued by some, but logistical, privacy, and technological hurdles were also identified. This stakeholder group largely viewed themselves as implementers of information generated by others (e.g., study data, pricing data, healthcare usage data, etc.) but as leaders in the development of new payment models. These stakeholders generally viewed their remit as internally focused—that is, largely delimited to the use of their own data and published data to promote modifications to their internal systems.

**Further Exploration of Intra-Stakeholder Differences as Revealed via Code Application**

Because all stakeholder groups were interviewed with the same core survey questions, an analysis of variations in code application provides insight into areas of differential focus and priority. Trends in code frequency were evaluated qualitatively and in relation to the pooled interview data for each stakeholder category. Plots of the frequency of use of a given code for each stakeholder group were generated using Dedoose's online analysis tools. (*Note:* The default setting for these plots includes a reporting of percentages. However, quantitative assessment is not appropriate for this dataset and statistical/quantitative variance assessment was not conducted.) The investigator used these plots to look for gross visual trends in code application. Figure 11 provides an example of a plot representing a "major trend" and a plot where no major trends are observable with respect to code use (plots contain actual data).

**FIGURE 11: An illustrative example of an approach to visual trend analysis of codes**




The top chart (as generated with the Dedoose software) illustrates a clear variance in use of the code "Motivators to Generating or Using Data" by the payer sector relative to others. The bottom chart is representative of datasets where no visual trends in code application are observable.

Of the 10 codes utilized in this study, the *frequency of application* of the codes was consistent[11] for all but the following three codes: "Roles in Data Generation," "Motivators to Generating or Using Data," and "Specific Data Resources." A discussion of this variance and its implications for understanding differences in stakeholder roles follows below.

The code "Roles in Data Generation" was applied with far greater frequency in relation to feedback from respondents from the drug development sector as compared to others. This differential likely reflects this sector's self-professed role in developing primary data associated with adjuvant therapy design and use and their significant focus on fulfilling regulatory data generation requirements (see above). Although all stakeholder groups involved in this study provided some examples of their roles in data generation, most groups focused proportionally more on their roles in information use and/or dissemination.

The code "Motivators to Generating or Using Data" was used significantly more to characterize feedback from payers as compared to other stakeholders. In this context, payers often focused on novel payment bundling models that, according to the respondents, create economic incentives to use or collect information that would result in a more efficient system and/or better active care for the patient. The absence of focus on motivators is a theme that will be further addressed in the conclusion of Chapter 5.

The code "Specific Data Resources" (used to denote respondent discussion of named data sources or reference materials) was applied most often to feedback from clinicians and patient advocates as compared to other respondent categories. This frequency likely reflects the

[11]It is important to note that the frequency of application does not equate to consistency of themes or topics. As reported here, codes such as roles, barriers, and future needs were used consistency and frequently across all stakeholder groups. However, per the detailed reports in this chapter, specific focus and priorities identified within these topical areas varied considerably from stakeholder to stakeholder.

significant role that these stakeholders play in integrating and/or sharing specific information and resources that are developed by others (see detailed discussions above). Although many respondents described the general categories of information that they utilize, the patient advocate and clinician groups were far more likely to discuss specific named resources. Many times, these named resources were compilations of existing studies (treatment guidelines, ASCO or NCCN reports or summaries, etc.).

In addition to evaluation of individual code frequency, an analysis of code co-occurrences provides further insight into the structure and thematic focus of the respondent commentaries. Co-occurrence is defined as follows. Each substantive section of text in the interview is assigned one or more codes (see Chapter 3). With the aid of the Dedoose analytical tool, it is possible to review the collective texts to determine which codes were most often assigned concurrently to sections of text. When codes commonly co-occur, it indicates that respondents addressed the themes embedded in those codes in an integrated or linked manner. The text below explores the co-occurrences observed in this study and their implications for understanding cross-stakeholder perspectives.

The codes "Barriers to Generating or Using Data" and "Future Needs for System" were the two codes most commonly applied to common sections of text. This co-occurrence is not entirely unexpected given the focus of the conversation (e.g., participants describing how they see barriers being overcome in the future). However, it is interesting to observe that the future needs discussion frequently did not link to discussion of motivators. This may suggest that respondents were more focused on or aware of hurdles rather than incentives in their feedback. The infrequent reference to incentives/motivators is consistent with the stakeholders' reported uncertainties around their accountability for undertaking novel data generation, facilitating novel conversations, building new tools, and so forth.

The next most common code co-occurrence was between "Barriers to Generating and Using Data" and either "Roles in Information Sharing" or "Roles in Information Use." This linkage is likely explained by respondent focus on describing specific challenges associated with the effective and efficient use and sharing of available information on AEs as they relate to adjuvant therapy. The fact that the code "Roles in Information Generation" was not equally prevalent in co-occurrence with "Barriers" is likely a result of the fact that very few stakeholders in this study described themselves as information generators (drug developers were most likely to characterize their role as data generators). It is interesting to note that within the drug development sector responses, there were numerous comments around barriers to generating novel data of relevance for characterizing AEs in adjuvant therapy. Yet the barriers cited by drug developers in this context were not routinely cited (if at all) by any of the other stakeholder groups in this study. Given the number of stakeholders that *utilize* the data generated by the drug development sector, this disparity could be symptomatic of a systemic gap in awareness around inherent challenges in generating new data and could signal the need for greater communication of these challenges across the stakeholder community.

**Summary and Application of Results**

This chapter provides novel insights into differential roles, perceived challenges, and proposed future action across the five stakeholder groups engaged in this study. As described above, each of these stakeholders holds a unique role in the ecosystem of effort associated with supporting patients on adjuvant therapy. Many of the future needs and challenges are aligned (e.g., need for greater engagement of patient preference in care decisions), whereas others were noted by only one or two sectors (e.g., need for novel nonclinical models to develop safety biomarkers for AEs). The perspectives reported in this chapter are anticipated to serve as an

important resource for those seeking to understand broad role differentials across the landscape and/or those seeking to build alliances on areas of mutual interest. A comprehensive discussion of cross-stakeholder challenges and opportunities, as well as priority areas for future action, is provided in the thematic analysis conducted in Chapter 5.

# CHAPTER 5: CROSS-STAKEHOLDER RESULTS AND DISCUSSION—USE OF THEMATIC ANALYSIS TO IDENTIFY OPPORTUNITIES FOR CHANGE

## Overview

This chapter evaluates cross-stakeholder alignment in recommendations and challenges regarding the use of AE information to improve cancer patient care (study sub-aims 3 and 4). The analysis complements the intra-stakeholder summaries in Chapter 4 with a comparative assessment of stakeholder views on systems-level trends, needs, accountabilities, and opportunities. A cross-stakeholder evaluation approach was chosen in support of the study's objective of identifying *systemic opportunities* for improvement.

The respondent perspectives synthesized in Chapter 4, and an inductive approach, were used to build cross-sectional themes relating to systemic challenges in the adjuvant therapy setting. In the discussion below, each of these themes is summarized with respect to those key messages that span across the stakeholders. To achieve the study goal of defining *novel* opportunities to realize systemic change, these syntheses are also compared with ongoing and proposed initiatives as described in Chapters 1 and 2 of this study**.** The resultant analysis reveals a previously unrecognized systemic gap. This novel finding is incorporated into a new conceptual model for the effective integration of AE information to improve cancer patient care and serves as the basis for the Plan for Change included here as Chapter 6.

## Aligning Stakeholder Responses Against Common Themes

After thorough and inclusive review of the stakeholder-specific perspectives on roles, current challenges, and future needs (Chapter 4), four inductive themes were developed. The application of inductive logic in qualitative research is characterized by the development of organizing themes and categories based upon a researcher's review of open-ended responses from interview participants (Creswell, 2014). Inductive logic approaches also recognize the use of these themes to build novel theories and models.

The following themes comprehensively represent the feedback captured in Chapter 4:

- **Information Resources.** Stakeholder discussion of perceived data/knowledge needs and opportunities relating to the development or use of adjuvant therapy.
- **Integration and Implementation.** Stakeholder discussion of perceived gaps and opportunities for improved use or synthesis of available information to guide the design, evaluation, or delivery of adjuvant therapy.
- **Value Systems and Culture.** Stakeholder discussion of desired changes in cultural and financial value models that would beneficially impact adjuvant therapy development and delivery.
- **Alignment and Ownership.** Stakeholder perspectives on the incentives, drivers, and coordination necessary for supporting proposed changes in the design or use of adjuvant therapy that would benefit cancer patient outcomes.

Table 11 illustrates the thematic alignment of *all* of the current challenges (C) and future opportunities/needs (O) identified in bold text in Chapter 4, along with syntheses of the accountability/ownership discussions.

**TABLE 11: Summary results: synthesis of stakeholder perspectives on alignment, challenges, and future opportunities**

| Stakeholder | Information Resources | Integration and Implementation | Value Systems and Culture | Alignment and Ownership |
|---|---|---|---|---|
| **Drug Development** | **C:** Difficult to replicate the timescale of treatment<br>**C:** Difficulties in measuring and/or detecting relevant safety endpoints<br>**C:** New metrics on patient experience lack standardized use | **O:** Increase connectivity between clinical and nonclinical research teams within a given pharmaceutical company<br>**O:** Improve approaches to data generation and sharing around safety across companies and researchers<br>**O:** Better engage the "patient perspective" | **C:** Regulatory data generation requirements focus on efficacy more than chronic safety for oncologic therapies<br>**O:** Promote and support a culture shift in drug development<br>**O:** Link financial incentives to reduced AE profiles in adjuvants | Uncertainty around what groups or forces would drive both the positive and negative pressures (including regulatory or financial) necessary to generate new approaches for reducing the impact of AEs associated with adjuvant therapy |
| **Regulatory** | **C:** Data to inform decisions are variable in their relevance and availability<br>**O:** Improve/develop better metrics for assessing "burden of treatment"<br>**O:** Enhance public access to clinical data | **C:** Regulatory approval process for adjuvant cancer therapy requires a difficult balance of weighing future risks against future benefits<br>**O:** Improve communication to patients | **O:** Re-evaluate societal values regarding risk:benefit trade-offs in cancer therapy | Potential to recalibrate societal expectations for "acceptable" with respect to a burden of treatment for adjuvant therapy was posed as a critical future discussion point, but with few details as to who should be accountable for furthering such discussions |

| | | | | |
|---|---|---|---|---|
| **Clinical** | **C:** Insufficient information on some adjuvant-related AEs<br>**O:** Leverage standard-of-care settings to generate meaningful information on PROs and outcomes<br>**O:** Expedite access to data from clinical trials | **C:** Difficult to maintain currency with available information<br>**C:** Integrating information is complex<br>**O:** Build evidence-based guidelines for managing AEs<br>**O:** Enhance coordination between oncologists and other medical fields via raised awareness of shared issues<br>**O:** Create robust tools to allow clinicians and their patients to better understand risk:benefit trade-offs | **O:** Reduce the cost of care | Identified need for systemic change in the collection, use, and dissemination of AE information for adjuvant care<br>Accountability for change includes many stakeholder groups but also significant challenges around feasible alignment and incentives to work collaboratively |
| **Patient Advocate** | **C:** Insufficient therapeutic options<br>**C:** Lack of accessible and understandable sources of information<br>**C:** Need more research on long-term effects of treatment<br>**C:** Need more tailored information to know what is relevant for specific patients | **O:** Clinician-patient relationships should be partnerships that reflect greater mutual understanding of options and preferences | **C:** Focus on treating symptoms and not the patient<br>**C:** Patients' unwillingness to take ownership of their own care<br>**O:** Patients and clinicians should more openly confront issues around mortality<br>**O:** U.S. healthcare system should be more efficient and less expensive | Change should be pursued by many groups including patients, drug companies, clinicians, and patient navigators.<br>Resourcing and incentives to systematically support future efforts are highly limited and from uncertain sources |

| | | | | |
|---|---|---|---|---|
| **Payer** | **C:** Patient awareness of the impact of nonadherence is inadequate<br>**C:** Data relating to treatment options and care pathways are complex and rapidly changing<br>**O:** Enhance the systematic capture of patients' experience of QoL when evaluating quality measures associated with insurance coverage<br>**O:** Provide more frequent access to clinical information (24/7) so that minor problems do not become major ones | **C:** Healthcare plans are limited in their ability to be nimble and personalized<br>**C:** The use of datasets held by payers to improve future care has significant limitations<br>**O:** Improve support for chronic AEs associated with therapy<br>**O:** Enhance data sharing across plan participants and with insight from the clinical community<br>**O:** Adopt new payment models (such as the OCM and the PCMH model) as new standards | **C:** Patients on adjuvant therapy are a distinct subcategory of cancer patients with respect to balancing treatment and outcomes<br>**C:** Cost of drugs negatively impacts patient's quality of care and adherence<br>**O:** Reduce the cost of drugs | Self-described implementers of information generated by others (e.g., study data, pricing data, healthcare usage data, etc.)<br>Accountability for generation of new treatment approaches or healthcare practices outside of purview<br>Accountability for new healthcare models and using internal data located within individual payer systems |

AE, adverse event; C, challenge; O, opportunity; PCMH, Patient-Centered Medical Home; PRO, patient-reported outcome; QoL, quality of life.

The discussion that follows here provides a broad synthesis of the scope of recommendations within each of the four thematic areas and a high-level comparison of these recommendations with the findings in Chapters 1 and 2.

### *Theme 1: Information Resources*

Challenges associated with the development of and access to patient and adjuvant treatment-relevant data sets were among the most pervasive themes across all stakeholders. Most

stakeholders responded by citing data-related challenges or opportunities most relevant to their specific roles (see Chapter 4), although areas of overlap were not uncommon. Perhaps most predominant was a call to develop data that reflect "real-world" patient scenarios in the adjuvant setting, including considerations of long-term effects of treatment and the impact of patient comorbidities and polypharmacy. The prevalence of this recommendation stands in stark contrast to the far less common acknowledgment of technological and logistical challenges associated with collecting such information.[12] The need for more consistent, rigorous, and accessible data reflecting PRO measures and calls for more rapid and extensive access to clinical trial data of relevance to adjuvants were also broadly recommended.

Although Chapters 1 and 2 are not limited to the adjuvant treatment arena specifically, the future needs identified in these chapters directly mirror the above KII-derived perspectives with respect to information resources. For example, Chapter 2 concludes that "Future initiatives seeking to provide integrated information to patients and clinicians relating to therapeutic choice in cancer settings would benefit from incorporation of AE data of greater relevance to the 'real-world' patient experience (i.e., 'more patient-relevant information')." It is important to note that, as described in Chapters 1 and 2, numerous ongoing efforts are seeking to address these gaps via investment of time, funding, and strategy. While the breadth and depth of feedback from the respondents suggests that current efforts are in some way (or many ways) failing to hit their mark, there can be no doubt that this thematic area is under active development and evaluation.

[12]Per Chapter 4, the drug development sector develops a significant majority of information on treatment-related AEs for adjuvants. However, those in the drug development sector also focused heavily on the scientific and logistical challenges associated with collecting data of relevance for some of the additional endpoints/scenarios recommended by many of the stakeholder groups. The drug development sector was also far more likely to discuss challenges associated with data generation than any other sector.

### *Theme 2: Integration and Implementation*

This thematic area captures multi-stakeholder struggles in combining complex, rapidly changing, and sometimes disparately constructed data sources to inform decision making or support information sharing. Integration and implementation are captured as a single thematic area, as discussions around a stakeholder's ability to implement action were inextricably linked with discussions around processes for integrating information, resources, and preferences.

To this end, many stakeholders specifically cited the need for improved tools and/or methodologies that would coalesce data on treatment efficacy, toxicity, cost, and impact on patient QoL in a way that would inform action. Although the context of use for such approaches varied depending on the stakeholder's role (e.g., regulatory, payer, clinician, patient), the call for innovation was consistent. It is notable that not all stakeholders called for literal "tools." However, each of the stakeholder groups in this study identified needs for more interdisciplinary approaches to informing care-related decisions and therapy development for adjuvants. A need for these types of integrative tools and approaches was also highlighted in Chapter 1 of this study. Chapter 1 includes a detailed discussion of the strengths and limitations of contemporary value frameworks that seek to address exactly these needs (Table 1).

Other commonly cited challenges included technical challenges (how to get information into comparable formats, templates, and algorithms), bandwidth challenges (how to find the time to maintain currency with evolving data and best practices), and privacy/intellectual property challenges (limitations on sharing of data across groups because of potential to violate privacy or intellectual property rights). These challenges were observed to inhibit stakeholders' ability to make optimal decisions, compare and contrast information sources, and/or innovate care

delivery. The majority of these challenges and limitations were also reported in Chapters 1 and 2 of this study and are, to varying degrees, the subject of ongoing initiatives.

Also of note was a call to more actively elicit patient preferences in making decisions around treatment or supportive care in the adjuvant therapy setting. Detailed recommendations as to how to calibrate treatment against a specific set of patient preferences were not offered. Interestingly, many of the stakeholder groups specifically cited challenges associated with having the *time*, *resources*, or *expertise* to facilitate the collection and integration of such preferences. As discussed in Chapter 1, the effective consideration of patient preference is a standing tenet of the "patient-centered care" philosophy. The stakeholder perspectives offered here not only provide support for the importance of these considerations, but they also demonstrate evidence of the need for continued effort to effectively realize this goal in practice.

### *Theme 3: Value Systems and Culture*

This thematic area addresses the stakeholder calls for changes in cultural and financial value models that could beneficially impact adjuvant therapy development and delivery. The topics of cultural values and finance are grouped together because recommendations in this arena shared a focus on modulating societal conversations and expectations.[13] Specifically, these discussions relate to proposed shifts in cultural expectations, social and financial structures, and/or personal versus societal "willingness to pay" for modified risk:benefit trade-offs.

Many of the stakeholder groups identified a need to actively reconsider what they perceive to be the current societal "set-point" for an acceptable balance of risks versus benefits in the adjuvant therapy setting. The impact of a modified set-point was envisioned differently by

[13]Specific drug pricing issues, options, and alternatives were generally considered to be beyond the scope of this study. However, they are addressed here as they relate to overall access to care and reimbursement via payers.

different stakeholders. For example, regulators envisioned that such discussion could lead to altered future regulatory standards with novel mandates to lower toxicities associated with adjuvants relative to their potential preventative benefits. Some drug developers envisioned that a cultural shift in risk:benefit expectations could lead to novel financial demand or societal pressures driving the private sector to produce/support adjuvants with diminished toxicity profiles. Other stakeholders envisioned cultural shifts leading to more frequent and candid doctor-patient, clinician-payer, and patient-payer conversations around quality and quantity of life trade-offs (including the financial implications of such). Across all stakeholders, there was significant uncertainty as to how and where such culturally impactful conversations might be mediated.

The cost of care, and payment models for supporting it, was also broadly cited as an issue to be tackled at a macro level. Some stakeholders asserted that the cost of treatment (particularly drug costs) is a barrier to treatment access and/or adherence for some patients. Stakeholders also commonly observed that traditional insurance and reimbursement models may be misaligned with the extended support needs of patients receiving or completing adjuvant therapy. As described in Chapter 4, several novel payment bundling models (e.g., OCM) are being explored, but cross-stakeholder calls for continued and expanded innovation in this arena were consistent in this study.

As described in Chapter 1, the recent initiation of regulatory programs like the Patient-Centered Drug Design effort at FDA, the launch of the federally mandated Patient-Centered Outcomes Research Institute (PCORI), private and clinical sector funding and focus on creation of shared decision-making models, the increasing prevalence of PRO data collection, and the innovation of payer models all suggest a broadening cross-sector discussion on the issues at the

heart of this thematic area. However, much like the prior three thematic areas, stakeholder feedback suggests that progress is both insufficient and fragmented.

### *Theme 4: Alignment and Ownership*

This thematic area conveys perspectives on the incentives, alignments, and accountabilities necessary to meet the challenges noted in Themes 1–3.

As described above, the cross-stakeholder feedback synthesized in these first three themes is largely valuable for its nuancing and reinforcement of previously established systemic challenges.[14] In contrast, a synthesis of stakeholder views with respect to this theme reveals a critical and previously unrecognized aspect: *The challenge of using AE information to more effectively inform cancer patient care is a challenge that* ***lacks clear ownership***. In various ways, all stakeholders questioned the assignment of responsibility and resourcing for both the collective and individual challenges described in this study. Per Chapter 4, many did discuss their *sector-specific* accountabilities. Yet they also acknowledged that successful realization of their broader objectives would require a currently nonexistent level of interactivity across stakeholder groups and focal areas. With respect to their proposed future actions, stakeholders alluded to the need for literal or figurative connectivity of content and effort across currently distinct silos. Consistently, they observed the absence of a clear framework to link these siloed efforts and philosophies. Many noted that these discontinuities and unclear accountabilities directly impacted resourcing. They pointed to the absence of either incentives or mandates to justify novel resource allocation for many of the cross-sector challenges identified in Themes 1–

[14]Although many of themes in Chapter 5 were previously reported, it is notable that the intra-stakeholder analysis conducted in Chapter 4 revealed important and novel details around sector-specific roles, limitations, and objectives. The intra-stakeholder roles and drivers identified will provide useful guideposts for focusing future action and building like-minded constituencies.

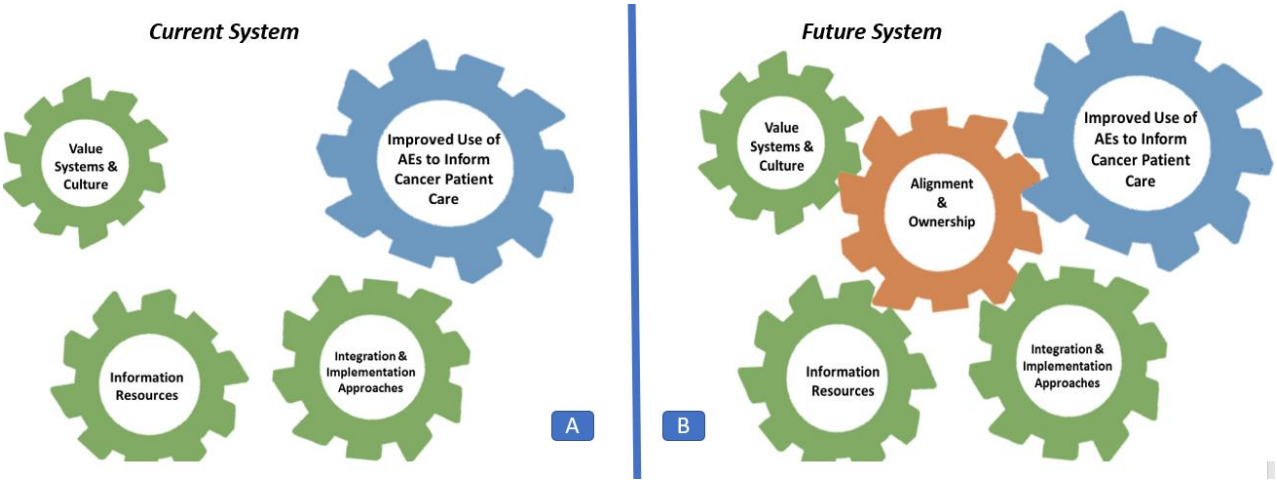
3 above. This theme was also observable in the code co-occurrence and code-differential analysis summary reported in Chapter 4, in which very few stakeholders commented on motivators to generating or using information and instead focused on the barriers.

### A New Conceptual Model and Next Steps

The analysis above confirms three previously reported areas of strategic challenge (Themes 1–3) and highlights a previously unrecognized challenge associated with the modified use of AE information to improve cancer patient care (Theme 4). A novel conceptual model (Figure 12) was developed to illustrate the current and potential future linkages between these four thematic areas and the defined systemic goal.

As illustrated in Field A, and evidenced by the stakeholder-derived feedback, the development of novel information resources and implementation and integration approaches are often proximate, but rarely directly connected. Furthermore, discussions around value systems and culture appear to operate in a space that is even further disconnected from the latter two fields. As described by the stakeholders in this study, all three areas illustrated in green in Figure 12 lack a defined linkage to each other and the broader goals of improving the use of AEs to inform cancer patient care. Field B illustrates how future incorporation of the stakeholder-reported gap in defined alignment and ownership could promote enhanced progress toward the stated systemic goals for cancer care. Simply stated, to turn the crank in this system, a novel focus on alignment and ownership must be pursued.

**FIGURE 12: Original conceptual model demonstrating the integral role of defined alignment and ownership in facilitating improved use of AEs to inform cancer patient care**




As illustrated in Field A, initiatives relating to information resources, integration/ implementation approaches, and value systems/culture considerations currently operate in a siloed manner without connectivity to other components aligned with achieving a broad goal of improved use of AEs. As illustrated in Field B, the inclusion of defined alignment and ownership provides the connectivity necessary to achieve the desired system goals.

To the investigator's knowledge, most prior publications on this topic have focused on the green components illustrated in Figure 12 with respect to proposed future action. As such, a future initiative to address issues around alignment and ownership is anticipated to provide a novel opportunity for systemic progress. A specific Plan for Change to address this opportunity is described in Chapter 6 of this study.

# CHAPTER 6: PLAN FOR CHANGE

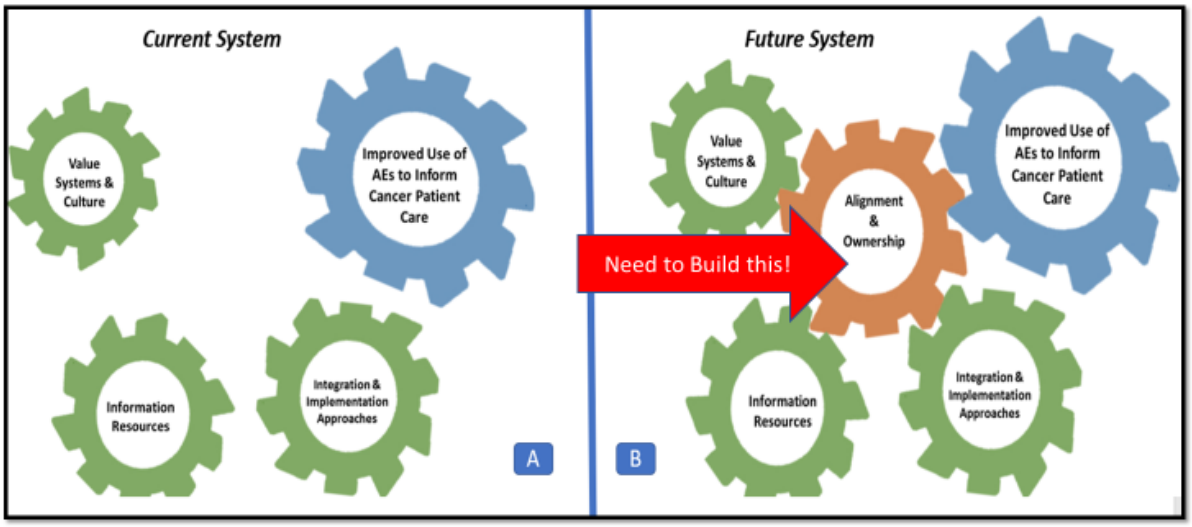
> The practical challenge for a wicked problem is the tendency for the effort to become fragmented and fail.
>
> —Conklin, Basadur, & VanPatter (2007)

## Overview

In this study, stakeholder groups (patient advocates, clinicians, regulators, drug developers, and payers) identified a number of specific inter and intra-stakeholder opportunities to improve the patient and societal benefit of the generation, dissemination, or use of adjuvant treatment-related AE information (Table 11). These opportunities fell into the following major areas: Information Resources (e.g., approaches to generate or capture adjuvant-related AE information), Integration and Implementation Approaches (e.g., tools for or practices in which AE information is incorporated into decisions on drug design, regulatory approval, clinical care, supportive care, insurance coverage, patient-level treatment choices, etc.), and Value Systems and Culture (e.g., considerations of societal standards, willingness to pay, and risk:benefit tolerance associated with the delivery of adjuvant therapy and the support for patients who are/have received it). As illustrated in Figure 13, this study also revealed an additional systemic deficit. Ongoing efforts to address Information Resources, Integration and Implementation Approaches, and Value Systems and Culture lack the connectivity (e.g., alignment and ownership) necessary for them to synergistically achieve their collective objectives of improving patient QoL and health outcomes via eliminating or reducing adjuvant therapy-related AEs. To this end, the stakeholders uniformly highlighted the deficit of *a lack of ownership* for the cross-sector and cross-

disciplinary issues associated with defining, managing, and/or reducing the impacts of adjuvant treatment-related AEs.

**FIGURE 13: Conceptual model driving the Plan for Change**




This chapter proposes an actionable plan to address this systemic limitation via construction of a new epicenter of "Alignment and Ownership." The proposal is based upon published approaches for similar multicomponent public health challenges, published strategies for affecting broad systemic change, and the investigator's 20 years of experience in coordinating and leading multisector collaborative initiatives. The stakeholders anticipated to engage in or be impacted by the proposed Plan for Change include those involved with drug design, regulatory standards, clinical care, healthcare insurance coverage, treatment decision making, supportive care services, and of course, patients and their families; however, other stakeholder groups may also find value in involvement.

## A Difficult Problem, But Not a Novel Construct

Before building specific action plans to address this challenge, it is first useful to consider the broader literature on the strategic limitation of unclear alignment and ownership of a societal

problem. Diffuse and/or overlapping accountabilities are common hurdles to the resolution of those societal challenges sometimes referred to as "wicked problems." Wicked problems, such as those identified in Chapter 5 of this study, are characterized by "multiple, overlapping, interconnected subsets of problems that cut across multiple policy domains… across hierarchy and authority structures within and between organizations" (Weber & Khademian, 2014). As such, the literature on wicked problems *and their resolution* is used here as a launching point for the development of an approach for forward action.

The term "wicked problem" was introduced into the urban planning literature in 1973 as a means of describing societal challenges that defy linear planning and problem resolution approaches. According to the seminal article on this topic, such issues are characterized by the complexity of "locating problems (finding where in the complex causal networks the trouble really lies)… [and] identifying the actions that might effectively narrow the gap between what-is and what-ought-to-be" (Rittel & Webber, 1973). Wicked problems touch a diverse and often divergent set of stakeholders and vested interests. In wicked problems, such as the one that is the focus of this study, stakeholders internalize different views of the overall problem(s) and often struggle to define coordinated interventions and resourcing toward resolution (Crowley & Head, 2017; Head & Alford, 2015; Innes & Booher, 2016; Weber & Khademian, 2014). In sum, the alignment between the types of challenges that surfaced in this study and the classical definition of "wicked problems" is very strong.

The theoretical and applied literature on approaches for addressing the hurdle of unclear "accountability and alignment" in the context of wicked problems is extensive. This literature describes a diversity of policy, management, economic, sociobehavioral, and governance approaches and considerations. An unstructured survey of the literature was conducted to

identify the most prominent considerations of relevance to this study. These findings and their relevance to the construct of an actionable plan to improve the use of AEs in informing cancer patient care follow below.

### *Cross-Sector/Cross-Disciplinary Initiatives Are Essential for Addressing Wicked Problems But Are Also Inherently Challenging*

A call for cross-sector and cross-disciplinary networks or collaboratives to build alignment in addressing wicked problems resounds across the literature (Head & Alford, 2015; Hearld, Bleser, Alexander, & Wolf, 2016; Norris, O'Rourke, Mayer, & Halvorsen, 2016; Van Tulder & Keen, 2018; Waddock, Meszoely, Waddell, & Dentoni, 2015). Such networks are, not surprisingly, identified as critical opportunities to better define cross-stakeholder problems, build agreement on potential solutions, and promote shared resourcing and implementation.

As one researcher noted, "Collaboratives will be more attractive relative to independent organizations or markets when the degree of ambiguity regarding the intervention(s)/solution(s) is high (e.g., multiple technologies or disparate industry inputs required, complex sequence of actions needed)" (Hearld et al., 2016). Because the issues at the heart of this study are inherently ambiguous, cross-sectoral, and cross-disciplinary, the creation of a novel networking opportunity that links all stakeholders initially appears as a ripe opportunity. At present, there is no consolidated forum or nexus for interaction for stakeholders to address the breadth of issues identified in Table 11.

However, the investigator's experience in designing and managing cross-sector consortia—and the published literature—provides reason for caution. An effort to coalesce all of the stakeholders and ongoing efforts into a unified and hierarchically managed collaborative would surely be infeasible, unwieldy, impractical, and as likely to slow progress as expedite it. As one

practitioner warned, “Don’t collaborate unless you have to!” (Huxham & Vangen, 2006). The specific recommendations to follow here will thus focus on the promotion of novel alignment and interaction across the stakeholders in ways that do not involve top-down command and control or forced interactions across stakeholders.

### *Defined Facilitation and Collaborative Capacity Building Roles Are Essential*

Many publications identified the critical importance of skilled and vested staff to facilitate interactions across stakeholders that are (or should be) engaged in tackling wicked problems (Bryson, Ackermann, & Eden, 2016; Head & Alford, 2015; Weber & Khademian, 2014). Typically, these individuals were envisioned as neutral conveners (not top-down directors) and “collaborative capacity builders” with expertise in problem formulation, team building, facilitation, communications, and administration. Adaptive leadership skills (e.g., building on the efforts, interests, and skills of subsidiary teams to inform the overall leadership/management strategy) were cited as key attributes in this setting (Northouse, 2016). Opportunities to leverage effective capacity builders for both top-down and more loosely interconnected cross-stakeholder efforts were noted.

To address the unmet needs around alignment and accountability identified in this study, the initiation of some type of collaborative capacity building staff (or facilitator) role will likely also be important. The investigator’s 20 years of experience in consortia management/coordination also supports the essentiality of these roles. The specific Plan for Change below clearly defines the scope and accountability for facilitation/capacity building roles at multiple stages of the proposed project process.

### *There Is No Perfect Approach for Translating Collaborative Interactions Into Systemic Change*

Although a systematic review is beyond the scope of this study, a preliminary review of the literature suggests that there is no consensus on ideal approaches for translating multi-stakeholder interactions into actionable initiatives to address wicked problems. Among the many concepts proposed were recommendations to convene advisory team meetings to define and coalesce around efforts with shared goals, to identify incentives and reward structures to promote continued collaborative engagement from across diverse stakeholders, to create platforms for pooling budgets, and to establish opportunities for iterative problem formulation efforts that reflect the fluidity of issues, resources, and information associated with wicked problems (Bryson et al., 2016; Innes & Booher, 2016; Norris et al., 2016). Some offered suggestions for specific methodologies to facilitate these objectives. For example, one group proposed that Theory of Change[15] models could be developed as a resource to promote "dialogue about how and why proposed actions will generate desired outcomes… and greater confidence in attributing subsequent changes to previous specified actions" (Van Tulder & Keen, 2018). These authors noted both the potential and challenges in applying this relatively linear approach (a + b =c) to highly complex systems like those inherent in cross-stakeholder wicked problems. Others described the use of stakeholder mapping ("collaborative goal mapping") to create visual maps to illustrate how stakeholders view their perceived roles, audiences for their efforts, and their linkages with both other stakeholders and the broader systemic objectives (Bryson et al., 2016). The lack of consensus around best practices could convey a failure to conduct data-driven

[15]Theory of Change models are used to build collective understanding of the way in which different interventions and initiatives are predicted to impact the overall systemic objective (Funnell & Rogers, 2011).

evaluations of the effectiveness of different approaches, insufficient collective experience in exploring different methodologies, and/or a practical reality that approach selection is inherently situational (and perhaps there is no "best" practice).

Collectively, this literature, as well as the experience of the investigator, provides support for construction of a plan for change that can be nimble with respect to the promotion of interactions across stakeholders. The specific plan below will describe a phased approach that incorporates the potential for modulating objectives and opportunities.

### *Resources to House Collaboratives, Hire Capacity Builders, and Execute Cross-Stakeholder Efforts Are Critical But Elusive*

Ironically, and unfortunately, the same literature that identifies resource allocation uncertainties as a critical challenge in addressing wicked problems broadly fails to adequately identify or acknowledge gaps in resources for executing the types of remedial approaches described above. The need to procure resources to fund a capacity builder or facilitate a "stakeholder mapping" meeting is woefully under-recognized in these papers. Similarly, these publications tend to omit discussion of practical approaches for building resourcing for future efforts.

To improve alignment and accountability with respect to the use of AEs in cancer patient care, it will be essential to not only propose novel interactive forums but also to identify sustainable resourcing for their execution. The proposal that follows below offers a strategic approach to address this critical component.

The following Plan for Change will build on the specific recommendations in Chapter 5 and incorporate the following elements:

- Creation of novel opportunities to enhance ownership of the systematic challenges and promote cross-stakeholder alignment, interaction and synergy;
- Identification of individuals or organizations with resources and expertise to build collaborative capacity across stakeholders;
- A flexible, fluid, and evolutionary approach to selecting and executing cross-stakeholder activities and areas of strategic focus for inter- and intra-stakeholder tactical efforts; and
- A defined resourcing and incentives strategy to support the three components above.

**Initiating Focused Change**

The following plan for action seeks to address this wicked problem based on lessons learned from the wicked problem literature (see above), the investigator's 20 years of experience in designing and facilitating collaborative programs, accepted practices for program design and evaluation, other collaborative models applied in the cancer space such as the White House Cancer Moonshot initiative, and a published framework designed to help create environmental conditions that are favorable for systemic change (Foster-Fishman & Watson, 2012; White House, 2016; Wholey, Hatry, & Newcomer, 2010).

The specific change framework chosen to help guide this plan for action is the ABLe Change Framework (Foster-Fishman & Watson, 2012). The ABLe Change Framework is a model developed to inform the design and implementation of system or community change efforts. While it is not specific to wicked problems, the model was selected for its specific focus on *facilitating the environment for* change (referred to as "below the line" focal points by the model's authors), not just the resourcing of specific tasks. The ABLe Change Framework describes four areas that should be addressed when readying an environment for change:

readiness, capacity, diffusion, and sustainability. The Plan for Change that follows here incorporates each of these elements as summarized in Table 12 and further described in detail below.

**TABLE 12: Application of selected ABLe Change Framework elements to the proposed Plan for Change**

| **ABLe Change Framework factors for readying the environment for change** | **Implementation in this Plan for Change** |
|---|---|
| **Readiness:** This factor emphasizes the importance of working with system actors to promote the belief that "*change is necessary, feasible, and desirable*." | In this plan, a leadership team will serve this role by conveying the overall mission and encouraging other stakeholders to believe in its potential to be realized successfully through collaborative effort. This group will communicate specific strategic objectives that may benefit from collective effort. (Steps 1 and 2) |
| **Capacity:** This factor relates to improving our understanding of how and which problems "*emerge from current system characteristics*." | In this plan, a set of defined opportunities and challenge areas will be agreed upon and published for access by stakeholders, as will opportunities to better understand how these problems relate to the overall system of information, accountability, and resourcing. (Step 3) |
| **Diffusion:** This factor relates to the **"***promoting broad scale awareness of change effort across system actors***"** and encouraging stakeholders to take new action. | In this plan, a series of communication efforts and incentives will be defined to create new systems of stakeholders and incentivize novel action. (Steps 4 and 5) |
| **Sustainability:** This factor relates to maintaining "policies, practices, and changes" wrought by an effort. | This plan contains approaches to address sustainability and resourcing. The plan defines and encourages changes that are tactical and achievable as discrete programmatic initiatives and incorporates approaches to evaluating the programmatic effectiveness. (Steps 5 and 6)<br>However, it also incorporates efforts to raise awareness of issues and opportunities that would otherwise fall between the cracks of accountability and resources via the actions of the leadership team. (Step 4) |

The investigator proposes to launch this strategic Plan for Change via her role as executive director of the Health and Environmental Sciences Institute (HESI). HESI is an international, nonprofit organization that serves as a neutral facilitator of scientific collaborations across

academe, government, clinical medicine, nongovernmental organizations, and industry and has decades of history in international initiatives to enhance the safety and efficacy of medicines. The organization has been growing its activities in the oncologic therapy safety arena under the investigator's leadership and has the support of the organization's Board of Trustees to continue to do so.

**Proposed Implementation Strategy**

The strategy below consists of six major steps as follows:

- **Step 1: Assign the Name and Mission.** This step involves the creation of an overall organizational mission to guide the collaborative and creation of a name for the proposed program of work.
- **Step 2: Form the Leadership Team.** This step involves identifying and engaging a leadership team that is motivated to contribute time and resources to the collaborative's mission.
- **Step 3: Define Systemic Needs.** This step requires the elucidation of both tactical and strategic challenge areas/needs that must be addressed to realize the mission.
- **Step 4: Initiate Leadership Team Outreach.** This step will engage the leadership team in catalyzing the mission through their actions as individual entities and through combined efforts as a collective team.
- **Step 5: Involve Other Stakeholders.** This step engages a broad base of stakeholders to contribute to addressing the challenges identified at Step 3 and to proactively align their roles with the overall mission.
- **Step 6: Evaluate the Program.** This step, to be conducted as the program evolves, is intended to inform refinements to the design and implementation strategy.

The specific implementation of these steps follows below.

### *Step 1: Assign the Name and Mission*

As a means of grounding the strategy and addressing the ABLe Change Framework "Readiness" factor, the initiative will be given a *proposed* name and mission statement: the **A**djuvant **C**are **T**ogether (**ACTogether**) effort. ACTogether is envisioned as a new "community of commitment"[16] that will focus awareness and resources on the challenging issues identified in this study:

> The mission of ACTogether is to improve quality of life for patients who are receiving or have received adjuvant therapy by enhancing our ability to understand, address, support, and convey benefits and risks of alternative approaches.

The mission statement is anticipated to play a critical role in this strategy as it will serve as a common currency to bridge otherwise disconnected teams and initiatives. (*Note:* As the mission statement is only "proposed" at Step 1, it is anticipated that once the leadership team is formed they will further discuss and potentially refine/modify the mission statement as noted in Step 3 below. The development of a draft mission statement/name before convening a leadership team is proposed as a means to facilitate outreach to potential leadership team members.)

### *Step 2: Form the Leadership Team*

As identified in the wicked framework literature and the ABLe Change Framework, a team of collaborative capacity builders must be formed in order to tackle otherwise "unowned issues" and bring readiness, resources, connectivity and catalytic energy to systemic change efforts

[16]The term "community of commitment" was initiated by Kofman and Senge in 1993 in reference to the need to build systems that foster learning and personal interaction across otherwise fragmented individuals and efforts (Kofman & Senge, 1993).

(Foster-Fishman & Watson, 2012; Weber & Khademian, 2014). This de novo leadership team will serve as the proactive facilitator, program evaluator, and leading voice for the ACTogether initiative. As noted above, the investigator and her organization, HESI, are expected to initiate formation of a leadership team. Populating the team with additional leaders (and maintaining HESI's organizational support for the investigator's efforts) will require a balance of strategy and pragmatism.

The leadership team should reflect the core strengths of the program: robust technical and reputational credibility, strong programmatic and strategic skills, operational flexibility, representation of the ACTogether stakeholder landscape, and a commitment to the ACTogether mission. Based on the professional experience of the investigator and recommendations from other business and government sector sources, an initial steering team of four to six individuals is proposed (Ohio Office of Budget and Management, n.d.; Wharton School of Business, 2009). Although there is some literature suggesting that steering teams should consider including representatives from all of a program's stakeholders, given the potentially huge stakeholder base and limited resources, it is proposed that the initial team be composed of leaders who in themselves span multiple stakeholder groups (HBR Staff, 2016).

For the ACTogether program, there is neither a top-down directive to mandate leadership participation nor is there stimulatory funding. As such, leadership team members will need to see value for their in-kind and financial resource support for the effort. Potential leadership team members are expected to be motivated to join because they both believe in the program mission *and* expect to realize an immediate or future benefit by stepping forward in a leadership capacity (Northouse, 2016). For example, organizations seeking to broaden or reinforce their perception as a community thought-leader in the cancer or patient care arena may choose to contribute in

this role. The reputational benefits (e.g., public relations value) of stepping forward on an "unowned" wicked problem may be enticing for some. Reputational benefits can bring returns such as new partnerships, increased engagement in ongoing efforts, enhanced credibility, and so forth. These reputational and thought-leadership benefits are of significant value to the HESI organization and will be used to justify resource allocation as a leadership team member. It is also possible that the investment of time, funds, and/or staff into leadership on the ACTogether problem could result in direct financial returns to a participating organization. For example, visibility as an ACTogether leadership team member may make that organization a stronger candidate to receive funding in areas within the ACTogether mission.

Additionally, organizations that have already invested in efforts related to the ACTogether mission may perceive value in the potential to better leverage these efforts by promoting a more connected and resourced system overall. For example, participation in ACTogether may allow stakeholders to demonstrate to funders that their investments are made more efficient by literal or topical connectivity with other efforts to drive improved systemwide outcomes.

Based on these criteria and the investigator's professional experience and contacts, the following organizations are anticipated to be potential candidates for leadership roles. (*Note:* This list is exemplary, not exhaustive. The organizations noted here have not made any defined commitments at this time.)

- **Health and Environmental Sciences Institute (HESI).** This organization is a nonprofit with decades of experience in facilitating collaborative science across stakeholders and has a growing strategic focus on cancer therapy safety issues. HESI participation brings a strong engagement of scientists from the pharmaceutical, regulatory, clinical, and research sectors. As noted above, HESI will commit to

providing initial staffing and financial resources to convene and facilitate the leadership team, launch and maintain the ACTogether website, and lead the initial metrics and evaluation process for ACTogether (further details on this at the end of the chapter).

- **Biden Cancer Initiative (BCI).** The BCI is a high-profile and recently founded nonprofit organization dedicated to serving a convening role on a broad range of cancer research and treatment issues in follow-on to the previous U.S. federal Cancer Moonshot program. HESI is a recognized partner of the BCI as of September 2018, and the investigator has strong points of contact within the BCI program staff and its advisory boards. A core component of the BCI mission is to serve as a high-visibility platform to elevate and catalyze the work of important, but less visible, initiatives. BCI's stakeholder base is very broad and includes patients, patient advocacy groups, government agencies and funders, payers, researchers, clinicians, and private industry.
- **Ellison Institute for Transformative Medicine.** The University of Southern California Lawrence J. Ellison Institute for Transformative Medicine is a leading research and clinical center that seeks to conduct research on cancer therapies, develop best practices in therapeutic treatment, and promote systemic change in cancer care to benefit patients. Leaders of the institute are active as senior advisors to the BCI and HESI organizations. The Ellison Institute's participation would bring active clinical and research expertise.
- **National Patient Advocate Foundation (NPAF).** This patient-focused nonprofit seeks to build and implement innovative policies and programs that recognize and

elevate patient perspectives and challenges across a broad range of health issues. Leaders in the NPAF are engaged as advisors on HESI's cancer therapy safety programs and in a variety of national cancer patient QoL initiatives.

- Additional leadership team members from the pharmaceutical sector (possibly from the PhRMA Foundation), clinical sector (e.g., ASCO), regulatory sector (possibly from the Oncology Center of Excellence at FDA), and payer sector may also be useful additions to the team, and their additions could be the subject of initial discussions with the stakeholders above. However, the broad scope of the initial leadership team above provides for an initial capture of all of these arenas and is thus anticipated to be a viable and manageable starting point for this new effort.

***Step 3: Define Systemic Needs***

In order to focus efforts within the ACTogether framework and better understand how and which problems "emerge from current system characteristics," a set of defined gaps and opportunities will serve as the focal point for a systemic call to action (Foster-Fishman & Watson, 2012). As a means of launching the ACTogether effort, and building upon the research conducted in this study, the stakeholder-derived challenges and opportunities identified in Chapters 4 and 5 (summarized in Table 11) will be used as a starting point (i.e., "ACTogether challenge areas"). As the HESI organization proposes to take the lead in launching this program, they are anticipated to commit financial resources for initial convening of the leadership team to discuss and build consensus on the challenge areas and draft mission (e.g., multiple web conferences and possibly one in-person meeting to facilitate reaching consensus).While agreement on the challenge areas will be important, the list is intended to be directional and not exhaustive. Refinements in the challenge areas are expected over time.

### *Step 4: Initiate Leadership Team Outreach*

A primary goal of the ACTogether leadership efforts is to promote the expansion, perpetuation, or initiation of activities that are responsive to the challenge areas. This step meets the ABLe Change Framework's recommendation to promote "broad scale awareness of the change effort across system actors" (Foster-Fishman & Watson, 2012). Leadership team members will be expected to pool resources (financial, staff, websites, social media accounts, etc.) to support communication, strategy, and networking efforts toward this objective. The efforts of the leadership team are expected to contribute to both direct changes (e.g., enaction of new research or programmatic work) and to the creation of an environment that is more aware of and conducive to making progress toward the ACTogether goals. A diagrammatic representation of the actions and impacts of Steps 4 and 5 follows here in Figures 14 and 15.

**FIGURE 14: Proposed system of interaction for ACTogether**

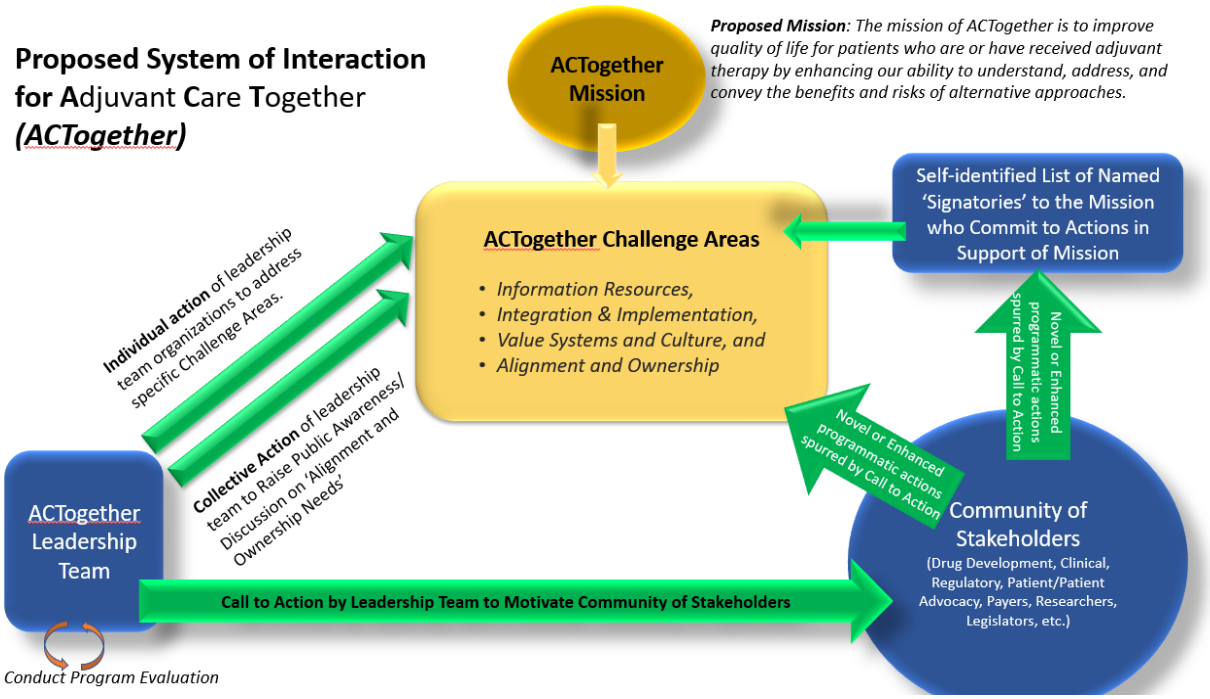
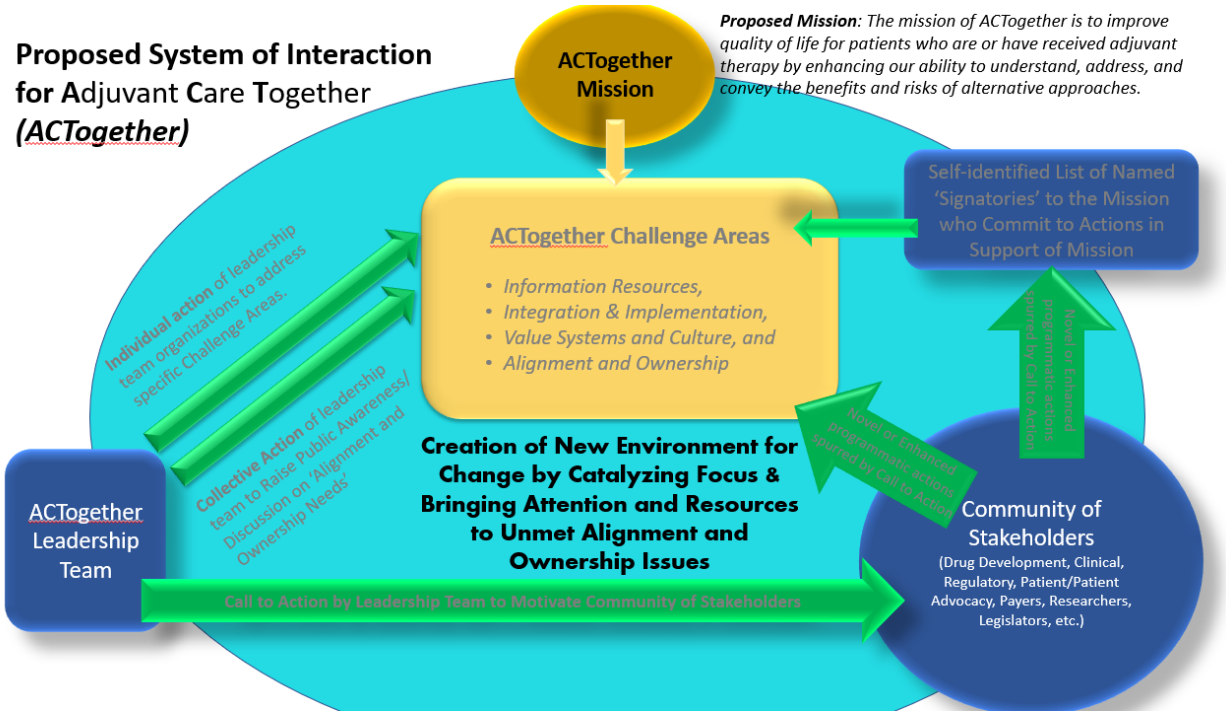


**FIGURE 15: Changes in overall environment resulting from ACTogether**




Having agreed upon the challenge areas, the leadership team will initiate its external activities as follows:

**Launch of the ACTogether web page.** This page/site will describe the mission, leadership team, and challenge areas and will be resourced and hosted by HESI.

**Publicize a "call to action" and recruit named supporters.** The leadership team will collectively design and execute a "call to action" to encourage other stakeholders to align their efforts with ACTogether challenge areas. This public "call to action" will define the need for and mission of ACTogether and call upon stakeholders to voluntarily align their current or planned efforts with the ACTogether challenge areas. Stakeholders will be encouraged to bring visibility to their efforts—and the overall ACTogether mission—by signing a noncontractual program commitment letter for 2019–2021. A sample of this commitment letter is included as Appendix G. Although this letter does not elicit binding commitments, nor does it commend enforcement

by the ACTogether leadership team, this model is anticipated to promote progress toward the ACTogether mission. Similar voluntary and unenforced commitment models have been used to great success in other initiatives in which binding commitments and enforcement would be programmatically stifling and economically infeasible. For example, the White House (2016) Cancer Moonshot achieved unfunded outcomes by calling on groups to make voluntary commitments to enhancing the pace of cancer research. Further, the Center for Open Science (https://cos.io/our-services/top-guidelines/) changed the practices of hundreds of scientific journals and researchers by asking signatories to make voluntary commitments to sharing scientific information, protocols, and so forth in compliance with the center's recommended guidelines. For more detailed discussion on why stakeholders might choose to participate in as signatories, see Step 5 below.

Publicizing the call to action could be achieved through a variety of mechanisms and may benefit from a multipronged approach. For example, a published commentary in a high-profile journal of relevance to the cancer community (e.g., *Journal of Clinical Oncology*) would raise visibility and create a resource that can be cited by others. This call to action should also be communicated via the proposed ACTogether website/web page, along with the social media and other communication platforms used by the leadership team members. This multicomponent outreach strategy is expected to be beneficial given the diverse stakeholder base (e.g., patients, advocacy groups, regulators, payers, clinicians, drug developers, academic researchers, funders, legislators, etc.) targeted by this initiative. The leadership team should periodically review and refine the alignment between their intended audiences and the outreach approaches that are undertaken. A discussion of a proposed metrics and evaluation approach is addressed in Step 6.

**Collectively execute strategies that promote progress in otherwise unowned issues (e.g., alignment and ownership issues identified in Table 11).** The challenges described in the "Alignment and Ownership" column in Table 11 will serve as the basis for novel collective action by the leadership team. These actions will be critical to the success of this program because they bring resources and visibility to issues that would otherwise fall "between the cracks." Per the ABLe Change Framework, providing support for such issues that would otherwise go unattended is critical to creating an environment in which change in sustainable (Foster-Fishman & Watson, 2012). Practically, the leadership team is not initially anticipated to have the funding or remit to actively resolve any of these issues. However, public discourse on these issues is so nascent that simply creating opportunities for stakeholders to provide perspectives and debate priorities is itself a meaningful forward step. For example, the leadership team may propose to convene stand-alone workshops or panel/symposium discussions at scientific conference (e.g., ASCO, American Association for Cancer Research, American Association for the Advancement of Science, etc) that focuses experts on issues such as the following:

- "What is an acceptable 'burden of treatment' for potentially curative adjuvant oncology therapies?"
- "Should regulatory systems ever re-evaluate societal risk versus benefit tolerances for adjuvant therapies and, if so, why and how?"
- "What incentives or information would encourage drug developers/researchers to design second-generation adjuvant therapies and what hurdles would disincentive it?"
- "Who is/should be/can be responsible for and proficient in collecting information on long-term patient outcomes following adjuvant therapy?"

- "Beyond data generation, who is responsible for data dissemination to different user groups and/or data conversion into formats that are understandable and/or useful for those groups?"

Funding for this effort might be contributed by the leadership or could be solicited as a grant from organizations such as PCORI, which offers "convening" grants for workshops. Similarly, these discussions could be elevated to the public domain via a series of published commentaries written by the leadership team and/or by invitation of guest authors to respond to questions or themes posed by the leadership team.

The goal of these efforts is to raise cross-stakeholder awareness of issues, structures, and needs that fall between traditional disciplinary, funding, and/or governance lines. The hope is that by promoting awareness, it may spur discussion of potential solutions and potentially encourage the commitment of new resources or launch of new collaborations. These efforts could also, over time, help change the landscape in which other efforts are undertaken, such that resource procurement for those efforts is less challenging (i.e., it may be easier to make the case for funding for any given program if the overall context of need is more clearly defined).

Leadership team members will be expected to pool resources (financial, staff, websites, social media accounts, etc.) to support communication, strategy, and networking efforts toward this objective.

**Each leadership team member will independently initiate and/or resource at least one new activity in support of one of the challenge areas.** A commitment to adopting one or more activities in support of the challenge areas will be defined as a prerequisite for membership on the leadership team. These tactical efforts will be essential to demonstrating leadership via action and will provide opportunities to realize near term (1-3 years) progress. The demonstration of

near term progress is an important component of maintaining collective interest in change efforts (Kotter, 2007) Examples of near-term 'wins' that might be pursued by the leadership team (and/or the broader stakeholder group to be engaged in Step 5) are described below. These are not exhaustive and are provided for illustrative purposes.

*In the area of 'information resources'*: A consortium could be launched to better define collaborative approaches for sharing adjuvant drug safety information generated by drug developers/other researchers and by aligning data collection with clear contexts for use of the information in safety decision-making. This effort could include collating data on AEs, models, or experimental approaches and in the near-term could be anticipated to generate novel shared learnings. *(Note: it is anticipated that the investigator's organization (HESI) may contribute (and elicit funding for) staff time and databases that will facilitate this effort.)*

Other achievable near-term actions could include the development of evidence-based case studies demonstrating similarities and differences in AE nature, scope, and frequency reports in clinical trials versus standard of care settings for specific adjuvant treatment scenarios, the engagement of pharmacies to collect data on prescription adjuvant use rates and adherence (as measured by prescription fulfillment), or the compilation of a public data repository to centralize published studies on benefits (or lack thereof) of 'wraparound' services in mitigating the impact of treatment-related AEs.

*In the area of 'integration and implementation'*: Near-term achievable approaches could include the initiation of a patient advocacy/pharma joint advisory group to develop actionable recommendations for integrating the 'patient perspective' in drug development. Patient-advocate and clinician led stakeholder teams might develop and implement a novel outreach and educational seminar series targeted at a broad range of audiences (e.g., research, regulatory,

clinical) to raise awareness of and elicit input on the assessment of 'burden of treatment' in the adjuvant setting.

*In the area of 'value systems and culture'*: Near-term actionable approaches could include development of a proposal to initiate an 'Adjuvant Safety and Efficacy' workstream within the existing FDA Oncology Center of Excellence. If such a proposal were adopted into the existing Oncology Center of Excellence, it could serve as a platform for facilitating novel regulatory conversations around risk:benefit and cultural values. The proposed AACR workshop series described above could also facilitate this objective in the near term. Other possibilities include the engagement of stakeholders not directly included in this study such as health economists/healthcare think tanks to develop case studies and build recommendations to better define the 'value' of AEs to patients, providers, payers, etc. in a way that promotes access to improved information and care.

Of course, there are endless additional tactical and strategic opportunities that might be pursued in both the short and longer terms. These examples are offered as possibilities that could help achieve some of ACTogether's objectives and realize observable impacts in the relatively near term.

### *Step 5: Involve Other Stakeholders*

As illustrated in Figure 14 and described above, the leadership team efforts seek to mobilize and synergize the effort of a broader stakeholder base toward realization of the ACTogether mission. These stakeholders include patients and patient advocates, clinicians, regulators, government research centers, academia, industry, foundations, professional societies, payers, and so forth. Just as the leadership team members can be expected to act with a combination of self-interest and mission-interest, the same is true for ACTogether's stakeholders. The following outcomes might be expected.

**Extension, expansion, redirection, or initiation of ACTogether-relevant efforts by stakeholders who choose to align with the effort as signatories.** The opportunity to gain public recognition and reputational benefits as a signatory may motivate some stakeholders to extend, expand, redirect, or initiate ACTogether-relevant efforts. In the proposed model, the signatories are not contractually bound to demonstrate results or meet any specific expectations. Although some stakeholders could seek to leverage reputation benefit as a signatory without expanding or committing resources, the downside risks to the ACTogether are low and outweighed by the potential benefits. If program resources were expanded at a later date, the implementation of a curated signatory program could be pursued.

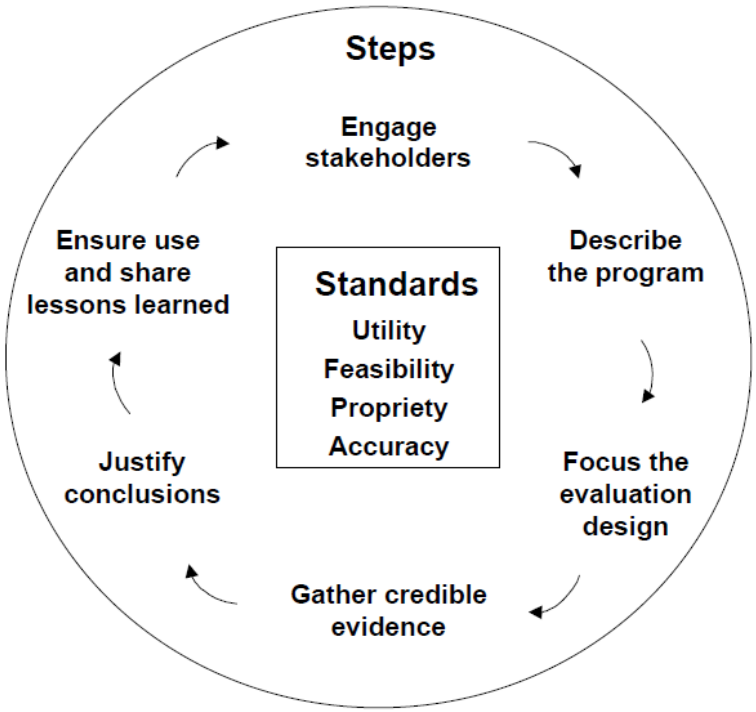
**Extension, expansion, redirection, or initiation of ACTogether-relevant efforts by stakeholders who do not align with the effort as signatories.** It is expected that not all stakeholders who are influenced by ACTogether outreach will chose to become a signatory. Stakeholders who opt not to sign on as supporters may feel that the nonbinding commitment lacks rigor or utility, may lack the organizational authority to sign such statements, may find the statement too limiting or burdensome, may not wish to formally associate with other ACTogether stakeholders, or may just not want to bother. However, it is plausible that those entities might choose to take action in support of ACTogether even without becoming a signatory. The publication of the "call to action" and challenge areas may be valued as a frame of reference for stakeholders who are already resourced to work in the adjuvant arena or are pursuing resources in these areas. These stakeholders may value ACTogether's specification of key needs (and their role in facilitating systemic change) as a citable resource to inform stakeholder project design, funding prioritization, grant applications, and so forth.

**Diffusion of the ACTogether mission and culture.** The development of a list of signatories committed to ACTogether may aid in communicating the mission, as it is reasonable to expect that those signatories will do some of their own "advertising" of their role in the initiative. This novel community could also serve as a network to spur new opportunities for collaboration, to recommend new challenge areas, and to achieve the goal of changing the overall environmental awareness.

### *Step 6: Evaluate the Program*

As part of the program launch, the leadership team will be responsible for designing and overseeing a manageable metrics and evaluation process for ACTogether, with staffing support from HESI. Because resources for this effort will be limited, the evaluation is envisioned as a relatively high-level exercise to be conducted during the course of the first 2 years of the program. The proposed goal for this effort is to generate sufficient information to inform leadership discussions on necessary refinements to the strategy, with a goal of enhancing ACTogether's reach and impact. This effort also addresses the goal of maintaining effective policies and practices as commended by the ABLe Change Framework (Foster-Fishman & Watson, 2012). The Centers for Disease Control and Prevention (CDC) evaluation framework (Figure 16) is proposed as a guide for this evaluation (CDC Evaluation Working Group, n.d.).

**FIGURE 16: Overview of the Centers for Disease Control and Prevention Framework for Program Evaluation**




Per the CDC framework, it is proposed that the leadership team members act as the "stakeholders" for the initial program evaluation. Much of the content in this project plan can serve to "describe the program." The largest challenge will be to focus the evaluation design and decide upon the evidence to be collected.

A sample outputs, impacts, and metrics table is offered below to illustrate what might be collected and evaluated in the first 2 years of the program that meets the CDC's call to collect metrics that have utility, feasibility, propriety, and accuracy (Table 13). It is notable that, with the current level of resourcing, tracking the launch and impact of specific new efforts in relation to the challenge areas is beyond the scope of this inaugural ACTogether effort (e.g., not feasible and likely not accurate). However, by collecting and reviewing the metrics described below, the leadership team should be positioned to understand how the program is progressing in achieving

the impacts described below, and to use these learnings to inform future strategy/design of the program. Iteration of this evaluation approach on an annual or bi-annual approach is recommended. If expanded resources for the program administration and leadership become available, an expanded evaluation and metric collection approach may be both feasible and appropriate.

**TABLE 13: Anticipated program activities, impacts, and metrics that could be collected in an initial metrics and evaluation effort for ACTogether**

| Program activity | Potential impacts | Metrics |
|---|---|---|
| Publication of "Call to Action" | Visibility for program and mission<br>Incentives to act<br>Creation of a reference | Reference for the publication<br>Citations of the publications by others (published or otherwise) |
| ACTogether website launched | Visibility for program and mission<br>Incentives to act<br>Creation of a reference<br>Creation of a focused community of practice | Date of website launch<br>Number of website hits |
| ACTogether communication strategy implemented (social media, websites, e-mail communication, etc.) | Visibility for program and mission<br>Incentives to act | Types of approaches used for outreach<br>Intended/anticipated audiences (who they are and if possible, how many) |
| ACTogether workshop or panel discussions on "unowned" issues around adjuvants | Visibility for program and mission<br>Novel public discussion on unaddressed issues<br>Changes in stakeholder perception of needs<br>Incentives to act or provide resources<br>Progress toward the ACTogether mission | Dates, locations, and audiences for workshops<br>Anecdotal feedback following the workshops<br>Survey to workshop participants to elicit feedback<br>Types of organizations who attend (to get to breadth of participation) |

| | | |
|---|---|---|
| Signatories commit to ACTogether mission | Visibility for program and mission<br>Progress toward the ACTogether mission<br>Creation of a community of concern | Number of signatures<br>Signatory reports on the projects they will undertake (per the commitment letter)<br>Types of signatories (which sectors, which topical areas, etc.)<br>Rate of signatory additions<br>Examples of signatories who reference the ACTogether program in other public forums/documents<br>Anecdotal feedback from signatories. |
| Stakeholders launch or expand efforts aligned with the challenge areas | Progress toward the ACTogether mission<br>Novel resourcing or prioritization of ACTogether issues | Funding provided to ACTogether leadership or novel ACTogether efforts<br>Anecdotal reports by stakeholders<br>Signatory reports on the projects they will undertake (per the commitment letter)<br>Publications or communications that reference ACTogether as a driver for efforts<br>Launch of new work that cites ACTogether as driver |

**Conclusion**

The Plan for Change described in this chapter proposes a strategic approach for driving progress in the improved the use adjuvant-related AE information to improve cancer patient care. Opportunities to actively implement this plan are currently under exploration by the investigator, who hopes to see this move from the pages of a dissertation into actual practice in the near future!

## APPENDIX A: OUTREACH SCRIPTS FOR KEY INFORMANT INTERVIEW PARTICIPATION

### E-Mail Outreach Script for Key Informant Interview Participation

*This e-mail template was used as a guide for initial outreach to proposed interviewees, requesting their participation in the study.*

Mr./Ms./Dr. _____,

My name is Syril Pettit and I am a doctoral candidate at the University of North Carolina's Gillings School of Global Public Health. For my dissertation, I am conducting a research study (Institutional Review Board [IRB] study no. IRB-17-2590) that includes a series of interviews with stakeholders engaged in the development or use of information on cancer therapy side effects to improve cancer patient care.

For your reference, I have attached a brief project description to this e-mail (Appendix E).

I would genuinely appreciate the opportunity to speak with you, as I believe your perspectives could offer great insights for this study. If you are willing to participate, I will schedule a discussion via phone at a time that is convenient for your schedule in the next couple of weeks. The interview will last no more 45 minutes.

Please note that your participation in this project is voluntary and, furthermore, should you agree to participate, you have the option to decline to answer any question. Additionally, I will not attribute any statements to you by name when reporting results.

I look forward to hearing from you and hope you will agree to participate.

Regards,

Syril Pettit
Doctoral Candidate
UNC Gillings School of Global Public Health

**Telephone Outreach Script for Key Informant Interview Participation**

*The following scripts provide guidelines for scheduling interviews with participants based on whether the potential interviewee picks up the telephone. Calls will be placed as a follow-up to an initial outreach e-mail if the proposed participant does not respond within a few days.*

***If Leaving a Voicemail***

Hello, Mr./Ms./Dr._____. I am following-up on an e-mail I sent you on _____ regarding a study I am conducting on whether improved information about unintended adverse effects of cancer therapy can be used to improve cancer patient care. This research includes the conduct of interviews with stakeholders engaged in the development or use of information on cancer therapy's unintended side effects.

Your participation is voluntary, and the interview would take place via phone, lasting no more than one hour. I would like to schedule the interview to take place in the next ____weeks at a time that is convenient for your schedule. Additionally, I will not attribute any statements to you by name when reporting results.

You can reach me at (703) 887-4046 or by e-mail at tjp3sd5@live.unc.edu. I look forward to hearing from you and hope you are willing to participate.

***If Speaking With a Contact***

Hello, Mr./Ms./Dr._____. I am following-up on an e-mail I sent you on _____ regarding a study I am conducting for my doctoral dissertation on whether information about unintended adverse effects of cancer therapy can be used to improve cancer patient care. Do you have a couple minutes to talk?

Part of my research includes a series of interviews with stakeholders engaged in the development or use of information on cancer therapy's unintended side effects and I believe your perspectives could offer great insights for this study. Your participation is voluntary, and the interview would take place via phone, lasting no more than one hour. I would like to schedule a discussion with you in the next ____weeks at a time convenient to your schedule.

Would you be willing to participate in this study?

*Individual agrees:* Excellent. As I mentioned, I would like to schedule a discussion in the next _____ weeks. *Offer two to three time slots in the interviewee's desired date range.* Are you available during any of these times? *Schedule the interview.*

*If individual asks to think about it:* Thank you for considering my request. I attached a brief project description to the e-mail I sent on _____, which I will resend following our call. If I don't hear back from you in a few days, I will follow up again. Do you prefer that I contact you via e-mail or phone?

Thank you. I look forward to hearing from you.

*If individual declines*: Okay, thank you for your time. I understand.

## APPENDIX B: INFORMED CONSENT FORM

**University of North Carolina at Chapel Hill**

**Consent to Participate in a Research Study**

**Adult Participants**

**Consent Form Version Date:** October 1, 2017

**IRB Study #** 17-2590

**Title of Study**: How can adverse events information be used to more effectively inform cancer patient care?

**Principal Investigator**: Syril Pettit

**Principal Investigator Department**: Health Policy and Management

**Principal Investigator Phone number**: (703) 887-4046

**Principal Investigator E-mail Address**: tjp3sd5@live.unc.edu

**Faculty Advisor**: Ethan Basch

**Faculty Advisor Contact Information**: (919) 966-6759

---

***What are some general things you should know about research studies?***

You are being asked to take part in a research study. To join the study is voluntary.

You may choose not to participate, or you may withdraw your consent to be in the study, for any reason, without penalty.

Research studies are designed to obtain new knowledge. This new information may help people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies.

Details about this study are discussed below and I have provided you with written information electronically in advance. It is important that you understand this information so that you can make an informed choice about being in this research study.

You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

***What is the purpose of this study?***

The purpose of this interview is to learn how your organization develops and/or uses information that helps inform patients and other stakeholders about potential unintended impacts of cancer therapy on their health and quality of life. I'm interested in your organization's role in developing, distributing, and/or using information of importance for making informed decisions about a potential therapy's impact of a patient's short- and long-term quality of life and overall health. This type of information can take many formats, including risk:benefit evaluation, AEs reporting, PROs, safety profiles, quality of life metrics, etc. for a specific therapy or therapeutic class. You may have other thoughts on the types of information important to cancer treatment decision making for you and your organization/sector.

You are being asked to be in the study because you have knowledge and expertise in your sector.

***Are there any reasons you should not be in this study?***

You should not be in this study if you feel you do not have adequate experience with the topic area or comfort level in discussing this topic.

***How many people will take part in this study?***

Between 20 and 25 individuals will be recruited to take part in the study and there will be 3–5 people from each stakeholder group (patient advocacy, regulatory science, drug development, clinical care) taking part in the study.

***How long will your part in this study last?***

This interview should take about 45 minutes. There is a chance that I will need to contact you for some follow-up information but that would be brief and can be completed by telephone or e-mail.

***What will happen if you take part in the study?***

If you agree to participate in the study, I will ask you some questions about your sector/organization's role in contributing information that supports decision making about cancer treatment selection. For my study, I will be interviewing a broad range of stakeholders involved in developing, approving, administering, or financing cancer therapy and those who are advocating for cancer patients. My research seeks to understand whether we can improve long-term patient quality of life by enhancing the way we generate or use information about unintended negative health effects associated with cancer therapy. I am specifically interested in understanding your current role(s) with regard to either generating or utilizing information around cancer therapy's impact on quality of life/toxicity (AE) and subsequent treatment decisions. This interview will focus on therapies administered for long-term cancer control (e.g., adjuvant therapy). I will ask you questions about the types of information you generate, audiences for the recommendations/information that you generate, and/or the types of information you do or would like to use to inform cancer treatment/therapy evaluation decisions.

It will be completely confidential and any information that you provide will be released as a

summary or combined into general themes. Your name will not be connected to your answers in any way. Furthermore, this worksite will remain blinded and will not be listed by name but only with reference to your general sector (e.g., patient advocacy, regulatory, clinical medicine, drug development, etc.). With your permission, I would like to record our interview. Digital audio files and transcripts will be confidentially destroyed at the end of the research study.

***What are the possible benefits from being in this study?***

Research is designed to benefit society by gaining new knowledge. You will not benefit personally from being in this research study.

***What are the possible risks or discomforts involved from being in this study?***

Although no risks are anticipated, there may be uncommon or previously unknown risks. You should report any problems to the researcher.

***What if we learn about new findings or information during the study?***

You will be given any new information gained during the course of the study that might affect your willingness to continue your participation.

***How will information about you be protected?***

I am taking multiple steps to ensure that your privacy and confidentiality will be protected.

- Your name will only appear on the consent form. All records will be kept in a locked location and electronic files will require a password.
- I am the only person who will have access to individually identifiable information. ID numbers will be used to identify the stakeholder and the file that links them will require a password to access them.

Participants will not be identified in any report or publication about this study. Direct quotes

will be used but not attributed to any person specifically. Although every effort will be made to keep research records private, there may be times when federal or state law requires the disclosure of such records, including personal information. This is very unlikely, but if disclosure is ever required, UNC-Chapel Hill will take steps allowable by law to protect the privacy of personal information. In some cases, your information in this research study could be reviewed by representatives of the University, research sponsors, or government agencies (for example, the FDA) for purposes such as quality control or safety.

As soon as the audio recordings are transcribed and checked for accuracy, the audio files will be destroyed. Transcripts will be kept in a folder requiring a password for one year after the study conclusion and the dissertation is accepted. After one year, the transcripts will be destroyed.

Check the line that best matches your choice:

_____ OK to record me during the study

_____ Not OK to record me during the study

***What if you want to stop before your part in the study is complete?***

You can withdraw from this study at any time, without penalty. The investigator also has the right to stop your participation at any time. This could be because the entire study has been stopped.

***Will you receive anything for being in this study?***

You will not receive anything for taking part in this study.

***Will it cost you anything to be in this study?***

It will not cost you anything to be in this study.

***What if you have questions about this study?***

You have the right to ask, and have answered, any questions you may have about this research. If you have questions about the study (including payments), complaints, concerns, or if a research-related injury occurs, you should contact the researchers listed on the first page of this form.

***What if you have questions about your rights as a research participant?***

All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject, or if you would like to obtain information or offer input, you may contact the Institutional Review Board at (919) 966-3113 or by e-mail at IRB_subjects@unc.edu.

## APPENDIX C: KEY INFORMANT INTERVIEW GUIDE

**Interview Data Sheet**

| Code for interviewee* | Stakeholder sector | Date and time of interview | Verbal consent given (Y/N) | Permission granted to record (Y/N) |
|---|---|---|---|---|
| *To be completed at interview time* | *To be completed at interview time* | *To be completed at interview time* | *To be completed at interview time* | *To be completed at interview time* |

*Links between codes and interviewee names to be kept on a separate form and stored with password protection. Interviewee name and identifiable information not to be included with response data.

**Introduction**

Hello, I am a UNC Gillings School of Global Public Health doctoral candidate and this outreach is part a study to understand stakeholders' roles in supporting cancer patient quality of life. As you know, there are more than 20 million cancer survivors in the United States currently and the number is growing. As many as 50% of these survivors, however, will experience some type of adverse health effect associated with their cancer therapy. This can include everything from minor ailments associated with a therapy—for example, minor fatigue, minor nausea—to more serious health impacts such as debilitating nerve pain or heart damage. These effects can impact overall health status as well as a patient's ability to earn an income, enjoy family, or achieve daily tasks. For my study, I will be interviewing a broad range of stakeholders involved in developing, approving, administering, or financing cancer therapy and those who are advocating for cancer patients. My research seeks to understand whether we can improve long-term patient quality of life by enhancing the way we generate or use information about unintended negative health effects associated with cancer therapy.

With this interview, I hope to learn more about your organization's role with regard to *adjuvant cancer therapies*. Adjuvant therapies are those that are administered after primary treatment to lower the risk that a cancer will come back, such as certain chemotherapy, hormone

therapy, targeted therapy, or biological therapy. One example of an adjuvant therapy that produced unanticipated adverse effects is the use of certain aromatase inhibitors to treat breast cancer patients. These drugs are effective in reducing the recurrence of breast cancer after initial therapy. However, an *unanticipated outcome* of their use is chronic pain (arthralgia) in many patients. In some cases, this pain can be debilitating to the patient and inhibit their quality of life, overall health, ability to work, and their ultimate adherence to the therapy. This means that some patients are unable to realize the full benefit of their treatment and that patients and payers may bear additional financial burdens. This scenario raises questions about who is responsible for generating information about benefits and risks; how this information is shared across researchers, regulators, clinicians, patients, and payers; and whether there are opportunities to more effectively support cancer patient care or treatment options in the future. While I don't want to focus on this case scenario specifically, I offer it as an example of the situations and roles I'm interested in exploring in our conversation.

I recognize that you are not an official spokesperson for (your organization, your sector, others like you) and I appreciate that you are offering your personal perspective based on your professional knowledge and experience.

This interview should take about 45 minutes. Again, it will be completely confidential and any information that you provide will be released as a summary or combined into general themes. Your name will not be connected to your answers in any way.

With your permission, I would like to record our interview. Digital audio files and transcripts will be confidentially destroyed at the end of the research study.

- Do you have any questions about the research study or the interview before we begin?
- Do you consent to be interviewed?
- Do I have your permission to record the interview?
- Once the recording starts, ask the same two questions again—Just for the record, do you consent to participate? Do you consent to be recorded?

**INTRODUCTORY QUESTION**

**1. "**Please tell me about your organization and its mission with regard to cancer therapy and cancer care. What is your role in this organization?"

**ROLE**

**2.** "Please describe your role in balancing the beneficial and negative effects associated with the provision of adjuvant therapy to cancer patients."

Probe:

*Does this role help to inform the way adjuvant therapy is developed or used? If so, how? If not, why not?*

*Is your organization unique in this role or are there others doing similar or synergistic work? Please describe.*

**RESOURCES**

**3A.** "In the context of the roles you have described, can you tell me about the resources you rely upon to support these roles (e.g. data, experts, studies, funding, medical records, invoices, etc.)?

Probe:

*Where do you get this information?*

*Do you or your organization generate information used? If so, what type?*

*Do you or your organization use information others generate for cancer therapy and cancer care? If so, how?*

*Is it easy or challenging to access?*

**3B.** "Do these resources meet your needs? Why or why not?"

Probe:

*How timely is the information?*

*How would you describe the quality of the information you use?*

**FUTURE NEEDS: SELF**

**4.** "Are there other types or sources of information or resources that you wish your organization had to help with respect to helping patients balance the beneficial and negative effects of adjuvant therapy?"

Probe:

*If so, what are they?*

*Tell me a little more about why you think that's needed.*

**FUTURE NEEDS: SYSTEM**

**5.** "Moving forward, is there anything you would you like to see change (either in your own organization or others) to improve our *overall approach* to balancing treatment-related risks and benefits related to adjuvant therapy?"

Probe (not all questions will be appropriate to all respondents):

*Do you think that the information generated is the right type of information? If not, what needs to change?*

*Do you think that the information is readily accessible and usable by those who need it? If not, what needs to change?*

*Is information provided in a timely way to the organizations who need it? If not, what needs to change?*

*Does your organization use the available information to inform decision making? If not, why not?*

*Do you provide feedback to those who generate information about the type of information you need?*

**OPPORTUNITY FOR OPEN-ENDED INPUT**

**6.** "Are there additional comments or thoughts you'd like to offer?"

**Thank you.**

## APPENDIX D: CODE BOOK

| INTERVIEW QUESTIONS | CODE NAME | DESCRIPTION |
|---|---|---|
| **Introduction Questions** | | |
| Please tell me about your place of employment and its mission/scope of service with regard to cancer therapy and/or cancer patient support.<br><br>Please describe your role in terms of support cancer patient quality of life and health. | **Participant Job and Personal Background** | Use this code when participants discuss their job title, personal background and role in general.<br><br>Also use this code when participants mention their current place of employment and its mission as it pertains to providing therapies and/or support to patients with cancer. |
| **Roles** | | |
| Can you describe your role more specifically in terms of adjuvant therapy?<br><br>For regulators: What is your role with regard to the review or evaluation of adjuvant therapies? Please explain.<br><br>In this role, have you had situations where you had to address/support the balance of beneficial and negative effects associated with the provision of adjuvant therapy to cancer patients? Please describe. | **Participant Role Regarding Adjuvant Therapy** | Use this code when participants discuss their roles within the organizations they serve and the scope of their work as it relates to making risk:benefit-based decisions about adjuvant therapy *in contrast to* other cancer therapy types.<br><br>Also use this code when participants talk about like-roles from other people or organizations that they have relied upon as it related to making risk:benefit-based decisions about adjuvant therapy *in contrast* to other cancer therapy types. |
| Do you feel that your role in (treating patients, supporting patients, funding treatment, conducting regulatory review, or designing research) is inherently different for longer-term adjuvant therapies versus primary treatment? Please describe.<br><br>Has your view of your role in supporting patients on adjuvant therapy changed in the last 5 years? If so, please describe. | **Job Role Changes Over Time** | Use this code when participants discuss how they perceive their roles to change, if at all, with longer-term adjuvant therapies versus primary treatment.<br><br>Include mention of how they have seen their role in supporting patients' change, if at all, over the past 5 years. |

| | | |
|---|---|---|
| If you/your organization generates the information needed, can you describe what type of information?<br><br>Where do the resources come from to support this data generation? | **Roles in Data or Information Generation** | Use this code when participants describe current practices of data generation (what kind of data and generated for whom).<br><br>Information should relate to generating information needed to inform patient quality of life and safety in the adjuvant treatment setting. |
| If you/your organization uses information others generate for cancer therapy and cancer care, can you describe how?<br><br>Do you or others in your organization use the available information to inform decision making? If not, why not?<br><br>Are there other organizations or roles that you relied upon to help/partner with you in these settings? Are there others playing parallel or similar roles? Please describe. | **Roles in Data or Information Use** | Use this code when participants describe the process for selecting the information available and the ways they have used the information to inform or support decisions for patients who are/were/may be on adjuvant cancer therapy. Decision making relates to the integration of information from different sources to make a judgement call (about treatment, regulation, drug development, payment, etc.).<br><br>Also use this code when participants describe how and to what degree they use information other organizations have generated. |
| Do you proactively share your experience in any format? If so, how? If not, why not?<br><br>Do you provide feedback to those who generate information about the type of information you need?<br><br>Do you feel that your experience/role with regard to supporting quality of life for patients receiving adjuvant therapy informs others?<br><br>Does this role help to inform the way adjuvant therapy is developed or used? If so, how? If not, why not? | **Roles in Data or Information Sharing** | Use this code any time participants discuss improvements or suggestions they have offered or would like to offer for the way information is being shared.<br><br>Use this code any time participant discusses the way in which their actions or efforts affect other stakeholder's ability to inform cancer patient care. |

| | | |
|---|---|---|
| Have the sources of information you use to support this role changed over time? Please describe.<br><br>How timely is the information?<br><br>Is information provided in a timely way to the organizations who need it? If not, what needs to change?<br><br>Do you think that relevant information is readily accessible and usable by those who need it? If not, what needs to change?<br><br>How would you describe the quality of the information you use?<br><br>Do you think that the information generated is the right type of information? If not, what needs to change?<br><br>Do these resources meet your needs? Why or why not? | **Barriers to Generating or Using Data** | Use this code when participants describe barriers or obstacles for generating or using adjuvant cancer therapy data or knowledge.<br><br>Include mention of when participants talk about the timeliness, quality, relevance, utility, and/or accuracy of the information that is generated and what changes should be made to the information, if any, to make the data better with regard to any of these criteria.<br><br>Use this code when participants discuss changes they have experienced in the timeliness, value, quality, relevance, etc. of data over the years regarding information used for risk:benefit evaluation of adjuvant cancer therapy. |
| Does this role help to inform the way adjuvant therapy is developed or used? If so, how? If not, why not?<br><br>What is its greatest strength? | **Motivators to Generating or Using Data** | Use this code when participants describe requirements, incentives, or motivations that drive stakeholders to develop or utilize information of relevance for evaluating risk:benefit and AE for patients receiving adjuvant therapy. |
| **Resources** | | |
| In the context of the roles you have described, can you tell me about the resources you rely upon to support these roles? (e.g. data, experts, studies, funding, medical records, invoices, etc.)<br><br>Where do you get this information? | **Specific Data Resources** | Use this code when participants describe specific data or information resources they use to inform risk:benefit considerations in the adjuvant therapy context. |

| Future Needs | | |
|---|---|---|
| Are there other types or sources of information or resources that you wish you had to help with respect to helping patients balance the beneficial and negative effects of adjuvant therapy?<br><br>If so, what are they?<br><br>Tell me a little more about why you think that's needed?<br><br>Why isn't this information available now?<br><br>Moving forward, is there anything you would you like to see changed (either in your own organization or others) to improve our overall approach to balancing treatment-related risks and benefits related to adjuvant therapy? | **Future Needs for System** | Use this code when participants discuss missed opportunities or unmet data generation or data usage needs. This includes descriptions of what participants wish was available but is currently not available and why they think the information or approaches are not available now. Use this code when participants describe any suggestions for how to improve balancing treatment for patients to related risks and benefits of adjuvant therapy at a systemic level, or by groups other than their own. |

## APPENDIX E: ONE-PAGE RESEARCH PROPOSAL SUMMARY

### How Can Adverse Event Information Be Used to More Effectively Inform Cancer Patient Care?

Life with cancer and its treatment—whether as a patient, survivor, or supporter—is an almost universal experience. Per the U.S. National Cancer Institute (NCI), 40% of the population will be diagnosed with cancer in their lifetime. Fortunately, the last decade has seen tremendous advances in cancer therapy design and delivery and thus an increase in survival rates for many cancer types (Edwards et al., 2014). This increasing efficacy means that patients are living longer while on therapy or following their primary course of therapy. Unfortunately, therapy-related adverse events (AEs) are an unintended, but not infrequent, outcome of these life-saving therapies (Cleeland et al., 2012). AEs can impact both the ability adhere to therapy and a patient's immediate and long-term physical, emotional, and financial health and quality of life.

Given the potential impact of AEs on patient outcome and experience, the relevance of AE data to inform decision making by drug developers, government regulators, patients, and clinicians seems evident. However, the cancer care community has only recently begun to robustly tackle this complex aspiration. A review of the current literature reveals an insufficient understanding of the processes and rationales that drive AE data generation, adaptation, dissemination, and use for cancer treatment-related decisions. This deficiency appears to extend to both individual stakeholder groups and across the network of stakeholders engaged as in treatment design, use, and supportive care decisions.

This study will utilize key informant interviews to assess stakeholder perspectives on their perceived roles as developers and/or users of treatment-related AE information for cancer care decision making (as well as their perceptions of the roles of others). In this context, the cancer treatment stakeholder network is defined as *patient advocacy*, *clinical care*, *regulatory science*, *cancer therapy research and development*, and *healthcare plans*. The qualitative stakeholder data, in combination with the published literature, will be used to evaluate the systemwide alignment (or misalignment) of perceived roles across the stakeholders. The study will seek to identify any systemic gaps where there are failures in effective AE information generation, dissemination, or use. Although this study is expected to generate findings with relevance across a range of cancer therapy classes and scenarios, the interviews will focus on "adjuvant therapy" (i.e., therapies provided to prevent/limit cancer recurrence following initial treatment) because of their generally longer-term treatment duration and higher patient survival rates.

The results of this research will be used to inform a plan for change that includes the development of multidisciplinary and multisector collaborative efforts to improve future cancer patient care by enhancing the overall relevance of future AE data collection and use.

## APPENDIX F: DEFINITIONS

**Adjuvant therapy.** Additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy.

**Disease-free survival (DFS).** The length of time after primary treatment for a cancer ends that the patient survives without any signs or symptoms of that cancer. In a clinical trial, measuring the disease-free survival is one way to see how well a new treatment works.

**Progression-free survival (PFS).** The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse.

## APPENDIX G: DRAFT LETTER OF SUPPORT

**DRAFT**

**Letter of Support for ACTogether**

**2019–2021 Challenge Period**

With this letter, we commit our support for **ACTogether**'s mission of improving quality of life for patients who are or have received adjuvant therapy by enhancing our ability to understand, address, and convey the benefits and risks of these approaches. We acknowledge that an improved future for patients will require consistent, creative, and collaborative efforts across a broad base of stakeholders and disciplines.

As a named collaborator in the ACTogether effort, (Name of Organization or Individual) will actively work toward the fulfillment of the mission by addressing one or more of the named challenge areas during the 2019–2021 challenge period.

Named collaborators will be acknowledged on the ACTogether website and in promotional materials at the discretion of the program organizers. Collaborators are asked to provide a brief, nontechnical description of their efforts below and align this with one or more challenge areas.

Description (150 words or less):
Related challenge area(s):
Contact e-mail:

## REFERENCES


Advisory Board Company. (2015). Cancer Patient Preferences Explorer. Retrieved from https://www.advisory.com/research/oncology-roundtable/resources/2015/cancer-patient-preferences-explorer

Allen, J. D., Stewart, M. D., Roberts, S. A., & Sigal, E. V. (2017). The value of addressing patient preferences. *Value in Health*, *20*(2), 283–285. https://doi.org/10.1016/j.jval.2016.11.029

Armstrong, G. T., Kawashima, T., Leisenring, W., Stratton, K., Stovall, M., Hudson, M. M., … Oeffinger, K. C. (2014). Aging and risk of severe, disabling, life-threatening, and fatal events in the Childhood Cancer Survivor Study. *Journal of Clinical Oncology*, *32*(12), 1218–1227. https://doi.org/10.1200/JCO.2013.51.1055

Atherton, P. J., Smith, T., Singh, J. A., Huntington, J., Diekmann, B. B., Huschka, M., & Sloan, J. A. (2013). The relation between cancer patient treatment decision-making roles and quality of life. *Cancer*, *119*(12), 2342–2349. https://doi.org/10.1002/cncr.28046

Ayvaci, M. U. S., Shi, J., Alagoz, O., & Lubner, S. J. (2013). Cost-effectiveness of adjuvant FOLFOX and 5FU/LV chemotherapy for patients with stage II colon cancer. *Medical Decision Making*, *33*(4), 521–532. https://doi.org/10.1177/0272989X12470755

Bajaj, P. S., Veenstra, D. L., Goertz, H.-P., & Carlson, J. J. (2014). Targeted erlotinib for first-line treatment of advanced non-small cell lung cancer: a budget impact analysis. *Journal of Medical Economics*, *17*(8), 538–546. https://doi.org/10.3111/13696998.2014.912987

Balicer, R. D., & Afek, A. (2017). Digital health nation: Israel's global big data innovation hub. *The Lancet*, *6736*(17), 8–10. https://doi.org/10.1016/S0140-6736(17)30876-0

Barker, K. K., Bosco, C., & Oandasan, I. F. (2005). Factors in implementing interprofessional education and collaborative practice initiatives: Findings from key informant interviews. *Journal of Interprofessional Care*, *19*(suppl 1), 166–176. https://doi.org/10.1080/13561820500082974

Barry, M. J., & Edgman-Levitan, S. (2012). Shared decision making — the pinnacle of patient-centered care. *New England Journal of Medicine*, *366*, 780–781. https://doi.org/10.1056/NEJMp1109283

Basch, E. (2016). Toward a patient-centered value framework in oncology. *JAMA*, *315*(19), 2073–4. https://doi.org/10.1001/jama.2016.4637

Basch, E., Deal, A. M., Kris, M. G., Scher, H. I., Hudis, C. A., Sabbatini, P., … Schrag, D. (2016). Symptom monitoring with patient-reported outcomes during routine cancer treatment: A randomized controlled trial. *Journal of Clinical Oncology*, *34*(6), 557–565. https://doi.org/10.1200/JCO.2015.63.0830

Basch, E., Geoghegan, C., Coons, S. J., Gnanasakthy, A., Slagle, A. F., Papadopoulos, E. J., … LM, E. (2015). Patient-reported outcomes in cancer drug development and US regulatory review. *JAMA Oncology*, *1*(3), 375. https://doi.org/10.1001/jamaoncol.2015.0530

Bennett, S., Pigott, A., Beller, E. M., Haines, T., Meredith, P., & Delaney, C. (2016). Educational interventions for the management of cancer-related fatigue in adults. *Cochrane Database of Systematic Reviews*, *11*, CD008144. https://doi.org/10.1002/14651858.CD008144.pub2

Bentley, T. G. K., Cohen, J. T., Elkin, E. B., Huynh, J., Mukherjea, A., Neville, T. H., … Broder, M. S. (2017). Measuring the value of new drugs: Validity and reliability of 4 value assessment frameworks in the oncology setting. *Journal of Managed Care & Specialty Pharmacy*, *23*(6 suppl), S34–S48.

Berridge, B. R., Pettit, S. D., & Sarazan, R. D. (2014). Opportunities to meet clinical cardio-oncology needs with new approaches to non-clinical safety assessment. *Progress in Pediatric Cardiology*, *36*(1–2), 31–32. https://doi.org/10.1016/j.ppedcard.2014.09.005

Bhatt, D. L., & Mehta, C. (2016). Adaptive designs for clinical trials. *New England Journal of Medicine*, *375*(1), 65–74. https://doi.org/10.1056/NEJMra1510061

Bilir, S. P., Ma, Q., Zhao, Z., Wehler, E., Munakata, J., & Barber, B. (2016). Economic burden of toxicities associated with treating metastatic melanoma in the United States. *American Health & Drug Benefits*, *9*(4), 203–13.

Booth, C. M., & Del Paggio, J. C. (2017). Approvals in 2016: Questioning the clinical benefit of anticancer therapies. *Nature Reviews Clinical Oncology*, *14*(3), 135–136. https://doi.org/10.1038/nrclinonc.2017.18

Bristow, R. E., Santillan, A., Salani, R., Diaz-Montes, T. P., Giuntoli, R. L. 2nd, Meisner, B. C., … Frick, K. D. (2007). Intraperitoneal cisplatin and paclitaxel versus intravenous carboplatin and paclitaxel chemotherapy for stage III ovarian cancer: A cost-effectiveness analysis. *Gynecologic Oncology*, *106*(3), 476–481. https://doi.org/10.1016/j.ygyno.2007.05.043

Bryson, J. M., Ackermann, F., & Eden, C. (2016). Discovering collaborative advantage: The contributions of goal categories and visual strategy mapping. *Public Administration Review*, *76*(6), 912–925. https://doi.org/10.1111/puar.12608

Buffery, D. (2016). Innovation tops current trends in the 2016 oncology drug pipeline. *American Health & Drug Benefits*, *9*(4), 233–238.

Burke, J. G., Lich, K. H., Neal, J. W., Meissner, H. I., Yonas, M., & Mabry, P. L. (2015). Enhancing dissemination and implementation research using systems science methods. *International Journal of Behavioral Medicine*, *22*(3), 283–291. https://doi.org/10.1007/s12529-014-9417-3

Burke, T. A., Wisniewski, T., & Ernst, F. R. (2011). Resource utilization and costs associated with chemotherapy-induced nausea and vomiting (CINV) following highly or moderately emetogenic chemotherapy administered in the US outpatient hospital setting. *Supportive Care in Cancer*, *19*(1), 131–40. https://doi.org/10.1007/s00520-009-0797-x

Burudpakdee, C., Zhao, Z., Munakata, J., Gao, S., Trochlil, K., & Barber, B. (2012). Economic burden of toxicities associated with metastatic colorectal cancer treatment regimens containing monoclonal antibodies. *Journal of Medical Economics*, *15*(2), 371–377. https://doi.org/10.3111/13696998.2011.650774

Calabrese, C., Kirchner, E., Kontzias, K., Velcheti, V., & Calabrese, L. H. (2017). Rheumatic immune-related adverse events of checkpoint therapy for cancer: Case series of a new nosological entity. *RMD Open*, *3*(1), e000412. https://doi.org/10.1136/rmdopen-2016-000412

Califf, R. M., Robb, M. A., Bindman, A. B., Briggs, J. P., Collins, F. S., Conway, P. H., … Sherman, R. E. (2016). Transforming evidence generation to support health and health care decisions. *New England Journal of Medicine*, *375*(24), 2395–2400. https://doi.org/10.1056/NEJMsb1610128

Castellanos, E. H., Chen, S. C., Drexler, H., & Horn, L. (2015). Making the grade: The impact of low-grade toxicities on patient preference for treatment with novel agents. *JNCCN Journal of the National Comprehensive Cancer Network*, *13*(12), 1490–1495.

CDC Evaluation Working Group. (n.d.). Summary of the Framework for Program Evaluation 1. Retrieved from https://www.cdc.gov/eval/materials/frameworksummary.pdf

Chambers, D. A., Feero, W. G., & Khoury, M. J. (2016). Convergence of implementation science, precision medicine, and the learning health care system. *JAMA*, *315*(18), 1941. https://doi.org/10.1001/jama.2016.3867

Chandra, A., Shafrin, J., & Dhawan, R. (2016). Utility of cancer value frameworks for patients, payers, and physicians. *JAMA: Journal of the American Medical Association*, *315*(19), 2069–2070.

Chen, A., & Setser, A. (2008). CTCAE v3.0 Revision Project Methods: Ranjana Srivastava. Retrieved from https://www.meddra.org/sites/default/files/page/documents_insert/20080702_wg_telecon.pdf

Chu, E., Schulman, K. L., Zelt, S., & Song, X. (2009). Costs associated with complications are lower with capecitabine than with 5-fluorouracil in patients with colorectal cancer. *Cancer*, *115*(7), 1412–1423. https://doi.org/10.1002/cncr.24131

Cleeland, C. S., Allen, J. D., Roberts, S. A., Brell, J. M., Giralt, S. A., Khakoo, A. Y., … Skillings, J. (2012). Reducing the toxicity of cancer therapy: Recognizing needs, taking action. *Nature Reviews Clinical Oncology*, *9*(8), 471–478. https://doi.org/10.1038/nrclinonc.2012.99

CMS. (2014). Medicare Program: General information. Retrieved from https://www.cms.gov/Medicare/Medicare-General-Information/MedicareGenInfo/index.html

Cohen, J. T., Anderson, J. E., & Neumann, P. J. (2017). Three sets of case studies suggest logic and consistency challenges with value frameworks. *Value in Health*, *20*, 193–199. https://doi.org/10.1016/j.jval.2016.11.012

Conklin, J., Basadur, M., & VanPatter, G. (2007). Rethinking wicked problems. *NextD Journal*, (10), 1–30. Retrieved from http://humantific.com/wp-content/uploads/2009/07/NextD_10/NextD_10_1.pdf

Craver, C., Gayle, J., Balu, S., & Buchner, D. (2011). Clinical and economic burden of chemotherapy-induced nausea and vomiting among patients with cancer in a hospital outpatient setting in the United States. *Journal of Medical Economics*, *14*(1), 87–98. https://doi.org/10.3111/13696998.2010.547237

Creswell, J. W. (2014). *Research design: Qualitative, quantitative, and mixed methods approaches*. Thousand Oaks, CA: SAGE.

Crowley, K., & Head, B. W. (2017). The enduring challenge of 'wicked problems': Revisiting Rittel and Webber. *Policy Sciences*, *50*(4), 539–547. https://doi.org/10.1007/s11077-017-9302-4

Dalton, H. J., Yu, X., Hu, L., Kapp, D. S., Benjamin, I., Monk, B. J., & Chan, J. K. (2012). An economic analysis of dose dense weekly paclitaxel plus carboplatin versus every-3-week paclitaxel plus carboplatin in the treatment of advanced ovarian cancer. *Gynecologic Oncology*, *124*(2), 199–204. https://doi.org/10.1016/j.ygyno.2011.09.028

Dambach, D. M., Simpson, N. E., Jones, T. W., Brennan, R. J., Pazdur, R., & Palmby, T. R. (2016). Nonclinical evaluations of small-molecule oncology drugs: Integration into clinical dose optimization and toxicity management. *Clinical Cancer Research*, *22*(11), 2618–2622. https://doi.org/10.1158/1078-0432.CCR-15-2645

Danis, L. M. F. and M. (2017). How should therapeutic decisions about expensive drugs be made in imperfect environments? *AMA Journal of Ethics*, *19*(2), 147–156. https://doi.org/10.1001/journalofethics.2017.19.2.ecas2-1702

de Golian, E., Kwong, B. Y., Swetter, S. M., & Pugliese, S. B. (2016). Cutaneous complications of targeted melanoma therapy. *Current Treatment Options in Oncology*, *17*(11), 57. https://doi.org/10.1007/s11864-016-0434-0

Del Paggio, J. C. (2017). Deconstructing clinical trials? Help from oncology value frameworks. *JAMA Oncology*, *3*(10), 1306–1307. https://doi.org/10.1001/jamaoncol.2017.1312

Del Paggio, J. C., Sullivan, R., Schrag, D., Hopman, W. M., Azariah, B., Pramesh, C. S., … Booth, C. M. (2017). Delivery of meaningful cancer care: a retrospective cohort study assessing cost and benefit with the ASCO and ESMO frameworks. *Lancet Oncology*, *18*(7), 887–894. https://doi.org/10.1016/S1470-2045(17)30415-1

Delea, T. E., Amdahl, J., Diaz, J., Nakhaipour, H. R., & Hackshaw, M. D. (2015). Cost-effectiveness of pazopanib versus sunitinib for renal cancer in the United States. *Journal of Managed Care & Specialty Pharmacy*, *21*(1), 46–54, 54a-b. https://doi.org/10.18553/jmcp.2015.21.1.46

Dimasi, J. A., Hansen, R. W., & Grabowski, H. G. (2003). The price of innovation: New estimates of drug development costs. *Journal of Health Economics*, *22*, 151–185. https://doi.org/10.1016/S0167-6296(02)00126-1

Edwards, B. K., Noone, A.-M., Mariotto, A. B., Simard, E. P., Boscoe, F. P., Henley, S. J., … Ward, E. M. (2014). Annual Report to the Nation on the status of cancer, 1975-2010, featuring prevalence of comorbidity and impact on survival among persons with lung, colorectal, breast, or prostate cancer. *Cancer*, *120*(9), 1290–1314. https://doi.org/10.1002/cncr.28509

Eichler, H.-G., Pignatti, F., Flamion, B., Leufkens, H., & Breckenridge, A. (2008). Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. *Nature Reviews Drug Discovery*, *7*(10), 818–826. https://doi.org/10.1038/nrd2664

Emens, L. A., Butterfield, L. H., Hodi, F. S., Marincola, F. M., & Kaufman, H. L. (2016). Cancer immunotherapy trials: Leading a paradigm shift in drug development. *Journal for ImmunoTherapy of Cancer*, *4*(1), 42. https://doi.org/10.1186/s40425-016-0146-9

ESMO. (2017). ESMO Magnitude of Clinical Benefit Scale. Retrieved from http://www.esmo.org/Policy/Magnitude-of-Clinical-Benefit-Scale

EuroQol. (2017). EuroQol. Retrieved from https://euroqol.org

Evans, W. K., Cheung, M. C., & Chan, K. K. (2017). Measuring value and benefit—a matter of perspective. *Lancet Oncology*, *18*, 839–840. https://doi.org/10.1016/S1470-2045(17)30339-X

FDA. (2018). S9 Nonclinical Evaluation for Anticancer Pharmaceuticals Questions and Answers Guidance for Industry. Retrieved from https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM520942.pdf

Fiore, L., Brophy, M., Ferguson, R., Shannon, C., Turek, S., Pierce-Murray, K., … Lavori, P. (2017). Data sharing, clinical trials, and biomarkers in precision oncology: Challenges, opportunities, and programs at the Department of Veterans Affairs. *Clinical Pharmacology & Therapeutics*, *101*(5), 586–589. https://doi.org/10.1002/cpt.660

Fiore, L. D., & Lavori, P. W. (2016). Integrating randomized comparative effectiveness research with patient care. *New England Journal of Medicine*, *374*(22), 2152–2158. https://doi.org/10.1056/NEJMra1510057

Fitzner, K., Oteng-Mensah, F., Donley, P., & Heckinger, E. A. F. (2017). Safety of Cancer Therapies: At What Cost? *Population Health Management*, *00*(00), pop.2016.0097. https://doi.org/10.1089/pop.2016.0097

Foster-Fishman, P. G., & Watson, E. R. (2012). The ABLe Change Framework: A conceptual and methodological tool for promoting systems change. *American Journal of Community Psychology*, *49*(3–4), 503–516. https://doi.org/10.1007/s10464-011-9454-x

Funnell, S. C., & Rogers, P. J. (2011). *Purposeful program theory: Effective use of theories of change and logic models*. San Francisco, CA: Jossey-Bass.

Goldstein, D. A., Chen, Q., Ayer, T., Howard, D. H., Lipscomb, J., Harvey, R. D., … Flowers, C. R. (2014). Cost effectiveness analysis of pharmacokinetically-guided 5-fluorouracil in FOLFOX chemotherapy for metastatic colorectal cancer. *Clinical Colorectal Cancer*, *13*(4), 219–225. https://doi.org/10.1016/j.clcc.2014.09.007

Goldstein, D. A., Krishna, K., Flowers, C. R., El-Rayes, B. F., Bekaii-Saab, T., & Noonan, A. M. (2016). Cost description of chemotherapy regimens for the treatment of metastatic pancreas cancer. *Medical Oncology*, *33*(5), 48.

Goulart, B., & Ramsey, S. (2011). A trial-based assessment of the cost-utility of bevacizumab and chemotherapy versus chemotherapy alone for advanced non-small cell lung cancer. *Value in Health*, *14*(6), 836–845. https://doi.org/10.1016/j.jval.2011.04.004

Graham, I. D., Logan, J., Harrison, M. B., Straus, S. E., Tetroe, J., Caswell, W., & Robinson, N. (2006). Lost in knowledge translation: Time for a map? *Journal of Continuing Education in the Health Professions*, *26*(1), 13–24. https://doi.org/10.1002/chp.47

Haiderali, A., Menditto, L., Good, M., Teitelbaum, A., & Wegner, J. (2011). Impact on daily functioning and indirect/direct costs associated with chemotherapy-induced nausea and vomiting (CINV) in a US population. *Supportive Care in Cancer*, *19*, 843–851. https://doi.org/10.1007/s00520-010-0915-9

Hare, J. I., Lammers, T., Ashford, M. B., Puri, S., Storm, G., & Barry, S. T. (2017). Challenges and strategies in anti-cancer nanomedicine development: An industry perspective. *Advanced Drug Delivery Reviews*, *108*, 25–38. https://doi.org/10.1016/j.addr.2016.04.025

Hassmiller Lich, K., Urban, J. B., Frerichs, L., & Dave, G. (2017). Extending systems thinking in planning and evaluation using group concept mapping and system dynamics to tackle complex problems. *Evaluation and Program Planning*, *60*, 254–264. https://doi.org/10.1016/j.evalprogplan.2016.10.008

Havrilesky, L. J., Broadwater, G., Davis, D. M., Nolte, K. C., Barnett, J. C., Myers, E. R., & Kulasingam, S. (2009). Determination of quality of life-related utilities for health states relevant to ovarian cancer diagnosis and treatment. *Gynecologic Oncology*, *113*(2), 216–220. https://doi.org/10.1016/j.ygyno.2008.12.026

Havrilesky, L. J., Chino, J. P., & Myers, E. R. (2013). How much is another randomized trial of lymph node dissection in endometrial cancer worth? A value of information analysis. *Gynecologic Oncology*, *131*(1), 140–146. https://doi.org/10.1016/j.ygyno.2013.06.025

Havrilesky, L. J., Secord, A. A., Kulasingam, S., & Myers, E. (2007). Management of platinum-sensitive recurrent ovarian cancer: A cost-effectiveness analysis. *Gynecologic Oncology*, *107*(2), 211–218. https://doi.org/10.1016/j.ygyno.2007.06.029

HBR Staff. (2016). Five critical roles in project management. Retrieved from https://hbr.org/2016/11/five-critical-roles-in-project-management

Head, B. W., & Alford, J. (2015). Wicked problems: Implications for public policy and management. *Administration & Society*, *47*(6), 711–739. https://doi.org/10.1177/0095399713481601

Hearld, L. R., Bleser, W. K., Alexander, J. A., & Wolf, L. J. (2016). A systematic review of the literature on the sustainability of community health collaboratives. *Medical Care Research and Review*, *73*(2), 127–181. https://doi.org/10.1177/1077558715607162

Hess, L. M., Rajan, N., Winfree, K., Davey, P., Ball, M., Knox, H., & Graham, C. (2015). Cost analyses in the US and Japan: A cross-country comparative analysis applied to the PRONOUNCE trial in non-squamous non-small cell lung cancer. *Advances in Therapy*, *32*(12), 1248–1262. https://doi.org/10.1007/s12325-015-0270-9

Hoerger, M., Epstein, R. M., Winters, P. C., Fiscella, K., Duberstein, P. R., Gramling, R., … Kravitz, R. L. (2013). Values and options in cancer care (VOICE): Study design and rationale for a patient-centered communication and decision-making intervention for physicians, patients with advanced cancer, and their caregivers. *BMC Cancer*, *13*, 188.

Howlader, N., Noone, A. M., Krapcho, M., Miller, D., Bishop, K., Altekruse, S. F., … Mariotto, A. (2016). *SEER Cancer Statistics Review, 1975-2013*. Bethesda, MD: National Cancer Institute. Retrieved from https://seer.cancer.gov/csr/1975_2013/

Huxham, C., & Vangen, S. (2006). Managing to collaborate, the theory and practice of collaborative advantage. *Journal of Purchasing & Supply Management*, *12*, 51. https://doi.org/10.1016/j.pursup.2006.02.002

ICER. (2017). ICER Value Assessment Framework. Retrieved from https://icer-review.org/methodology/icers-methods/icer-value-assessment-framework/

ICH. (2009). International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Nonclinical evaluation for anticancer pharmaceuticals, S9, Current Step 4 version. Retrieved from https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Safety/S9/Step4/S9_Step4_Guideline.pdf

Innes, J. E., & Booher, D. E. (2016). Collaborative rationality as a strategy for working with wicked problems. *Landscape and Urban Planning*, *154*, 8–10. https://doi.org/10.1016/j.landurbplan.2016.03.016

Institute of Medicine. (2001). *Crossing the quality chasm*. Washington, DC: National Academies Press. https://doi.org/10.17226/10027

Institute of Medicine. (2007). *The learning healthcare system*. Washington, DC: National Academies Press. https://doi.org/10.17226/11903

Jim, H. S. L., & McLeod, H. L. (2017). American Society of Clinical Oncology Value Framework: Importance of accurate toxicity data. *Journal of Clinical Oncology*, *35*(10), 1133–1134. https://doi.org/10.1200/JCO.2016.69.2079

Kofman, F., & Senge, P. M. (1993). Communities of commitment: The heart of learning organizations. *Organizational Dynamics*, *22*(2), 5–23. https://doi.org/10.1016/0090-2616(93)90050-B

Kotter, J. P. (2007). Leading Change: Why Transformation Efforts Fail. *Harvard Business Review*.

Kottschade, L., Brys, A., Peikert, T., Ryder, M., Raffals, L., Brewer, J., … Partnership, M. M. (2016). A multidisciplinary approach to toxicity management of modern immune checkpoint inhibitors in cancer therapy. *Melanoma Research*, *26*(5), 469–480. https://doi.org/10.1097/CMR.0000000000000273

Kowal-Podmore, S., Munakata, J., Tencer, T., & Smith, T. W. (2008). Economic burden of toxicities associated with salvage treatment in advanced and metastatic breast cancer. *Value in Health*, *11*(6), A479. https://doi.org/10.1016/S1098-3015(10)66598-9

Kuderer, N. M., & Wolff, A. C. (2014). Enhancing therapeutic decision making when options abound: Toxicities matter. *Journal of Clinical Oncology*, *32*(19), 1990–1993. https://doi.org/10.1200/JCO.2014.55.1903

Kumar, P., & Moy, B. (2013). The cost of cancer care--balancing our duties to patients versus society: Are they mutually exclusive? *The Oncologist*, *18*(4), 347–9. https://doi.org/10.1634/theoncologist.2013-0078

Kumar, V., Chaudhary, N., Garg, M., Floudas, C. S., Soni, P., & Chandra, A. B. (2017). Current diagnosis and management of immune related adverse events (irAEs) induced by immune checkpoint inhibitor therapy. *Frontiers in Pharmacology*, *8*, 49. https://doi.org/10.3389/fphar.2017.00049

Kurian, A. W., Thompson, R. N., Gaw, A. F., Arai, S., Ortiz, R., & Garber, A. M. (2007). A cost-effectiveness analysis of adjuvant trastuzumab regimens in early HER2/neu-positive breast cancer. *Journal of Clinical Oncology*, *25*(6), 634–641.

Lee, I., Garland, S. N., DeMichele, A., Farrar, J. T., Im, E.-O., & Mao, J. J. (2017). A cross-sectional survey of pain catastrophising and acupuncture use among breast cancer survivors. *Acupuncture in Medicine*, *35*(1), 38–43. https://doi.org/10.1136/acupmed-2016-011056

Macdonald, J. B., Macdonald, B., Golitz, L. E., LoRusso, P., Sekulic, A., Agha, R., … Skelton, H. G. (2015). Cutaneous adverse effects of targeted therapies: Part I: Inhibitors of the cellular membrane. *Journal of the American Academy of Dermatology*, *72*(2), 203-18; quiz 219-20. https://doi.org/10.1016/j.jaad.2014.07.032

Mahajan, R. (2015). Real world data: Additional source for making clinical decisions. *International Journal of Applied & Basic Medical Research*, *5*(2), 82. https://doi.org/10.4103/2229-516X.157148

Mak, I. W., Evaniew, N., & Ghert, M. (2014). Lost in translation: animal models and clinical trials in cancer treatment. *Am J Transl Res*, *6*(2), 114–118.

Mandelblatt, J. S., Ramsey, S. D., Lieu, T. A., & Phelps, C. E. (2017). Evaluating Frameworks That Provide Value Measures for Health Care Interventions. *VALUE IN HEALTH*, *20*(2), 185–192. https://doi.org/10.1016/j.jval.2016.11.013

Manolio, T. A., Chisholm, R. L., Ozenberger, B., Roden, D. M., Williams, M. S., Wilson, R., … Korf, B. (2013). Implementing genomic medicine in the clinic: The future is here. *Genetics in Medicine*, *15*(4), 258–267. https://doi.org/10.1038/gim.2012.157

Marshall, M. N. (1996). Sampling for qualitative research. *Family Practice*, *13*(6), 522–526.

Martin, K., Bégaud, B., Latry, P., Miremont-Salamé, G., Fourrier, A., & Moore, N. (2004). Differences between clinical trials and postmarketing use. *British Journal of Clinical Pharmacology*, *57*(1), 86–92. https://doi.org/10.1046/j.1365-2125.2003.01953.x

McKee, A. E., Farrell, A. T., Pazdur, R., & Woodcock, J. (2010). The role of the U.S. Food and Drug Administration review process: Clinical trial endpoints in oncology. *The Oncologist*, *15 Suppl 1*(Supplement 1), 13–8. https://doi.org/10.1634/theoncologist.2010-S1-13

Meropol, N. J., Egleston, B. L., Buzaglo, J. S., Benson, A. B., Cegala, D. J., Diefenbach, M. A., … Weinfurt, K. P. (2008). Cancer patient preferences for quality and length of life. *Cancer*, *113*(12), 3459–3466. https://doi.org/10.1002/cncr.23968

Miller, T. P., Aplenc, R., Schnipper, L. E., Schilsky, R. L., Jim, H. S. L., & McLeod, H. L. (2017). American Society of Clinical Oncology Value Framework: Importance of accurate toxicity data reply. *Journal of Clinical Oncology*, *35*(10), 1133+. https://doi.org/10.1200/JCO.2016.70.9253

Miller, T. P., Li, Y., Kavcic, M., Troxel, A. B., Huang, Y.-S. V., Sung, L., … Aplenc, R. (2016). Accuracy of adverse event ascertainment in clinical trials for pediatric acute myeloid leukemia. *Journal of Clinical Oncology*, *34*(13), 1537–1543. https://doi.org/10.1200/JCO.2015.65.5860

Mitchell, A. P., Harrison, M. R., George, D. J., Abernethy, A. P., Walker, M. S., & Hirsch, B. R. (2014). Clinical trial subjects compared to "real world" patients: Generalizability of renal cell carcinoma trials. *Journal of Clinical Oncology*, *32*(5 suppl), abstract 6510.

Mitchell, S. A., & Chambers, D. A. (2017). Leveraging implementation science to improve cancer care delivery and patient outcomes. *Journal of Oncology Practice*, *13*(8), 523–529. https://doi.org/10.1200/JOP.2017.024729

MSKCC. (2017). DrugAbacus: Drug Pricing Lab. Retrieved from https://drugpricinglab.org/tools/drug-abacus/

National Institute for Health and Care Excellence. (2009). Medicines adherence: Involving patients in decisions about prescribed medicines and supporting adherence. Retrieved from https://www.nice.org.uk/guidance/cg76

NCCN. (2017a). National Comprehensive Cancer Center Network Evidence Blocks. Retrieved from https://www.nccn.org/evidenceblocks/

NCCN. (2017b). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) with NCCN Evidence Blocks. Retrieved from https://www.nccn.org/professionals/physician_gls/default.aspx

NCI. (n.d.). NCI's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE): Selecting Items and Assessment Frequency for Cancer Trials: Seventh Annual Patient-Reported Outcome (PRO) Consortium Workshop. Retrieved from https://healthcaredelivery.cancer.gov/pro-ctcae/

NCI. (2017a). Definition of adjuvant therapy. Retrieved from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=45587

NCI. (2017b). Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). Retrieved from https://healthcaredelivery.cancer.gov/pro-ctcae/

NCI. (2018). Definition of progression-free survival. Retrieved from https://www.cancer.gov/publications/dictionaries/cancer-terms/def/progression-free-survival

Neugut, A. I., Hillyer, G. C., Kushi, L. H., Lamerato, L., Buono, D. L., Nathanson, S. D., … Hershman, D. L. (2016). A prospective cohort study of early discontinuation of adjuvant chemotherapy in women with breast cancer: The Breast Cancer Quality of Care Study (BQUAL). *Breast Cancer Research and Treatment*, *158*(1), 127–138. https://doi.org/10.1007/s10549-016-3855-3

Nilsen, P. (2015). Making sense of implementation theories, models and frameworks. *Implementation Science, 10*, 53. https://doi.org/10.1186/s13012-015-0242-0

Niraula, S., Amir, E., Vera-Badillo, F., Seruga, B., Ocana, A., & Tannock, I. F. (2014). Risk of incremental toxicities and associated costs of new anticancer drugs: A meta-analysis. *Journal of Clinical Oncology*, *32*(32), 3634–3642. https://doi.org/10.1200/JCO.2014.55.8437

Norris, P. E., O'Rourke, M., Mayer, A. S., & Halvorsen, K. E. (2016). Managing the wicked problem of transdisciplinary team formation in socio-ecological systems. *Landscape and Urban Planning*, *154*, 115–122. https://doi.org/10.1016/j.landurbplan.2016.01.008

Northouse, P. G. (2016). *Leadership: Theory and practice* (7th ed.). Thousand Oaks, CA: SAGE.

Ocean, A., & Vahdat, L. (2004). Chemotherapy-induced peripheral neuropathy: pathogenesis and emerging therapies. *Supportive Care in Cancer*, *12*(9), 619–625. https://doi.org/10.1007/s00520-004-0657-7

Ohio Office of Budget and Management. (n.d.). Value Management Framework: Steering Committee Basics, Composition. Retrieved from https://obm.ohio.gov/doc/VMO/Guidance and Instructions/2 Initiate/Steering Committee Basics, Composition and Management - Guidance for Sponsors and PMs.pdf

PCORnet. (2017). PCORnet, the National Patient-Centered Clinical Research Network. Retrieved from http://www.pcornet.org

Pearce, A., Haas, M., & Viney, R. (2013). Are the true impacts of adverse events considered in economic models of antineoplastic drugs? A systematic review. *Applied Health Economics and Health Policy*, *11*(6), 619–637.

Peron, J., Maillet, D., Gan, H. K., Chen, E. X., & You, B. (2013). Adherence to CONSORT adverse event reporting guidelines in randomized clinical trials evaluating systemic cancer therapy: A systematic review. *Journal of Clinical Oncology*, *31*(31), 3957–3963. https://doi.org/10.1200/JCO.2013.49.3981

Pettit, S. D., & Kirch, R. (2018). Do current approaches to assessing therapy related adverse events align with the needs of long-term cancer patients and survivors? *Cardio-Oncology*, *4*(1), 5. https://doi.org/10.1186/s40959-018-0031-4

Pettit, S. D., Lipshultz, S. E., Cleeland, C. S., Roberts, S., Davis, M., Berridge, B. R., & Kirch, R. A. (2016). Enhancing quality of life as a goal for anticancer therapeutics. *Science Translational Medicine*, *8*(344), 344ed9. https://doi.org/10.1126/scitranslmed.aag0382

Price, M. (2016). Circle of care modelling: An approach to assist in reasoning about healthcare change using a patient-centric system. *BMC Health Services Research*, *16*, 546. https://doi.org/10.1186/s12913-016-1806-7

Rajan, S. S., Carpenter, W. R., Stearns, S. C., & Lyman, G. H. (2013). Short-term costs associated with primary prophylactic G-CSF use during chemotherapy. *The American Journal of Managed Care*, *19*(2), 150–159.

Redig, A. J., & Jänne, P. A. (2015). Basket trials and the evolution of clinical trial design in an era of genomic medicine. *Journal of Clinical Oncology*, *33*(9), 975–977. https://doi.org/10.1200/JCO.2014.59.8433

Rittel, H. W. J., & Webber, M. M. (1973). Dilemmas in a general theory of planning. *Policy Sciences*, *4*(2), 155–169.

Santoni, M., Conti, A., De Giorgi, U., Iacovelli, R., Pantano, F., Burattini, L., … Cascinu, S. (2014). Risk of gastrointestinal events with sorafenib, sunitinib and pazopanib in patients with solid tumors: A systematic review and meta-analysis of clinical trials. *International Journal of Cancer*, *135*(4), 763–773. https://doi.org/10.1002/ijc.28544

Schnipper, L. E., & Bastian, A. (2016). New Frameworks to Assess Value of Cancer Care: Strengths and Limitations. *Oncologist*, *21*(6), 654–658. https://doi.org/10.1634/theoncologist.2016-0177

Schnipper, L. E., Davidson, N. E., Wollins, D. S., Blayney, D. W., Dicker, A. P., Ganz, P. A., … Schilsky, R. L. (2016). Updating the American Society of Clinical Oncology Value Framework: Revisions and Reflections in Response to Comments Received. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *34*(24), 2925–34. https://doi.org/10.1200/JCO.2016.68.2518

Shah-Manek, B., Galanto, J. S., Nguyen, H., & Ignoffo, R. (2017). Value frameworks for the patient-provider interaction: A comparison of the ASCO Value Framework versus NCCN Evidence Blocks in determiningvalue in oncology. *Journal of Managed Care and Specialty Pharmacy*, *23*(6 Suppl), S13–S20.

Sherman, R. E., Anderson, S. A., Dal Pan, G. J., Gray, G. W., Gross, T., Hunter, N. L., … Califf, R. M. (2016). Real-world evidence — What is it and what can it tell us? *New England Journal of Medicine*, *375*(23), 2293–2297. https://doi.org/10.1056/NEJMsb1609216

Sherman, R. E., Davies, K. M., Robb, M. A., Hunter, N. L., & Califf, R. M. (2017). Accelerating development of scientific evidence for medical products within the existing US regulatory framework. *Nature Reviews Drug Discovery*, *16*(5), 297–298. https://doi.org/10.1038/nrd.2017.25

Shingler, S. L., Bennett, B. M., Cramer, J. A., Towse, A., Twelves, C., & Lloyd, A. J. (2014). Treatment preference, adherence and outcomes in patients with cancer: Literature review and development of a theoretical model. *Current Medical Research and Opinion*, *30*(11), 2329–41. https://doi.org/10.1185/03007995.2014.952715

Siddiqui, M., & Rajkumar, S. V. (2012). The high cost of cancer drugs and what we can do about it. *Mayo Clinic Proceedings*, *87*, 935–943. https://doi.org/10.1016/j.mayocp.2012.07.007

Singh, S., Butow, P., Charles, M., & Tattersall, M. H. N. (2010). Shared decision making in oncology: Assessing oncologist behaviour in consultations in which adjuvant therapy is considered after primary surgical treatment. *Health Expectations*, *13*(3), 244–257. https://doi.org/10.1111/j.1369-7625.2009.00587.x

Sorensen, S. V, Goh, J. W., Pan, F., Chen, C., Yardley, D., Martin, M., … Iyer, S. (2012). Incidence-based cost-of-illness model for metastatic breast cancer in the United States. *International Journal of Technology Assessment in Health Care*, *28*(1), 12–21. https://doi.org/10.1017/S026646231100064X

Speck, R. M., Sammel, M. D., Farrar, J. T., Hennessy, S., Mao, J. J., Stineman, M. G., & DeMichele, A. (2013). Impact of chemotherapy-induced peripheral neuropathy on treatment delivery in nonmetastatic breast cancer. *Journal of Oncology Practice*, *9*(5), e234–e240. https://doi.org/10.1200/JOP.2012.000863

Stopeck, A., Rader, M., Henry, D., Danese, M., Halperin, M., Cong, Z., … Chung, K. (2012). Cost-effectiveness of denosumab vs zoledronic acid for prevention of skeletal-related events in patients with solid tumors and bone metastases in the United States. *Journal of Medical Economics*, *15*(4), 712–723. https://doi.org/10.3111/13696998.2012.675380

Subramanian, R., & Schorr, K. (2016). Musings on value frameworks in cancer. *Journal of Comparative Effectiveness Research*, *5*(5), 437–439. https://doi.org/10.2217/cer-2016-0041

Thanarajasingam, G., Hubbard, J. M., Sloan, J. A., & Grothey, A. (2015). The imperative for a new approach to toxicity analysis in oncology clinical trials. *Journal of the National Cancer Institute*, *107*(10), djv216. https://doi.org/10.1093/jnci/djv216

Tina Shih, Y.-C., Xu, Y., & Elting, L. S. (2007). Costs of uncontrolled chemotherapy-induced nausea and vomiting among working-age cancer patients receiving highly or moderately emetogenic chemotherapy. *Cancer*, *110*(3), 678–685. https://doi.org/10.1002/cncr.22823

Ting, J., Tien Ho, P., Xiang, P., Sugay, A., Abdel-Sattar, M., & Wilson, L. (2015). Cost-effectiveness and value of information of erlotinib, afatinib, and cisplatin-pemetrexed for first-line treatment of advanced EGFR mutation-positive non-small-cell lung cancer in the United States. *Value in Health*, *18*(6), 774–782. https://doi.org/10.1016/j.jval.2015.04.008

Tremblay, M.-A. (1957). The key informant technique: A nonethnographic application. *American Anthropologist*, *59*(4), 688–701. https://doi.org/10.1525/aa.1957.59.4.02a00100

Twelves, C. J., & X-ACT Investigators. (2006). Xeloda (R) in adjuvant colon cancer therapy (X-ACT) trial: Overview of efficacy, safety, and cost-effectiveness. *Clinical Colorectal Cancer*, *6*(4), 278–287. https://doi.org/10.3816/CCC.2006.n.046

U.S. Department of Veterans Affairs. (2017). Million Veteran Program (MVP). Retrieved from https://www.research.va.gov/mvp/

University of Washington. (n.d.). Key informant interview handbook. Retrieved from http://courses.washington.edu/nutr531/HEBD/KIInterviews/KeyInformantInterviewHandbook.pdf

USAID. (1996). Conducting key informant interviews: Performance monitoring and evaluation tips. Retrieved from http://pdf.usaid.gov/pdf_docs/pnabs541.pdf

Usmani, S. Z., Cavenagh, J. D., Belch, A. R., Hulin, C., Basu, S., White, D., … Facon, T. (2016). Cost-effectiveness of lenalidomide plus dexamethasone vs bortezomib plus melphalan and prednisone in transplant-ineligible US patients with newly-diagnosed multiple myeloma. *Journal of Medical Economics*, *19*(3), 243–258. https://doi.org/10.3111/13696998.2015.1115407

Van Der Weijden, T., Pieterse, A. H., Koelewijn-Van Loon, M. S., Knaapen, L., Légaré, F., Boivin, A., … Elwyn, G. (2013). How can clinical practice guidelines be adapted to facilitate shared decision making? A qualitative key-informant study. *BMJ Quality & Safety*, *22*, 855–863.

Van Tulder, R., & Keen, N. (2018). Capturing collaborative challenges: Designing complexity-sensitive theories of change for cross-sector partnerships. *Journal of Business Ethics*, *150*, 315–332. https://doi.org/10.1007/s10551-018-3857-7

Waddock, S., Meszoely, G. M., Waddell, S., & Dentoni, D. (2015). The complexity of wicked problems in large scale change. *Journal of Organizational Change Management*, *28*(6), 993–1012. https://doi.org/10.1108/JOCM-08-2014-0146

Waldeck, A. R., Botteman, M. F., White, R. E., & van Hout, B. A. (2017). The importance of economic perspective and quantitative approaches in oncology value frameworks of drug selection and shared decision making. *Journal of Managed Care and Specialty Pharmacy*, *23*(6–a Suppl), S6–S12.

Wallner, M., Köck-Hódi, S., Booze, S., White, K., & Mayer, H. (2016). Nursing management of cutaneous toxicities from epidermal growth factor receptor inhibitors. *Clinical Journal of Oncology Nursing*, *20*(5), 529–536. https://doi.org/10.1188/16.CJON.529-536

Weber, E. P., & Khademian, A. M. (2014). Wicked problems, knowledge capacity builders in network challenges, settings and collaborative. *Public Administration Review*, *68*(2), 334–349. https://doi.org/10.1111/j.1540-6210.2007.00866.x

Weinfurt, K. P., Hernandez, A. F., Coronado, G. D., Debar, L. L., Dember, L. M., Green, B. B., … Curtis, L. H. (2017). Pragmatic clinical trials embedded in healthcare systems: Generalizable lessons from the NIH Collaboratory. *BMC Medical Research Methodology*, *17*, 144. https://doi.org/10.1186/s12874-017-0420-7

Westrich, K., Buelt, L., & Dubois, R. W. (2017). Why value framework assessments arrive at different conclusions: A multiple myeloma case study. *Journal of Managed Care & Specialty Pharmacy*, *23(6-a Sup*(6), S28–S33.

Wharton School of Business. (2009). Does your company's steering committee function as well as it should? Retrieved from http://knowledge.wharton.upenn.edu/article/does-your-companys-steering-committee-function-as-well-as-it-should/

White House. (2016). The Vice President's Cancer Moonshot. Retrieved from https://obamawhitehouse.archives.gov/cancermoonshot

Wholey, J. S., Hatry, H. P., & Newcomer, K. E. (2010). *Handbook of practical program evaluation* (3rd ed.). San Francisco, CA: Jossey-Bass.

Wong, Y.-N., Egleston, B. L., Sachdeva, K., Eghan, N., Pirollo, M., Stump, T. K., … Meropol, N. J. (2013). Cancer patients' trade-offs among efficacy, toxicity, and out-of-pocket cost in the curative and noncurative setting. *Medical Care*, *51*(9), 838–845.

Wong, Y. N., Meropol, N. J., Speier, W., Sargent, D., Goldberg, R. M., & Beck, J. R. (2009). Cost implications of new treatments for advanced colorectal cancer. *Cancer*, *115*(10), 2081–2091.

Woodcock, J., Ware, J. H., Miller, P. W., Mcmurray, J. J. V, Harrington, D. P., & Drazen, J. M. (2016). Clinical trials series. *New England Journal of Medicine*, *374*, 2167. https://doi.org/10.1056/NEJMe1601510

Woolf, C. J. (2010). Overcoming obstacles to developing new analgesics. *Nature Medicine*, *16*(11), 1241–1247. https://doi.org/10.1038/nm.2230

World Health Organization. (2003). *Evidence for action*.

Xie, J., Diener, M., Sorg, R., Wu, E. Q., & Namjoshi, M. (2012). Cost-effectiveness of denosumab compared with zoledronic acid in patients with breast cancer and bone metastases. *Clinical Breast Cancer*, *12*(4), 247–258. https://doi.org/10.1016/j.clbc.2012.04.001

Yabroff, K. R., Lund, J., Kepka, D., & Mariotto, A. (2011). Economic burden of cancer in the United States: estimates, projections, and future research. *Cancer Epidemiology, Biomarkers & Prevention*, *20*(10), 2006–2014. https://doi.org/10.1158/1055-9965.EPI-11-0650

Yang, G. S., Kim, H. J., Griffith, K. A., Zhu, S., Dorsey, S. G., & Renn, C. L. (2017). Interventions for the treatment of aromatase inhibitor-associated arthralgia in breast cancer survivors: A systematic review and meta-analysis. *Cancer Nursing*, *40*(4), E26–E41. https://doi.org/10.1097/NCC.0000000000000409

Yu, P. P. (2016). Challenges in measuring cost and value in oncology: Making it personal. *Value in Health*, *19*(5), 520–4. https://doi.org/10.1016/j.jval.2016.04.017

Zafar, S. Y., Currow, D., & Abernethy, A. P. (2008). Defining best supportive care. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *26*(31), 5139–40. https://doi.org/10.1200/JCO.2008.19.7491

Zhang, S., Liang, F., Tannock, I., Peron, J., Pond, G., Gan, H., … Colevas, A. (2016a). Use and misuse of common terminology criteria for adverse events in cancer clinical trials. *BMC Cancer*, *16*(1), 392. https://doi.org/10.1186/s12885-016-2408-9

Zhang, X., Zhang, Y., Ye, X., Guo, X., Zhang, T., & He, J. (2016b). Overview of phase IV clinical trials for postmarket drug safety surveillance: a status report from the ClinicalTrials.gov registry. *BMJ Open*, *6*(11), e010643. https://doi.org/10.1136/bmjopen-2015-010643

Zucca, A., Sanson-Fisher, R., Waller, A., & Carey, M. (2014). Patient-centred care: Making cancer treatment centres accountable. *Support Care Cancer*, *22*, 1989–1997. https://doi.org/10.1007/s00520-014-2221-4