Assessing the Impact of Health Economics and Outcomes Research Evidence on Reimbursement Decisions in the United States

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ABSTRACT

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Objectives: Health economics and outcomes research (HEOR) is a growing field that has gained substantial momentum in recent decades. While studies establishing a product's safety and efficacy have a well-understood role in drug development and commercialization processes, the impact of HEOR in the U.S. is less clear. We sought to understand the impact of HEOR evidence on reimbursement success in the U.S.

Methods: We conducted a literature review to understand the evolution of HEOR and existing knowledge about its impact on reimbursement decisions in the U.S. We conduced focus group sessions and planning surveys with pharmaceutical industry HEOR executives to understand the scope of HEOR evidence that is produced and to assess how investments are selected. We developed and administered a survey with this audience to more formally assess how HEOR investment decisions vary based on product and market scenarios. Based on our findings, we crafted detailed hypotheses as to when specific types of HEOR evidence are important to U.S. payers and tested these hypotheses in a survey of HEOR decision-makers in pharmaceutical companies and formulary decision-makers for payer organizations.

Results: Previous studies suggest a growing importance of HEOR evidence in U.S. reimbursement decisions; however, much of the existing literature fails to account for the growing scope of HEOR. We

defined HEOR to include eight types of evidence that are produced to support new products. Our survey of HEOR executives from pharmaceutical companies suggests significant agreement as to when HEOR is likely to have a positive impact on U.S. reimbursement decisions. Our survey of payers confirmed the growing interest in HEOR evidence. In some instances, the scenarios in which HEOR evidence is perceived to be important varies between pharmaceutical and payer decision-makers.

Conclusions: Pharmaceutical companies are investing in a range of HEOR to support payers' reimbursement decisions. This evidence has a substantial role in formulary decision-making processes and its use is expected to grow. There is some evidence of misalignment as to when specific types of evidence are important; understanding when payers value HEOR evidence will allow pharmaceutical companies to produce more relevant evidence in the future.

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CHAPTER 1

A Brief History of the Evolution of Health Economics and Outcomes Research and Its Impact on Reimbursement Decisions in the U.S.

Introduction

The History and Growth of HEOR in the United States

Health economics and outcomes research (HEOR) is a growing field that has gained substantial momentum in recent decades. While studies establishing the safety and efficacy of new pharmaceutical products are required for marketing approval and have a well-understood role in the processes of drug development and commercialization, the role and impact of HEOR, especially in the U.S., is less clear and continues to evolve. However, with growing complexity in the mechanisms of reimbursement, in regulation, and in other factors that affect market uptake, potential for commercial success is a critical component when assessing the expected value of a new patented medicine: the growing importance of what is often called "market access" on the path to commercial success seemingly supports the case for investment in HEOR.

HEOR in the pharmaceutical market is a relatively new field, and the utilization of economic evidence to support pharmaceutical reimbursement is still evolving in the U.S. and elsewhere. The advent of health economics as a specialization of economics began in the late 1950s and early 1960s. Though not the first use of disease-specific quality of life instruments, the field of outcomes research came into prominence in the 1970s through the development of the SF-36 for the RAND Health Insurance Experiment.[1] And while heavily emphasized recently due to rapid and unsustainable growth in healthcare expenditures, resource allocation decisions in health care have been a longstanding focus, and cost-effectiveness analyses (CEAs) remain the hallmark of health economic studies in supporting such decisions. Though decision-making is inevitably limited by imperfect data, CEAs have been touted as a scientific framework with the ability to evaluate the net costs of a new intervention against the net health benefits afforded by the intervention, accounting for both clinical and quality of life measures.[2] The use of CEAs to inform resource allocation decisions has gained traction with some key decision-makers globally. Beginning in 1993, Australia's Pharmaceutical Benefits Advisory Committee (PBAC) has conducted detailed reviews of cost-effectiveness for new drugs to determine the prices at which drugs are cost-effective and to inform decisions about which drugs to subsidize and what restrictions should be applied to their use.[3] In 1999, the U.K. established the National Institute for Health and Clinical Excellence (NICE) as an authority charged with appraising new and existing technologies; a study by Bryan et al. determined

economic analyses to be of "central importance" for decision-making by NICE.[4] In addition to Australia and the U.K., CEAs are also explicitly used in decision-making in Canada and the Netherlands.[5,6] The ascension of economic analyses in healthcare is highlighted by the fact that only five economic evaluations related to healthcare interventions were published in 1966, 518 were published in 1996, and over 2,000 were published between 1991 and 1996.[7]

A flurry of activity in the 1990s and 2000s was suggestive that U.S. payers might formally integrate the use of economic evidence in reimbursement decision-making as is done in other countries with centralized health technology assessment (HTA). The presence and role of HEOR functions in pharmaceutical companies expanded in the mid-to-late 1990s, with departments contributing to commercially-focused activities and beginning to provide input into early, strategic decisions in drug development.[8,9] With this, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) was birthed in 1995, aimed at promoting the use of pharmacoeconomics and outcomes research by healthcare decision-makers.[10] Around the same time, the Pharmaceutical Research and Manufacturers of America (PhRMA) issued a guidance for the conduct and evaluation of pharmacoeconomic research.[11] Shortly thereafter, the U.S. Panel on Cost-Effectiveness and Medicine issued an assessment of and guidelines for the development of CEAs.[12] In 2000, the Academy of Managed Care Pharmacy (AMCP) endorsed its own guidelines, the AMCP Format for Formulary Submissions, which encouraged formal requests for dossiers of clinical and economic evidence from pharmaceutical companies by health plans.[13,14]

Yet, twenty years later, the perception remains that decision-makers in the U.S. are reluctant to include cost-effectiveness as a criterion for coverage determinations, and efficacy and safety data remain the primary focus of reimbursement decisions.[6,15] Indeed, some Medicaid programs are statutorily required to cover any drug approved by the Food and Drug Administration (FDA), and the Centers for Medicare and Medicaid Services (CMS) purport that cost and cost-effectiveness are not factors in their coverage decisions.[16,17] Still, the larger HEOR scientific community has continued to embrace CEA and the quality-adjusted life-year (QALY) metric as providing the preferred tools to make societal decisions about access to new technologies.[18,19] The Tufts CEA Registry has now accumulated and summarized the findings of some 4,000 CEA studies.[20] Nonetheless, the recent Affordable Care Act established the

Patient-Centered Outcomes Research Institute (PCORI) to perform comparative effectiveness research but effectively prohibited PCORI from leveraging CUAs.[21]

The U.S. pharmaceutical market has long been considered a "free pricing" environment, particularly in comparison to international systems where there exists an explicit negotiation between the monopsony government payers and monopolist/oligopolist pharmaceutical companies before a product can be sold. Limited use of economic data in the U.S. is attributed to the political risks of denying coverage on the basis of costs, perception of bias in models developed by pharmaceutical companies, lack of payer expertise to evaluate models, and the use of irrelevant timeframes and populations in models that do not translate to the payer setting.[6,15,17,22,23] However, while payers have historically been reluctant to deny coverage on the basis of costs, copayments, deductibles, and restrictions on use are common mechanisms of cost-control that are employed. Interestingly, in 2013, pharmacy benefit managers (PBMs) Express Scripts and CVS Caremark announced plans to exclude numerous drugs from their national formularies. In this unprecedented move, Express Scripts excluded 48 drugs from their formulary in 2014 and 66 drugs in 2015; CVS Caremark excluded 72 drugs in 2014 and 96 drugs in 2015.[24] These drops in coverage were publicly attributed to the use of co-payment cards by pharmaceutical companies that counteracted co-payments as a mechanism of moderating use of expensive drugs, and it remains unclear to what degree product-level economic data may have informed this decision. As Mullins et al. indicate, "between the late 1990s and 2008, payer perceptions and the use of pharmacoeconomic data changed substantially, even dramatically… but for most payers, a mixture of structured and judgmental methods – not standard cost-effectiveness analyses – drive adoption and tiering decisions".[17]

The U.S. Pharmacoeconomics Puzzle

Historically, while payers in international markets have made pharmacoeconomic evidence a prerequisite for obtaining reimbursement, the U.S. healthcare system has been very open to the adoption of new medicines. Once drugs have been approved by the FDA as having a sufficient benefit-risk balance to allow marketing authorization, payers have given physicians considerable power to prescribe these products, oftentimes even paying for "off-label" use. Despite the unclear linkage between HEOR investments and reimbursement or commercial success in the U.S., strategic and tactical support from

HEOR units in pharmaceutical companies is believed to have a substantial impact on the success of a compound. Specifically, it is believed that the impact on reimbursement success is a major contribution of HEOR studies.

Therein exists what has been termed the "U.S. pharmacoeconomics puzzle": why do we observe so many HEOR research scientists in the U.S. given the apparent limited use of cost-effectiveness analysis and its outright prohibition for Medicare coverage decisions? Given the U.S.'s aversion to health care rationing decisions, it would seem that pharmacoeconomics is of limited value in this context. While the exact impact of HEOR evidence on U.S. payer decisions is unclear, pharmaceutical companies continue to invest in research in this field; it is therefore reasonable to assume that the field is playing some role in the U.S. pharmaceutical marketplace.

One important consideration is the scope of HEOR: the traditional view of health economics and outcomes research seems to be focused narrowly on CEAs and CUAs. Over the years, however, the breadth of studies undertaken by HEOR departments in pharmaceutical companies has expanded. While variation exists in the structure and remits of HEOR organizations across companies, the evidence generated certainly extends beyond CEAs. Yet the question remains as to how pharmaceutical companies select investments to support U.S. reimbursement decisions and how payer organizations value the many types of HEOR evidence.

Research Objectives

It is hypothesized that HEOR evidence is used to support private payer tiering decisions and restrictions on product use and is a major contributor to the achievement of reimbursement success for pharmaceutical products. Further, it is believed that broader HEOR evidence that is less controversial – such as treatment pattern studies and burden/cost of illness studies – is of significant importance to payers making formulary decisions.

To guide future investment decisions, it is valuable to understand how HEOR investments, including but also beyond CEAs, influence the likelihood of success in achieving broad reimbursement and market access within the U.S. Such an understanding will enable pharmaceutical companies to determine the incremental value of various HEOR investments and to prioritize such investments in an evidence-based manner.

The purpose of this dissertation research is:

- To better understand the functioning and role of HEOR in the U.S. marketplace. What types of HEOR studies do pharmaceutical companies invest in and when?
- To shed light on the pharmacoeconomics puzzle by seeking to understand how both HEOR practitioners and formulary decision-makers for payer organizations in the U.S. regard the need for HEOR evidence with respect to achieving reimbursement success.
- To assess the level of alignment between payers and pharmaceutical companies with respect to when HEOR evidence is necessary to inform reimbursement decisions in the U.S.

Review Of Existing Literature

Literature Review Strategy

We conducted a literature review of all studies that examined the importance of HEOR evidence to payer organizations, both from a payer perspective and from a pharmaceutical company perspective. We restricted our search to English language, U.S.-focused studies only. We conducted searches of PubMed and the grey literature. Search terms included: 'health economics', 'pharmacoeconomics', 'outcomes research', 'payer decisions', 'formulary decisions', 'coverage decisions', and 'reimbursement'. We excluded studies that did not involve primary research (e.g., opinion/thought pieces). We leveraged a snowball search strategy and reviewed citations of the literature identified in our primary searches. An overview of the key studies is provided in Table 1-1.

Impact of HEOR Evidence on U.S. Payer Decision-Making

Previous studies have attempted to understand the impact of pharmacoeconomic/health economic evidence on reimbursement decisions in the U.S. In the 1990s and early part of the 2000s, studies undertaken to answer this question were focused on the importance of CEAs and generally did not evaluate the importance of other types of HEOR.[25-27] These studies reported a range of findings, but as Luce et al. acknowledge, the concept of CEAs and QALYs were not well understood at the time, bringing the reliability of these findings into question.[26] This was evidenced by the fact that 92% of the managed care decision-makers surveyed by Luce et al. indicated that they use cost-effectiveness evidence in drug assessments, but only 65% stated they were familiar with modeling as a technique. As summarized in the

Report of the ISPOR Task Force on Use of Pharmacoeconomic/Health Economic Information in Health-Care Decision Making, most studies conducted around this time found that concerns about health economic data were related to internal and external validity of the findings – i.e., reliability concerns due to the numerous assumptions and potential biases and relevance concerns given the differences between clinical trial and payer populations.[19] Other reasons for the limited use of CEAs were attributed to the lack of training and resources to interpret evidence by managed care organizations and the drug silo mentality.[28-31]

During the first few years of the early 2000s, the use of HEOR evidence by payers in the U.S. started to pick up. In 2000, Cox et al. conducted telephone surveys with 16 pharmacy benefit decision-makers and presented participants with statements incorporating pharmacoeconomic and health outcomes concepts, and asked participants to judge the relevance of each statement.[30] More than 80% of respondents thought the following concepts were relevant: quality of life, cost of prevention, cost per year of life saved, increased life expectancy, and two-year cost savings. The following concepts were *irrelevant* to more than 35% of respondents: willingness to pay, cost to society, and global cost of illness. In the same year, Motheral et al. conducted three separate surveys with payers related to the use and importance of pharmacoeconomic information, sources of pharmacoeconomic information, internal research activities, and barriers to the use of pharmacoeconomic information.[32] The authors found that the importance of pharmacoeconomic evidence varies by therapeutic area, but that short-term medical savings were considered the most important pharmacoeconomic data with respect to drug benefit decision-making. Additionally, they found that 88% of respondents used pharmacoeconomic information in some capacity of decision making: 50% use it for most or every decision, 33% use it for some decisions, and 15% used it for few decisions. However, 62% of respondents indicated that only occasionally did pharmacoeconomic information result in a change or other action. Also in 2000, Evans et al. conducted a survey of twenty pharmacy directors from managed care organizations; respondents were asked to rate the level of importance of seven types of evidence when making formulary decisions.[31] Efficacy, safety, cost-effectiveness, and cost of treatment were rated as “important” or “very important” on average. None of the respondents stated that pharmacoeconomic evidence was “very important”. In addition, a test of pharmacoeconomic terms revealed that most respondents did not have a strong

understanding of common terms. Finally, in 2002, Delate et al. conducted focus group sessions with pharmacy benefit decision-makers in the U.S. and U.K., focused specifically on the importance of health-related quality of life (HRQOL) data.[33] They found that HRQOL data was considered most important when efficacy and cost were equal. However, the use of HRQOL data to inform decisions was determined to be generally limited, and the key barriers identified were that relevant and timely data were often not available at the time of decision-making, and decision-makers are not trained to interpret HRQOL data. The authors also asked participants to rate the importance of various factors in their pharmacy benefit decisions; the following were rated as top factors (in order of importance): efficacy, cost-effectiveness, cost, and safety.

It is important to consider these varied findings in the context of the timeframe in which they were conducted. In the 1990s and early 2000s, tiered formularies and copayments were still gaining momentum as a mechanism to control drug expenditures. In a survey of pharmacy directors, only 62% had implemented a tiered copayment structure by 2000.[34] Further, almost all of these studies were conducted prior to the establishment of the AMCP Format for Formulary Submission; these guidelines were issued in 2000 and uptake by payer organizations ensued in the subsequent years.[13] The generation and distribution of health economic evidence may have also been hampered during this time by section 114 of the Food and Drug Administration Modernization Act of 1997, which regulated the economic claims that drug companies could make and created much ambiguity as to what was allowable.[35,36] Thus, we would expect that familiarity with and interest in HEOR evidence on the part of formulary decision-makers would significantly increase after this time.

Indeed, more recent studies certainly indicate an increase in the generation and uptake of HEOR studies. The issues became less about whether payers had access to HEOR evidence or whether they understood the data, and more about how they used health economic evidence and how it was prioritized among all of the factors that played into their decision-making. A 2007 survey of 20 stakeholders from managed care organizations found that 87.5% of respondents reviewed dossiers within their organizations, though only 40% of drugs reviewed had dossiers.[37] Almost two-thirds said they modified the models received to reflect their own patient populations, and 40% said they developed their own models. Yet, most respondents indicated that clinical efficacy and safety were still the primary focus.

Another 2007 study examined whether receipt of a dossier impacted a product's formulary placement for one Pharmacy and Therapeutics (P&T) Committee.[38] The authors requested 43 AMCP dossiers from various drug companies; in response, 58% of companies provided dossiers, 23% provided other drug information, 9% provided a formulary kit, and 9% did not respond. Of the dossiers received, 68% included pharmacoeconomic models: 20% included budget impact models and 48% included modeling reports with no model provided. Provision of a dossier had no effect on whether the product was given preferred status on the formulary: in fact, none of the products for which dossiers were provided were assigned to the second copayment tier, whereas 33% of products with no dossier were placed on the second tier.

In another study, Mullins et al. conducted interviews with decision-makers representing 17 organizations to examine recent changes in payers' use of, perceived value of, and attitudes towards the generation and dissemination of pharmacoeconomic evidence. The findings of these interviews indicate that payers understand pharmacoeconomic evidence and believe such evidence is useful; further, almost all consider pharmacoeconomic evidence in their decision-making process.[17] As the authors noted, this represents a major shift in payers' perceptions over the last 10 to 20 years. Still, payers differ in how they use pharmacoeconomic evidence. Barriers to use include: perception of biased selection, analyses answering the wrong questions from a payer perspective, clinical trial populations that do not translate to payer populations, and the separation of rebating and value assessment which results in rebates holding more weight.

Holtorf et al. also took on a survey-based approach to understand how HEOR data are used by payers and assessed expectations for change in the future.[39] Conducted in 2010, the study involved two surveys – one with managed care decision-makers (n=72) and one with P&T committee members (n=30). 74-77% of survey respondents indicated that they currently use HEOR information in the formulary decision-making process, and 82% of respondents indicated they expect the use of HEOR to increase in the future. In the survey of P&T committee members, participants were asked to rate the importance of 13 attributes in their formulary decision-making. The most important factors in the P&T decision-making process were safety and efficacy, followed by head-to-head comparisons and cost. Other attributes tested include: current drug market share, net ingredient cost, outcomes data, drug differentiation, drug

superiority, ability of manufacturer to drive market share, customer programs, manufacturer relationship, rebates, and size of manufacturer.

In a study published in 2012, Leung et al. conducted one-hour telephone interviews with medical and pharmacy directors responsible for prescription drug benefit design and formulary management (n=32 respondents representing 26 companies).[40] Respondents were asked to rate the importance of various types of evidence on a scale of 1 to 5 (1=not very important, 5=very important). The highest rated sources of evidence were published peer-reviewed studies (4.68), technology assessments (4.22), and internal data on utilization (4.14). The highest-rated types of evidence were randomized controlled trials (4.40), and systematic reviews or meta-analyses (3.66). Prospective observational studies (3.31), budget impact analyses (3.27), cost and economic studies (3.09), and retrospective observational studies (3.03) were rated lower, relatively, but the absolute values do indicate some level of importance to decision-makers.

Pharmaceutical Perspectives of the Impact of HEOR Evidence

Though pharmacoeconomic research was being conducted long before, the formalized institution of HEOR functions within pharmaceutical companies began in the mid-1990s.[9] At the time, members of the pharmaceutical industry argued that pharmacoeconomic research, and specifically CEAs, were becoming increasingly important as strategic considerations during drug development to ensure that pipeline products were commercially viable based on their cost-effectiveness.[8,41-43] A survey of the heads of pharmacoeconomics departments (n=45 representing 31 companies) conducted in 2001 found that 88% of respondents expected to submit more dossiers to reimbursement authorities in the following two to three years.[9] In addition, only 11% of respondents indicated they never use pharmacoeconomic studies for reimbursement planning in the U.S.; 40% indicated they use them but less than half the time, and 49% reported they use them more than half the time. Seventy-nine percent expected the frequency of use for reimbursement purposes to increase in the next two to three years. Highest-ranked barriers to the more optimal conduct and use of pharmacoeconomics included: insufficient resources dedicated to the pharmacoeconomics function, conflicting internal priorities, and lack of understanding of the role of pharmacoeconomics by senior management. A survey by Armstrong et al. in 2001 of managed care liaisons, account managers, and outcomes research professionals (n=21 representing 15 companies)

rated the top factors in payers' coverage decisions to be: drug cost, clinical condition being treated, contract issues with the drug, and availability of comparable drugs.[44] The factors that were rated least important to payers were: nonmedical costs, quality of life information, and long-term medical savings. Further, 62% of respondents indicated they had received requests for models from payers.

Another study, conducted in 2002, found that pharmacoeconomics research scientists believe that models do impact managed care formulary decisions: 19 out of 20 respondents indicated they had atleast one experience where a pharmacoeconomic model resulted in more optimal formulary placement.[45] There was no consensus among respondents as to which therapeutic areas pharmacoeconomic data had the greatest impact in, or which type of pharmacoeconomic evidence was most important to formulary decision-makers.

Trends in study findings demonstrate the significant uptake in the development and consumption of pharmacoeconomic evidence in the first decade of the 21st century. Nichol et al. conducted telephone surveys with stakeholders from pharmaceutical companies (n=7) in 2004 and 2005.[37] Most respondents (five out of seven) stated that their companies always included an economic model within the AMCP dossier; the other two respondents indicated that 85% and 50% of their companies' dossiers included economic models. Most recently, in 2013, Neumann et al. surveyed 74 U.S.-based leaders in HEOR departments in 41 drug and device companies.[46] Ninety-two percent of respondents indicated they expect their company's use of HEOR to increase, 80% indicated their organization's senior management views HEOR work as critical, and 62% agreed that the AMCP Dossier is useful to health plans.

Implications Of Literature Review Findings

A review of the literature suggests a significant increase in the importance of HEOR evidence to U.S. formulary decision-makers in the past twenty years. However, the existing literature has largely focused on cost-effectiveness analyses, and to some extent, health-related quality of life studies. We did not identify any studies that consider a broader, more comprehensive scope of HEOR. Additionally, only one study, conducted a decade ago, assessed the importance of HEOR from both the payer and pharmaceutical company perspectives.[37] Even so, the ability to draw any strong conclusions from this

study is significantly impaired by the small sample size of pharmaceutical respondents. In general, fewer published studies have focused on the perspective of decision-makers within pharmaceutical companies.

The literature provides evidence of the importance of HEOR in U.S. reimbursement decisions. Many of the barriers that were cited twenty years ago are less of an obstacle today: payers have invested in resources allowing them to more critically evaluate economic evidence supplied by manufacturers, general familiarity and comfort with CEAs and QALYs has increased, and payers have an ever-increasing stake in the bid to manage the costs of treatment. Atleast one payer has even taken the step to develop a value-based formulary for which the formulary tiers are determined based on product's cost-effectiveness.[47]

The evolution of the use of pharmacoeconomic evidence in industry allows us to now ask more nuanced questions about the development and impact of such evidence:

- How do decision-makers for pharmaceuticals decide which types of evidence to invest in for a given product?
- When is HEOR evidence important to payers?
- What types of HEOR evidence are payers interested in for new medicines?
- Are the two stakeholders aligned and is the generation of HEOR evidence optimized for reimbursement success?

We seek to answer these questions in the forthcoming chapters.

Table 1-1. Summary of Key Studies.

Author (Year)	Study Population	Methods	Sample Size	Key Findings
Payer Perspective				
Luce (1995)[25]	Decision-makers from hospitals, HMOs, third party payers	Interviews	48	• Formulary decision-makers pay attention health consequences of new drug use • CEAs have a limited to moderate role in technology assessment; varies by payer type
Luce (1996)[26]	Managed care organizations	Telephone survey	51	• Respondents consistently endorsed the use of economic considerations for new drugs; 92% say they use cost-effectiveness in assessing drugs • Only 65% were familiar with modeling as a technique • >50% of the plans conduct assessments for atleast half of all new drugs • Clinical effectiveness was rated as most useful type of assessment; 2nd highest was for CEAs. The lowest ratings were for treatment cost and QOL
Grabowski (1997)[27]	PBMs	Interviews with and materials provided by PBMs	5	• Formularies are becoming more restrictive over time • The use of cost-effectiveness in formulary decisions has been limited but is expected to increase with the implementation of disease management programs
Burns (2000)[28]	Government, private, and employer-based purchasers	Focus Groups	55 (U.S.: 25)	• Purchasers value HTA information but few use it • Barriers in the use of studies are: greater concern with cost vs. quality, difficulties in accessing/ interpreting clinical and cost-effectiveness data
Grizzle (2000)[29]	Managed care decision-makers	Telephone survey	31	• Most believe PE information is important • The main barriers to using study results are lack of relevance, drug silo mentality, lack of credible information, lack of resources, no focus on long-term costs, and lack of expertise

Author (Year)	Study Population	Methods	Sample Size	Key Findings
Cox (2000)[30]	Pharmacy benefit decision-makers	Telephone interviews	16	• QALYs are difficult to conceptualize • QOL, cost of prevention, cost/year of life saved, increased life expectancy, and 2-year savings were relevant to >80% of respondents • WTP, cost to society and global cost of illness statements were considered irrelevant by >35%
Evans (2000)[31]	Medical and Pharmacy Directors from MCOs	Telephone survey	MD: 21 PD: 20	• 29.3% indicated that <=25% of agents received a PE/QOL review prior to formulary acceptance; 20% said that 26-50% of products received this review; 20% indicated that 51-75% of products received this type of review; and 24% said that 76%-100% did. • Efficacy, safety, and cost-effectiveness were scored as "important" to "very important" in formulary decision-making. Pharmacy directors ranked safety data the highest; both groups ranked C-E data third. • 60% of pharmacy directors said that the cost of treatment was "important" or "very important" • 63.4% of respondents were "somewhat concerned" or "very concerned" with indirect costs of a disease • Almost all respondents felt that they had at least an adequate understanding of PE, yet in a test of terms, most PE terms were not well understood • PE information plays a more important role in decision-making than it did 5 years ago and most (95%) felt its role would increase in the future
Motheral (2000)[32]	HMO/PPO pharmacists/physicians	Mail surveys (3)	409 (total across 3 surveys)	• 88% indicated that PE information is used in some capacity of decision-making: 50% use PE information for most/every decision, 33% use it for some decisions, 15% used it for few decisions • 60% stated that PE information was more important for some therapeutic classes than others • 62% indicated that only occasionally did it translate into action or result in change • Published pharmacoeconomic studies showing short-term medical savings were rated as the most important to drug benefit decision-making

Author (Year)	Study Population	Methods	Sample Size	Key Findings
Delate (2002)[33]	Pharmacy benefit decision-makers	Focus Groups	20	• HRQOL information more useful when other more important factors (e.g., efficacy and cost) are equal • Efficacy was ranked the most important factor in decision-making, followed by C-E, cost, and safety
Nichol (2007)[37]	MCO stakeholders	Telephone Interviews	20	• 87.5% of MCO personnel reviewed dossiers within their organization; only 40% of drugs had dossiers • Nearly 2/3s of MCO respondents modified the economic models with their own population statistics • Most MCO respondents stated their primary focus was on efficacy and safety • 40% of MCOs said they had developed original economic models to support their decisions
Spooner (2007)[38]	P&T Committee	Retrospective review of dossiers sent to P&T Committee	1 Committee; 43 Dossiers	• Received dossiers for 58% of requests and other drug information (journal reprints, product labeling) for 23%, formulary kit for 9%, no response for 9% • Receipt of AMCP dossier does not appear to influence the likelihood of a product attaining preferred formulary status
Holtorf (2012)[39]	Managed Care & P&T Committee	Surveys	Managed Care (n=72) P&T Comm. (n=30)	• 74-77% state HEOR is currently used in decision-making; 82% expect use to increase in the future • Safety and efficacy are the most important factors in the P&T decision-making process, followed by head-to-head comparisons and cost; decisions are based on price when clinical factors are equal
Mullins (2011)[17]	Formulary decision-makers (private insurers, employers, PBMs, public payers)	Intensive interviews	17 organizations	• Payers are more accepting of PE data and generally find it useful; differ in how rigorously they use it • Factors impeding use of PE information: (1) perception of biased selection, (2) analyses are answering the wrong questions, (3) difficulties translating RCT results to payer population, and (4) bifurcation of value assessment and price assessment (rebating)

Author (Year)	Study Population	Methods	Sample Size	Key Findings
Leung (2012)[40]	Those involved with P&T Committees	In-depth qualitative interviews	20	• RCTs and systematic reviews/meta-analyses were the most valued types of evidence; economic and observational data studies received low ratings • Substantial variation in the process of evidence review, who and how individuals participated in the process, and outcomes related to formulary tier placement and utilization management
Pharmaceutical Perspective				
DiMasi (2001)[9]	Heads of pharmacoeconomics departments	Survey	40	• PE functions are new and growing rapidly • Strategic role of PE is not well understood in the org • PE analyses have been increasingly initiated early in development and have been a factor in trial design and in key decisions made during development
Armstrong (2001)[44]	Medical science liaisons, account managers, and outcomes research professionals	Telephone survey	21	• Most important factors in coverage decisions are: drug cost, indication, contracting issues, availability of comparable drugs • Least important factors: nonmedical costs, quality of life information, long-term medical savings • Nearly all indicated their company provided PE information to customers during the previous year • 62% indicated they had received requests for a mathematical or economic model • 1 customer required PE information before they would consider the drug for inclusion
Olson (2003)[45]	PE research scientists in pharmaceutical and biotech companies	Telephone survey	20	• 19/20 respondents had at least one experience where a PE model played a role in optimizing the formulary positioning of a product • There was no consensus as to which type of model (e.g., decision analysis, spreadsheet analyses, Markov models, regression models) is most effective
Nichol (2007)[37]	PhRMA Foundation's Health Outcomes Committee	Telephone interviews	7	• 5/7 respondents indicated their companies always included an economic model with the dossiers; one indicated 85% of dossiers included models, another said 50% of dossiers included economic models

Author (Year)	Study Population	Methods	Sample Size	Key Findings
Neumann (2013)[46]	U.S.-based HEOR departments	Web-based survey	74	• 92% expect their company's HEOR use to increase • 80% reported that their organizations' management viewed HEOR work as critical • 62% agreed that the AMCP dossier is useful

PE = pharmacoeconomic; WTP = willingness to pay; C-E = cost-effectiveness.

CHAPTER 2

Conceptual Framework

Project Scope

The overall goal of our research is to assess the drivers of HEOR investment and impact of HEOR evidence on payers' formulary decisions. The scope of this research is limited to U.S. payers, with an emphasis on private payers. As previously described, the demand for HEOR evidence varies significantly across the major markets, and focusing on the U.S. will allow more detailed examination of a market where the value of HEOR evidence to payers is less well understood, especially compared to systems where it is mandatory. Our focus is further narrowed to a review of private U.S. payers, as government payers in the U.S. have statutory limitations regarding their ability to consider costs and cost-effectiveness in making formulary decisions.

The study focuses on pharmaceutical products only, as other medical technologies differ significantly in evidentiary requirements and evaluation. We focus on HEOR evidence developed during clinical development and provided to payers to inform the initial reimbursement decision for a new medicine following regulatory approval. The scope of HEOR evidence under consideration is that produced by pharmaceutical companies: studies conducted by other parties are unlikely to be available at the time of reimbursement decisions and deviate from the intention of this research to identify decision-making criteria and the impact of investments made by pharmaceutical companies. Finally, as market success for innovative medicines in the U.S. is largely based on the extent of coverage and since the binary decision to include a drug on the formulary is typically based on clinical and not cost data, the emphasis of this research will be to examine the decision to restrict access (e.g., by use of tiering resulting in variable copayments and deductibles, therapeutic interchange, restricted use to sub-populations and/or requirements for pre-authorization).

Key Actors And Their Objectives

Pharmaceutical/Biotechnology Companies

Stakeholder Perspectives, Goals, and Incentives

Pharmaceutical companies' primary goals are to develop innovative medicines, maximize profits in a global marketplace, and to expand market share of their products in the market. Pharmaceutical companies either have a monopoly if first in class or operate in an oligopolistic market (prior to generic

entry in the class). Given the high costs of drug development, companies likely want to obtain the highest price the market will bear for their product, and in the U.S., to achieve product placement on the lowest tier possible to maximize market share. Any additional value (in terms of health benefits or cost-offsets) they can demonstrate will help them to achieve these goals.

Strategy

Pharmaceutical companies operate in a global marketplace; however, the U.S. marketplace, as the least price-sensitive market and potentially the most profitable, has a substantial impact on the design of the clinical, regulatory, and commercial strategies. The HEOR strategy is typically aligned with the overall product strategy, and models and evidence are generated during product development to quantify the economic value of a product or to evaluate the longer-term outcomes of patients related to the product's use. This evidence, which supplements the traditional safety and efficacy data required for product approval by the U.S. FDA, is believed to play a role in a product's commercial success. A key aspect of this is the effect on reimbursement decisions and formulary placement in the U.S. Optimal formulary placement also functions as "push promotion": better formulary placement increases physician prescribing and patient use of products.

However, the models and evidence constructed as part of the HEOR strategy can have relevance for multiple markets and therefore are subject to economics of scale and scope. Larger companies typically have HEOR subunits in their affiliates that may be responsible for tailoring evidence generated for larger markets to meet the unique needs of other markets.

Beyond the inherent value of evidence generated in informing payer, physician, and patient decisions and uptake, there exist other possible reasons for the generation of HEOR evidence. One such reason is the concept of an "arms race": if companies with competing products have developed HEOR evidence to support their products, a pharmaceutical company may be remiss not to have similar evidence to present to payers. Further, as found in the literature, payers perceive the information presented by pharmaceutical companies to be biased and purposively selected if it paints the product in question in a positive light; however, if HEOR evidence is not presented at all, does this suggest to payers that the product's value story is undesirable? Another reason for the generation of HEOR evidence may be to create a "buzz" about a product: in our early conversations with the sponsoring

pharmaceutical companies (“Steering Committee”, comprised of 14 HEOR executives from various pharmaceutical companies), we found that strong clinical products are often allotted larger budgets for HEOR as more resources are dedicated to pipeline products that are deemed to have the greatest commercial potential. However, this warrants the question: is the generation of HEOR evidence strategic or simply to create awareness of new products? Any “buzz” generated around a product would certainly increase awareness among physicians and patients, thereby potentially increasing prescriptions written and product sales.

Tactics

HEOR functions leverage numerous tools to demonstrate the economic value of a product or to evaluate the longer-term outcomes related to a product's use. These tools include studies and methodologies to generate evidence on:

- Adherence/Compliance
- Budget Impact
- Burden/Cost of Illness
- Cost-Effectiveness/Cost-Utility
- Indirect Treatment Comparisons
- Health-Related Quality of Life / Utility (Patient-Reported Outcomes)
- Resource Utilization/Cost-Offsets

Commercial Payers/Pharmacy Benefit Managers (PBMs)

Stakeholder Perspectives, Goals, and Incentives

Commercial payers in the U.S. finance the cost of health care and seek to improve patient health while controlling or minimizing costs. Payers seek to maximize market share and the number of subscribers and for-profit companies also seek to maximize profits. PBMs, or companies that may administer pharmacy benefits on behalf of payers or employers, manage drug formularies and also seek to manage utilization and to make prescription drugs more affordable, while maximizing profits. For the purposes of this research, commercial payers and PBMs are collectively referred to as “payers”.

Strategy

While U.S. payers are incentivized to minimize health care expenditures, they have historically been reluctant to deny coverage of new medicines on the basis of price. Instead, tiered copayments and restrictions on use (e.g., step therapy and prior authorization requirements) are mechanisms of cost-control that are employed.

Interestingly, U.S. payers had historically created internal organizational siloes that separated decision-making about medical versus drug benefits. The previous separation of these benefits and claims in some cases meant that Pharmacy Directors had less interest in any medical cost-offsets generated by the use of a pharmaceutical product. However, as these siloes are slowly being disrupted, disease management strategies have become more comprehensive and the impacts that drugs have on medical expenditures are becoming of greater consideration.

Tactics

U.S. payers leverage two types of formularies: closed and open. A closed formulary is one in which the payer does not provide coverage of any non-formulary drugs; in an open formulary, payers will typically provide coverage for both formulary and non-formulary drugs, though to different degrees. The majority of plans leverage open formulary designs.[48]

The binary decision to include a drug on the formulary, when employed, is likely based on clinical and not cost data. In addition, due to political reasons, payers are extremely unlikely to deny coverage for drugs that are clinically superior to other drugs available for a specific indication. Conversely, payers are likely to take measures to limit access to drugs that are clinically inferior or when drugs are priced higher but their relative effectiveness appears comparable to other treatment options.

Most plans leverage three or four tier formularies that involve higher out-of-pocket costs with increasing tiers. According to a report by the Pharmacy Benefit Management Institute, 92% of employers surveyed indicated that their plan design includes three or more tiers; additionally, 67% indicated that their plans require copayments (versus coinsurance), and 14% indicated they use deductibles.[49] Below is an example of a common four-tier formulary structure in today's market:

Tier 1: Generic drugs

Tier 2: Preferred branded drugs

Tier 3: Non-preferred branded drugs

Tier 4: Specialty pharmaceuticals

Products on tiers 1 through 3 typically are assigned copayment amounts that increase with higher tiers. Products on tier 4 may have the highest copayments or increasingly involve a coinsurance percentage that may be capitated at a certain amount.[49]

Other tools used by payer organization to control drug utilization include:[48,50]

- Prior authorization: A plan must pre-authorize use of a drug with the pharmacy or prescribing physician before the patient can fill a prescription for the drug.
- Step therapy: Enrollees must try one drug (typically, a less expensive drug on a lower tier) before the payer will authorize use of another drug (typically, a more expensive drug on a higher tier).
- Therapeutic substitution: Pharmacists are instructed to work with the prescribing physician to change a prescription for a non-formulary drug to a formulary drug.
- Patient and prescriber education: Patients/prescribers are informed by the plan that lower cost drugs for the same indication are available.

Tiered formularies serve as a mechanism to motivate physicians and incentive patients to seek the lowest cost treatment. Since the evidence generated for FDA approval may differ from the evidence needed by payers, these formulary structures are also a motivating for pharmaceutical companies to generate the necessary evidence required to achieve optimal formulary placement. Additionally, tiered formularies increase the bargaining power of payer organizations with respect to rebate negotiations and can motivate pharmaceutical companies to offer net prices that provide value for money.

Defining HEOR And HEOR Evidence

In addressing the question of how HEOR is used in the patented pharmaceutical and biotechnology markets in the U.S., it is necessary to delineate the scope of HEOR and identify the types of studies that are conducted during clinical development.

ISPOR defines health economics (HE) as “a discipline that analyzes the economic aspects of health and health care and that usually focuses on the costs (inputs) and the consequences (outcomes) of healthcare interventions using methods and theories from economics and medicine”.[51] The

organization defines pharmacoeconomics (PE) as “the scientific discipline that assesses the overall value of pharmaceutical health care products, services, and programs. Of necessity, it addresses the clinical, economic and humanistic aspects of health care interventions in the prevention, diagnosis, treatment, and management of disease”.[51] Further, outcomes research is defined as “the scientific discipline that evaluates the effect of health care interventions on patient-related, if not patient-specific, clinical, humanistic, and economic outcomes. Outcomes research is generally based on the conceptual framework that evaluation of treatment alternatives involves simultaneous assessment of multiple types of outcomes that are disease-related”.[51] These terms are not mutually exclusive; as defined above, health economics is a broader discipline that encompasses pharmacoeconomics, but would also include economic assessment of medical devices, and broader health care services and programs. For the purposes of this research, we use the terms interchangeably.

HEOR may have both a strategic and tactical role in the development and commercialization of innovative medicines. The strategic role addresses questions of the commercial consequences of development strategies (e.g., the targeted indication, comparator, and endpoints leveraged in clinical trials), and it can be used to assess the commercial viability of a new product. The tactical tools and activities that can be undertaken support the “value proposition” for a product: that is, the argument that the product offers “good value”. While it is more difficult to observe and measure the strategic role of HEOR, as it may not be demonstrated by specific investments but rather the knowledge capital provided by HEOR scientists, the tactical role can be observed by a discrete set of investments that may be undertaken to demonstrate a product’s value. In a survey with the Steering Committee members (see Appendix 2-1), we found that the large majority of pharmaceutical companies’ HEOR spend occurs in Phase 3 and post-approval (n=9, Figure 2-1), indicating the large role HEOR plays in supporting the value proposition of new drugs.

HEOR investments may include two types of research: (1) research related to the economics and costs, and (2) research related to the measurement of health outcomes. While these aspects are related and are in some cases used conjointly, there are a substantial number of HEOR research scientists who specialize in one or the other. For the purposes of this research, we identified a list of potential types of HEOR evidence based on a literature review of the scope of HEOR publications and

expert opinion. We tested this list in our initial survey with the Steering Committee by asking respondents to confirm whether their organizations conduct the specified studies or whether they are conducted by other functions within their company. Our survey confirmed 17 activities, and their associated costs, that are undertaken by HEOR organizations (Figures 2-2, 2-3). Given the variation across companies, the scope of activities is not perfectly clear; often, the types of activities conducted by the HEOR function may coincide with what is traditionally considered epidemiology or market/pricing research.

The initial list had a confluence of HEOR *study types* or *research methods* and HEOR *evidence types*. The differentiation between the two terms is relevant, as it is possible for multiple types of studies to product a single type of evidence. For example, cost-offsets can be measured using prospective observational studies or retrospective database studies. We elected to focus our research on types of HEOR *evidence,* as the methods used to generate evidence are a secondary concern to identifying the types of HEOR evidence that are important to decision-makers. Further, as our research interest is focused on the initial reimbursement decision after a product's approval, we restricted this list to include only those types of evidence that can be generated during product development. For this reason, we did not include any evidence types that involve generation of real-world evidence, as such data would not be available prior to FDA approval.

The list of HEOR evidence types was tested and revised during two focus group sessions with the Steering Committee. Based on this, we developed a list of eight HEOR evidence types that fall into the scope of investments an HEOR function might undertake during a product's development to demonstrate its value for the purposes of reimbursement. The evidence types are listed and briefly described below:

- Budget impact - Estimates the financial impact to a plan for covering a drug in a given a setting. Models can include drug costs, treatment costs, adverse event costs and other costs that may be added or offset with the use of treatment.
- Burden/cost of illness – Measures the amount of disease problem in a specific population at a given point of time. Burden is measured in terms of costs, quality of life, and/or length of life lost due to the presence of a given disease and therefore potentially avoidable with the use of a treatment.[51]

- Cost-effectiveness/cost-utility – Quantifies the incremental benefits/consequences and incremental costs of a new therapy versus the standard of care. Incremental benefits are measured in the same units, and cost-utility is a special case where benefits/consequences are measured using QALYs.
- Disease incidence/prevalence – Estimates the frequency of new cases of a disease that develop in a specified time period or the proportion of a population affected by a disease at a point in time; ultimately used to calculate the size of the targeted patient population.[51]
- Indirect treatment comparisons – Compares treatments that were not directly evaluated in head-to-head studies by synthesizing data from clinical studies and adjusting for the different patient populations in each study to evaluate how treatments might fare against one another if they had been directly compared.
- Patient health-related quality of life/utility – HRQOL measures health status, attitudes, values, and perceived levels of satisfaction and general well being with respect to specific health states or life as a whole from the individual's perspective. Utility quantitatively expresses an individual's preference for a particular health state under conditions of uncertainty.[51]
- Resource utilization/cost-offsets – Quantifies the health care resources that patients consume when being treated with a given disease. Often these are compared to the resource utilization costs of patients on other treatments or when patients are not treated.
- Unmet need (adherence/compliance of the standard of care) – Measures the consistency and accuracy with which a patient follows the recommended treatment regimen.

The various types of HEOR evidence may have differential impacts for different consumers. The table below indicates the authors' hypotheses as to the types of evidence that are important to each possible consumer of HEOR evidence. It is believed that HEOR evidence is most impactful to payers making decisions about coverage for new medicines; for this reason, we have elected to focus this research on better understanding if and when HEOR evidence is important to formulary decision-makers.

Evidence Type	Payers	Physicians	Patients
Adherence/Compliance	X	X	
Budget Impact	X		
Burden/Cost of Illness	X		
Cost-Effectiveness/Cost-Utility	X	?	
Disease Incidence/Prevalence	X		
Indirect Treatment Comparisons	X	X	X
Patient HRQOL/Utility	X	X	X
Resource Utilization/Cost-Offsets	X	X	?

Product & Market Attributes

As previously summarized, a review of the literature indicated that HEOR evidence is generally of increasing value to U.S. payers when making formulary placement decisions for new products. However, it is probable that HEOR evidence is not always important; specific types of evidence may be more relevant in certain scenarios. The underlying hypothesis of this study is that there are product-market scenarios for which HEOR evidence is likely to be of greater value in informing U.S. private payer reimbursement decisions. For example, it is possible that CUAs, which translate the health benefits afforded by an intervention into QALYs, may be of greater value to payers in scenarios where the clinical evidence for a product is based on intermediate outcomes and not explicitly on mortality benefits.[52] Many pivotal clinical trials use surrogate or intermediate measures as primary endpoints due to the costs of conducting long trials or trials that measure infrequent outcomes[5], but surrogate measures are usually a limited and imperfect proxy for everything that payers care about.

To identify the relevant product and market attributes with which to frame the scenarios, we conducted two focus group sessions with our Steering Committee of pharmaceutical company representatives to begin understanding how HEOR investments decisions, for the purpose of achieving optimal reimbursement in the U.S., are made, and to identify the important product and market attributes that guide the selection of specific HEOR investments (see Appendix 2-2 for a discussion guide/questionnaire). We elicited 21 attributes that the executives felt were important considerations when assessing the importance of HEOR. These attributes were categorized into product attributes, market attributes, data quality attributes, and other exogenous factors. The attributes identified are presented in Figure 2-4. Further, we found that Steering Committee members invest more in new molecular entities, followed by product approved for a new indication, new combinations, and new dosage

forms, respectively. Some studies are considered “standard investments” for some companies; five out of ten companies indicate they always invest in burden of illness studies, and four out of ten indicate they always invest in resource utilization / treatment pattern studies.

We then developed more nuanced hypotheses as to when specific types of HEOR evidence may be important, described in terms of product-market scenarios (Table 2-1). As we were unable to identify existing literature that explores the importance of HEOR evidence in this level of detail, these hypotheses were based on expert opinion, our focus group sessions with the Steering Committee, and one-on-one interviews conducted with payers (described in Chapter 4).

For the product-market scenarios listed in Table 2-1, HEOR evidence is hypothesized to be of value to payers because, under the stated conditions, HEOR evidence provides information beyond the requisite safety and efficacy data generated during clinical development that is relevant to the specified situation. In these situations, HEOR evidence reduces the uncertainty for payers and allows them to make decisions that maximize value and efficiency. These additional data points allow payers to make tiering decisions and restrict access to drugs in ways that meet their primary short-term objective: to maximize the value – health and peace of mind – obtained for their beneficiaries from the premiums paid.

Implications And Next Steps

The findings of our initial discussions with the Steering Committee indicate that HEOR is believed to have a significant and growing impact on the achievement of optimal formulary placement in the U.S. However, given the broadening scope of HEOR efforts, it is unknown how specific types of HEOR evidence impact reimbursement success.

Based on this conceptual framework, we conducted stated choice surveys with our Steering Committee to gain further insights into the specific product-market scenarios that drive investment in HEOR by pharmaceutical companies. With slight revisions to the framework based on those findings, we conducted broader surveys with HEOR research scientists and formulary decision-makers to test the hypotheses described in Table 2-1. These studies are summarized in the subsequent chapters.

Table 2-1. Hypotheses on the Importance of HEOR Evidence.

#	Hypothesis	Rationale
Budget Impact (BI)		
1	BI evidence is more important for diseases/indications with higher prevalence.	Payers may be concerned about the budget impact when large patient populations are targeted.
2	BI evidence is more important when the relative price of the product is higher.	When price is higher, it may be more critical to calculate the budget impact.
3	BI evidence is more important when a product has a worse adverse event profile.	Payers may be interested to see how the costs of AEs affect the total cost of treatment.
Burden/Cost of Illness (BCOI)		
4	BCOI evidence is more important when a product is earlier (1st) vs. later market entrant.	BCOI may be less well established for products that are first in class.
5	BCOI evidence is more important when the disease treated is rare, a less well-known disease, or when subpopulations of a disease are targeted.	Rare diseases may have less well-understood consequences. Targeted subgroups may have a different risk profile or treatment pattern than the larger population.
6	BCOI evidence is more important when the drug is indicated as an add-on therapy.	Quantifying the residual BCOI may justify the need for an add-on treatment.
Cost-Effectiveness/Cost-Utility (CEA/CUA)		
7	CEA/CUA evidence is more important when the trial endpoint is a surrogate.	CEA/CUA evidence attempts to extrapolate the impact on length/quality of life.
8	CEA/CUA evidence is more important for more severe diseases.	For more severe diseases, the impact on quality of life may be more important.
9	CEAs/CUAs evidence is more important when a drug is first in class.	When 1st in class, the drug sets the benchmark; CEA/CUA evidence may be less useful for followers that get benchmarked to the 1st in class.
10	CEA/CUA evidence is more important when a product's price is higher and efficacy is better than the standard of care.	CEA/CUA is necessary to justify the cost.
Indirect Treatment Comparisons / Network Meta-Analyses (ITC)		
11	ITCs are more important to payers when trials are conducted versus placebo.	ITCs are less important when trials are conducted versus the relevant SOC.
12	ITCs are more important when a product's efficacy or safety relative to the SOC is unclear.	A formal analysis is required to assess relative efficacy/safety.
Health-Related Quality of Life/Utility (HRQOL/U)		
13	HRQOL/U evidence is more important when the drug is indicated for a severe or life threatening disease.	Assessing patient impact for severe diseases is most important.
Resource Utilization/Cost-Offsets (RU/CO)		
14	RU/CO evidence is more important for less severe diseases.	Demonstrating cost-offsets provides value arguments for products for less severe disease.
15	RU/CO evidence is more important for add-on versus monotherapies.	RU/CO evidence may be important for add-on therapies to demonstrate value.
Unmet Need – Adherence/Compliance of SOC (UNAC)		
16	UNAC evidence is more important for chronic diseases.	Adherence/compliance tend to be lower for chronic diseases.

Figure 2-1. Trends in Distribution of HEOR Spend by Phase.

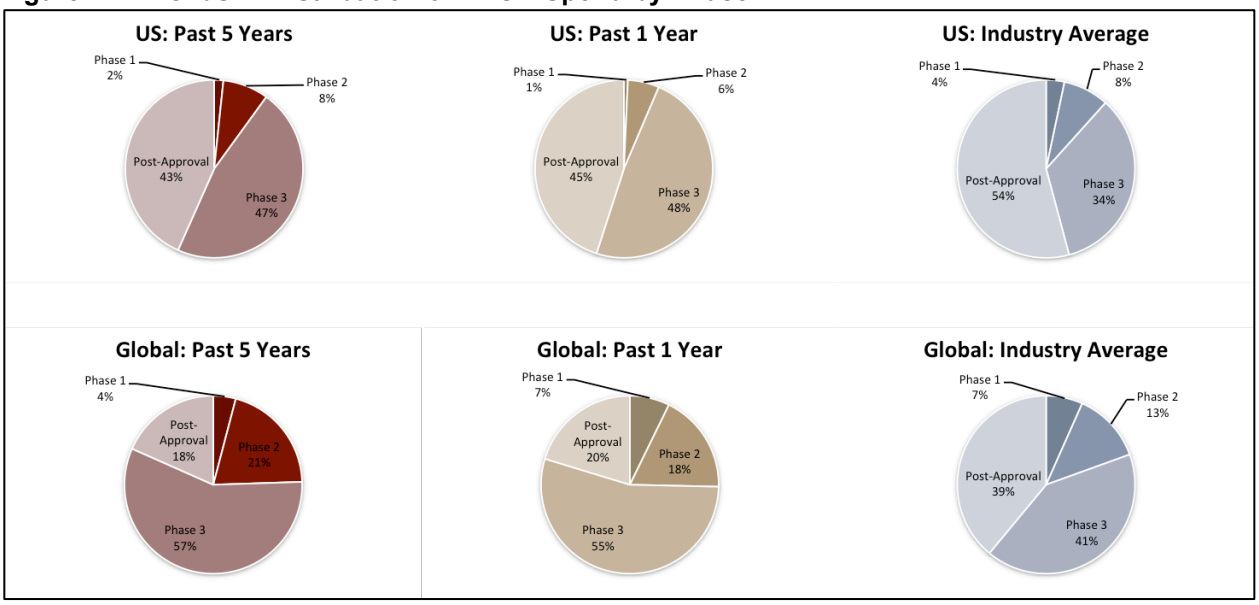


Figure 2-2. Types and Costs of HEOR Studies Conducted by Pharmaceutical HEOR Functions.

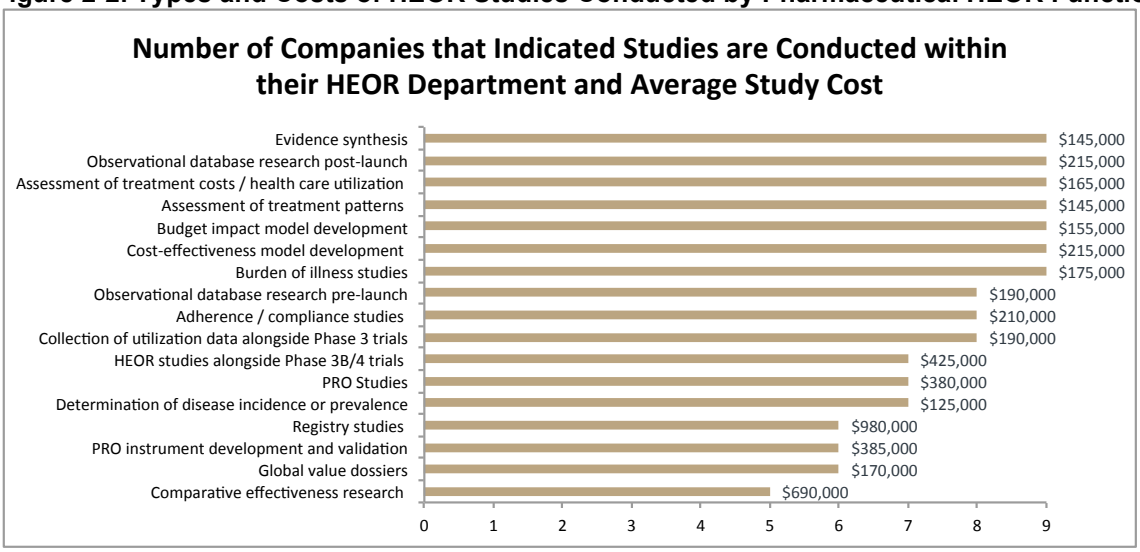


Figure 2-3. Average Costs of HEOR Studies.

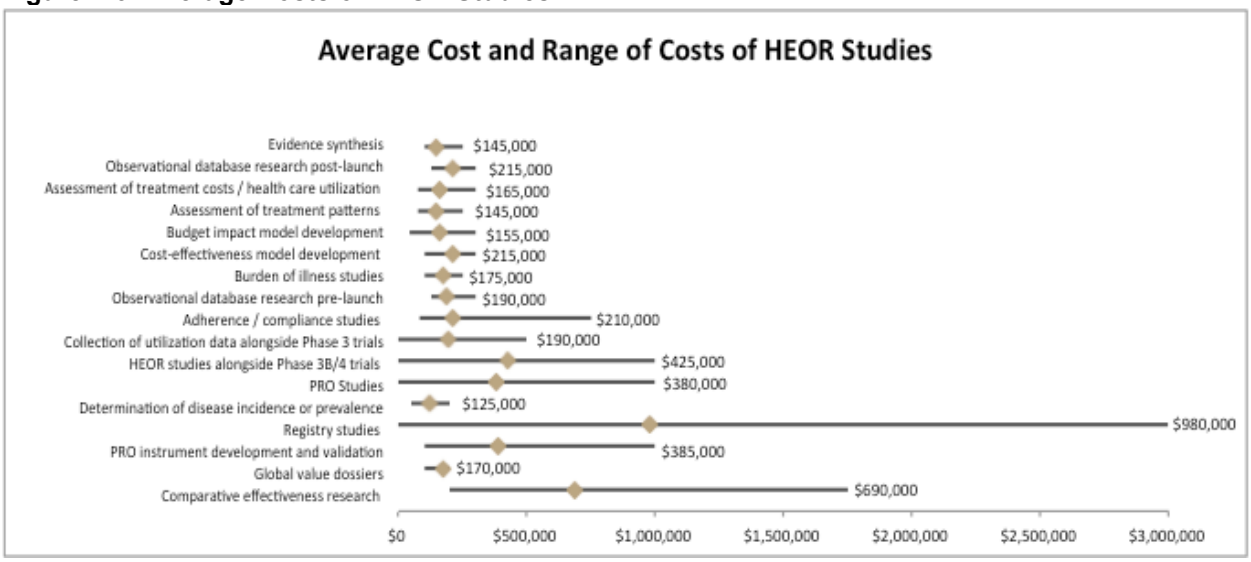
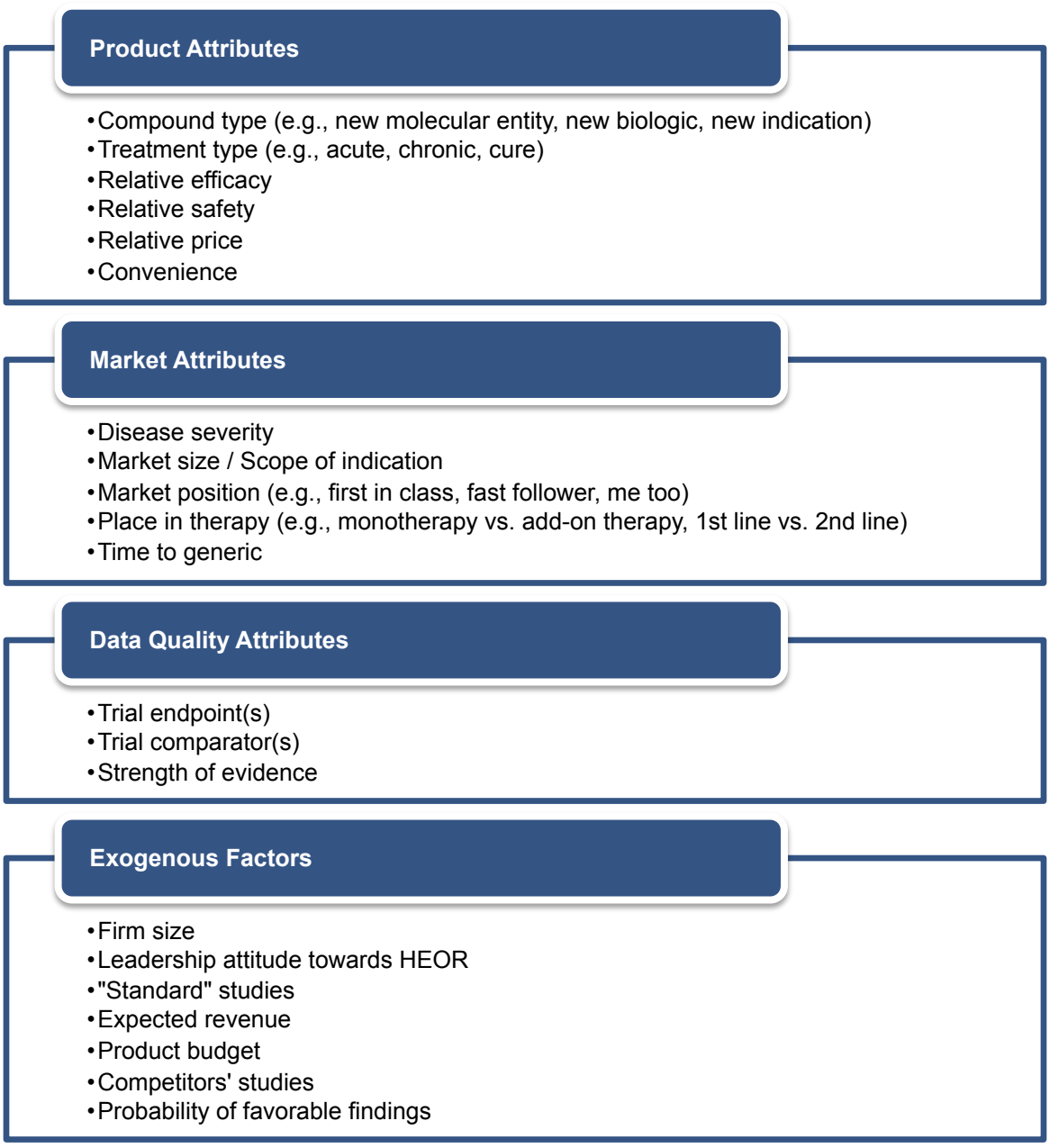


Figure 2-4. Attributes Identified in Focus Group Sessions.



CHAPTER 3

Understanding Pharmaceutical Company Investment In HEOR: A Survey Of HEOR Executives

Abstract

Objectives: Health economics and outcomes research (HEOR) is a growing field that has gained substantial momentum in recent decades. While studies establishing the safety and efficacy of pharmaceutical products have a well-understood role in the processes of drug development and commercialization, the impact of HEOR in the U.S. market is less clear. We sought to understand pharmaceutical decision-makers' perception of the importance of HEOR evidence to U.S. payers.

Methods: We conducted an online survey with HEOR leadership in pharmaceutical companies. We presented participants with twenty de-identified target product profiles and asked them to rate the likelihood that HEOR evidence would have a positive impact on reimbursement decisions in the U.S. and to select and prioritize up to four types of evidence that would be valuable to U.S. payers. We evaluated the association between the product and market attributes of each profile and the stated likelihood that HEOR evidence would have a positive impact using ordinal logistic regression. For ten products, we conducted literature reviews to identify HEOR publications and assess how stated importance correlated with actual investments.

Results: We received complete responses from 11 participants. There was significant agreement among respondents as to when HEOR is likely to have a positive impact on reimbursement decisions in the U.S. ($p<0.0001$). Respondents rated the impact of HEOR evidence to be significantly lower for products where the clinical trial was conducted with an active comparator versus placebo ($p<0.001$), when the product's relative efficacy was worse versus comparable relative to the standard of care ($p=0.011$), when the time to the approval of a generic product increased ($p<0.001$), and for products priced at a discount versus parity relative to the standard of care ($p=0.008$). Budget impact evidence was selected by a majority of respondents for almost every product profile. Respondents also selected indirect treatment comparison and resource utilization/treatment pattern evidence frequently. Respondents rarely indicated that they would not invest in any type of HEOR evidence. In general, there were a greater number of publications

for the products for which HEOR was rated as having a higher likelihood of positively impacting payer decisions (ρ=0.5926, p=0.0710).

Conclusions: Pharmaceutical companies are investing in a broad range of HEOR to support payers' reimbursement decisions in the U.S. There is evidence of agreement among HEOR leadership as to when such evidence is important to payers; variation in the responses across products suggests that there are certain product-market scenarios where HEOR evidence may be more impactful for payers.

Introduction

The use of health economics and outcomes research (HEOR) methods in the pharmaceutical industry enables companies to demonstrate the value of their products by establishing the costs and consequences of interventions, measured in clinical, economic, and humanistic terms.[51] HEOR is a growing field that has gained substantial momentum in recent decades. With growing complexity in the mechanisms of reimbursement, regulation, and in other factors that affect market uptake, the potential for commercial success is a critical component when assessing the expected financial value of a new patented medicine: the increasing importance of what is often called "market access" on the path to commercial success seemingly supports the case for investment in HEOR. However, while studies establishing the safety and efficacy of new pharmaceutical products are required for marketing approval and have a well-understood role in the processes of drug development and commercialization, the impact of HEOR in the U.S. market is less clear.

In the U.S., where most patients pay only a portion of the cost of prescription medicines under private health insurance coverage, the primary consumer of HEOR evidence is likely to be the payer organizations that cover the bulk of drug costs. Previous research indicates limited use of HEOR evidence, and specifically cost-effectiveness analyses (CEAs), by U.S. payers when making drug coverage and formulary placement decisions. This has been attributed to virtually automatic coverage of FDA-approved medicines in Medicaid programs[53], the political risks of denying coverage on the basis of costs, lack of payer expertise to evaluate models, and perception of bias in models developed by pharmaceutical companies, among other reasons.[6,15,17,22,23] However, with the growing focus on health care costs in the U.S., increased payer understanding of HEOR, and the development of more transparent and customizable models by pharmaceutical companies, payers' use of HEOR evidence does seem to be growing.[17,39,40] This may also be attributable to an expansion of the scope of HEOR to focus on evidence other than CEAs.

Less is known about how pharmaceutical companies perceive the importance of the HEOR evidence they generate for payers in the U.S. The existing literature indicates that pharmaceutical companies frequently develop CEAs and budget impact models (BIMs) to include in the Academy of Managed Care Pharmacy (AMCP) dossiers that are developed for payers, which provide some indication

of the perceived importance.[37,38,46] However, other than high-level qualitative assessments of how often models are developed, little is known about how companies choose the level and type of HEOR investments to support their products.

Given the seemingly growing appreciation and need for HEOR evidence on the part of U.S. payer organizations and the broadening scope of the types of HEOR evidence that pharmaceutical companies produce, we sought to achieve a more nuanced understanding of the supply of and demand for HEOR evidence for purposes of reimbursement decisions in the U.S. It is probable that specific types of HEOR evidence are more necessary or relevant in certain scenarios. In this study, we aim to better understand the supply side of the market by answering the following questions:

1) Which product and market attributes are taken into consideration when pharmaceutical HEOR decision-makers assess the importance of HEOR for a given product?
2) Is there agreement among pharmaceutical HEOR decision-makers as to the types of HEOR evidence that are important in specific product-market scenarios?
3) Are actual types and levels of investments made consistent with the stated importance of HEOR evidence?

Methods

Stated Choice Survey of Target Product Profiles

Survey Approach

In order to conduct a more structured assessment of the importance of HEOR and the relevant product and market attributes that are taken into consideration when making investment decisions, we conducted an online, stated choice survey with HEOR executives from the sponsoring pharmaceutical companies ('Steering Committee'), as described in Chapter 2. We presented participants with twenty "target product profiles" (TPPs) and asked them to review each profile as if it were a product currently in Phase 2 of development (See Appendix 3-1 for a sample TPP). We asked them to rate the likelihood that HEOR evidence would have a positive impact on reimbursement decisions in the U.S. on a four-point scale from very unlikely to very likely. In addition, participants were asked to select and prioritize up to four types of HEOR evidence that would be valuable to optimize U.S. payer reimbursement decisions for each product. (See Appendix 3-2 for the survey questions.)

Survey Development and Design

The TPPs were comprised of attributes elicited during focus group sessions with members of the Steering Committee, representing a range of pharmaceutical companies, each of whom provided some financial support to the larger project of which this study is one element. Not all attributes identified in the focus group sessions were included in the survey as some are difficult to measure or otherwise implicit within other attributes provided in the TPP (e.g., disease severity is implicit when the disease is specified). Additionally, attributes not explicitly identified during the focus groups were included if necessary to provide context for the product/market. The thirteen attributes that were included in the TPPs were: chemical type, indication, drug class, mechanism of action, dosage and administration, trial comparator(s), primary trial endpoint(s), efficacy, safety, market position, key competitor, time on market until the first key competitor's patent expires, and pricing versus key competitors. We provided parallel information for the key competitor in the footnotes of the profile.

The TPPs were based on actual products that were approved by the FDA between 2008 and 2010; however, the product profiles were de-identified in the context of the survey to reduce the chances that survey respondents would recognize the products, thereby reducing the likelihood that answers would be biased by the knowledge of a product's actual commercial success. The use of actual products allowed us to estimate the true level of investment for these products and compare stated versus revealed choices. The methods used to identify actual investments are described in the subsequent section.

In order to identify products for the TPPs, a sampling frame of all drugs approved by the U.S. Food and Drug Administration (FDA) between 2008 and 2010 was developed. This timeframe was selected to ensure sufficient time had passed post FDA approval such that we could identify HEOR publications for the products that were produced during development (i.e., with the intent to inform payers' reimbursement decisions) but which did not appear in the literature immediately due to the time required for publication and/or delays between product approval and launch. Additionally, we did not consider product approvals prior to 2008, as the recency of approval should minimize bias due to temporal changes in the field of HEOR.

We restricted the sampling frame of products to include only those that were developed by companies represented in our Steering Committee so that they could alert us to any nuances of the development or commercialization processes for these products that would have affected levels of HEOR investment (e.g., if a product was in-licensed during Phase 3 development). A subset of products was selected from this sampling frame to include only new molecular entities/new biologics, new indications, and new combinations. We further restricted the sample to exclude generic medicines, over the counter (OTC) medicines, any approvals that were minor amendments to approved products (e.g., supplements, formulation revisions, label revisions, manufacturing changes, alterations to the patient population), and special markets (e.g., cash market products, lifestyle products). The final sample utilized in the survey included 20 products, in an effort to minimize respondent burden. The process for identifying the shortlist of products is depicted in Figure 3-1.

Data were collected to inform the TPP attributes for each product that reflects, to the best of our ability, the likely TPP that was in place when actual HEOR investments for the product were being selected and prioritized. Data was aggregated from the Drugs@FDA Database, the American Society of Health-System Pharmacists (AHFS) Drug Information® compendium, each product's prescribing information/product label, Alliance Life Sciences' PRICENTRIC™ database, and expert opinion.

Respondents were asked to evaluate each TPP as if the TPP represented a product in Phase 2 of clinical development, such that responses would be based on the perceived relevance of HEOR evidence to the *initial* reimbursement decision after product approval and prior to the availability of real-world evidence. The TPPs were presented in randomized order for each participant to mitigate bias due to respondent fatigue. Additionally, respondents were given the option to skip profiles if they indicated they did not have sufficient familiarity with the disease/market.

This survey was administered online using SurveyMonkey® software, and was available from December 2013 until March 2014. This allowed respondents to complete the survey at their own convenience. No time restrictions were instituted, and respondents were able to save responses and return at a later date to complete the survey.

Population, Sampling, & Sample Size

The target population for this survey included members of the project Steering Committee. This committee is comprised of HEOR leadership from 14 pharmaceutical companies, though at the time of the survey, representatives from three pharmaceutical companies were unavailable. We sought a 100% response rate. While this sample size may not be sufficiently powered for statistical significance, the intent of the survey was to assess the trends that identify the most important attributes – a step beyond focus groups and qualitative research only. In addition, each respondent was asked to review 20 product profiles, increasing the number of observations from which we could draw conclusions.

Analysis

We used descriptive analyses to study the frequency with which respondents indicated they would conduct each type of HEOR study for each product. To identify the factors that are associated with the perceived impact of HEOR, the product and market attributes of each TPP were categorized into factors of each variable (Table 3-1). We then conducted a proportional odds ordered logistic regression to assess the association of product and market attributes (independent variables) with the perceived impact of HEOR (dependent variable). The model was specified as follows:

$$\text{ologit}\,[P(Y)] = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 X_5 + \beta_6 X_6 + \beta_7 X_7 + \beta_8 X_8$$

where Y = HEOR Impact, X_1 = compound type, X_2 = trial comparator, X_3 = relative efficacy, X_4 = market position, X_5 = relative pricing, X_6 = time to generic, X_7 = disease severity, and X_8 = respondent familiarity.

The model accounts for clustering of respondents/individuals as each individual completed 20 profiles. In addition, we adjusted for the respondent's stated level of familiarity with the market/disease for each TPP. We report the odds ratios of the likelihood that HEOR evidence would have a positive impact on U.S. payers' formulary decisions for each product/market attribute, and we assess the significance of each attribute ($p<0.05$).

We also assessed agreement among respondents in their ratings of the likelihood that HEOR evidence would have a positive impact on payer formulary decisions and their selection of the types of HEOR investments that would be most valuable. To do so, we categorized responses to the question of likelihood that HEOR would have a positive impact on reimbursement decisions into two categories: likely (original categories: 'very likely', 'somewhat likely') and unlikely (original categories: 'very unlikely',

'somewhat unlikely'), and counted the number of responses within each category for each TPP. To assess agreement across respondents for the types of evidence prioritized for each TPP, we tallied the number of respondents who did and did not select each evidence type for each TPP. For example, we counted the number of respondents who selected BIMs as an important investment and the number of respondents who did not select BIMs as an important investment for each TPP. Using these categories, we calculated the kappa statistic to assess the inter-rater reliability (two outcomes, multiple raters) for the overall likelihood that HEOR evidence would have a positive impact and for the types of HEOR evidence that would be important for each product.

Revealed Choice Assessment of Target Product Profiles (Literature Review)

Based on participants' responses with respect to the likelihood that HEOR evidence would have a positive impact on reimbursement decisions for each product, we created rankings of the products based on the median and mode of responses, as well as the proportion of respondents that rated the products as very likely to very unlikely to benefit from HEOR. Using these rankings, we selected ten products that fell at the tail ends and roughly in the middle of the spectrum of responses.

For the ten products identified, we conducted literature reviews to identify U.S.-focused HEOR publications that were published in the period five years prior to and two years after FDA approval. Restricting the search to this timeframe was intended to specifically identify HEOR evidence that may have been leveraged to influence payers' formulary decisions for the initial reimbursement decision following product approval. Publications were only included if author affiliations or funding sources indicated that the study was sponsored by the pharmaceutical company which developed/commercialized the product. Searches were conducted using PubMed, Web of Science, Scopus, and the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Scientific Presentations database, which includes presentations from all ISPOR meetings since 1998. Our search strategy included combinations of the following search terms: drug name, manufacturer name, disease/indication name, cost, outcomes, economic, quality of life, patient-reported outcomes, adherence, compliance, budget impact, resource utilization, treatment patterns, indirect treatment comparison, and observational.

We studied the correlation between total number of HEOR publications and the proportion of respondents that indicated that HEOR was very likely or somewhat likely to have a positive impact on reimbursement decisions in the U.S. using Spearman's rank correlation coefficients. We also used Spearman's correlation to examine the association between the numbers of specific types of HEOR publications identified and the percentage of respondents who selected that evidence type as a prioritized investment.

Results

We received responses to the survey from 11 members of our Steering Committee that represented 11 unique companies (response rate of 79%). Each participant responded to 20 profiles: however, in 36 instances, participants indicated they were not familiar with the disease area and elected not to respond to the particular profile. Thus, we had a total of 184 observations.

Do respondents feel there is a differential impact of HEOR depending on the product-market scenarios?

Table 3-2 presents the frequencies, medians, and modes of responses for each product with respect to the likelihood that HEOR would have a positive impact on reimbursement decisions in the U.S. The variation in the responses across products suggests that the respondents do believe there are certain scenarios where HEOR evidence may be more impactful for payers. There are numerous products for which respondents generally agreed that HEOR would have a positive impact; however, there is only one product where respondents felt almost unanimously that HEOR evidence was unlikely to have any impact (Fanapt, brand name for iloperidone). In addition, for those products where respondents did not consistently believe HEOR was either very likely or very unlikely to affect payer decisions, the distribution of responses indicates a divergence in opinions as to the importance of HEOR in these scenarios.

Which product and market attributes are associated with the perceived likelihood that HEOR evidence would have a positive impact on U.S. payers' decisions?

The results of the ordinal logistic regression analysis examining which product and market attributes are associated with the perceived likelihood that HEOR evidence would have a positive impact on reimbursement decisions are presented in Table 3-3. Trial comparator, relative efficacy, time to approval

of a generic treatment, and relative pricing were all significantly associated with perceived likelihood that HEOR would have a positive impact on payers' reimbursement decisions. Respondents rated the impact of HEOR evidence to be significantly lower for products where the clinical trial was conducted with an active comparator versus if the trial had been conducted versus placebo ($p<0.001$). Respondents reported that the impact of HEOR evidence is significantly less when the product's relative efficacy was worse than the standard of care than when it is comparable to standard of care ($p=0.011$). The results also indicated that respondents rated the likelihood that HEOR would have a positive impact significantly lower as the time to the approval of a generic product increased ($p<0.001$). Finally, in terms of pricing, respondents rated the likelihood that HEOR evidence would have a positive impact significantly lower for products priced at a discount relative to the standard of care versus those priced at parity ($p=0.008$). Results from ordinal logistic regression analyses are exploratory and should be interpreted with caution as multiple statistical tests were performed, which increases the type I error rate.

Which types of HEOR evidence are believed to have the greatest impact on payer decision-making?

To assess whether pharmaceutical decision-makers perceive specific types of HEOR evidence to be more important to payers, we asked respondents to rate the top four types of HEOR evidence that would be valuable investments to optimize payer decisions for each products. Figure 3-2 summarizes the percentage of respondents who selected each evidence type as one of the top four investments for a given profile. Figure 3-3 depicts a breakdown of the number of times each type of evidence was selected as a first, second, third, fourth, or lesser priority. Budget impact evidence was selected by a majority of respondents for almost every product profile, indicating that Steering Committee members believe budget impact evidence is important to payers for all products. Though to a lesser degree, indirect treatment comparisons and resource utilization/treatment patterns were also selected frequently by respondents. Alternatively, evidence related to disease incidence/prevalence was infrequently selected as a priority HEOR investment to optimize payer decision-making.

It is important to note that respondents rarely indicated that they would not invest in any type of HEOR evidence. Across the 20 products, only seven times did a respondent indicate they would not invest in HEOR. Notably, four of the seven times when "none" was selected were in relation to the TPP

for Fanapt. In their comments, the respondents who selected “none” attributed this to the fact that, based on the TPP, Fanapt was expected to have comparable efficacy and safety to the standard of care, but would be priced at premium. Based on this, as one respondent indicated in this scenario, rebate negotiation would be the determining factor in the product’s formulary placement.

The results of the inter-rater reliability assessments are provided in Table 3-4. The findings indicate significant agreement among respondents as to when HEOR is likely to have a positive impact on reimbursement decisions in the U.S. ($p<0.0001$). In addition, there is significant agreement among respondents as to when budget impact evidence and patient-reported outcomes (PRO) evidence would be valuable to payers ($p=0.0245$ and $p=0.0413$, respectively). There was no significant agreement across the other categories of evidence, indicating there is no consensus among respondents as to when the other types of HEOR evidence are important to payers.

Revealed Choice Assessment of Target Product Profiles (Literature Review)

The findings of the literature searches are summarized in Table 3-5, and the tests of the correlation between respondents’ ratings of the likely impact of HEOR evidence (or for individual evidence types, the selection of the type of evidence as a priority investment) and actual number of HEOR publications is summarized in Table 3-6. We found few instances of published BIMs, CEAs, or disease incidence/prevalence studies. The most frequently observed publications included burden/cost of illness studies, resource utilization/treatment pattern studies, and PRO studies. It is worth noting that the PRO studies reflect both those related to the development of PRO instruments and studies that leveraged PRO instruments to measure the impact on patients’ health-related quality of life or utility. We felt it important to include both, as the number of total publications reflects the level of investment in PRO-related evidence. However, excluding those studies related to the development of PRO instruments (presumably of less direct relevance to payers when making formulary placement decisions) would significantly reduce the number of studies in this category.

In general, we see a greater number of publications for the products for which HEOR was rated as having a higher likelihood of positively impacting payer decisions (see Figure 3-4). This is corroborated in a test of the correlation between the total number of HEOR publications and the percentage of

respondents who indicated that HEOR would was very likely or somewhat likely to positively impact U.S. payers' reimbursement decisions (p=0.0710). There is one outlier—Toviaz (fesoterodine fumarate)—for which we observed a greater number of actual HEOR publications than expected based on the overall rating of the likelihood that HEOR would have a positive impact on payer decisions and relative to the observed trend. This is largely attributed to the 25 PRO publications identified for Toviaz. Of these, 17 were related to the development of PRO instruments, and 8 were related to the use of PRO instruments to measure patient health-related quality of life or utility. The number of PRO publications is aligned with stated importance of PRO evidence, as 80% of respondents prioritized PRO evidence for Toviaz.

There is a significant association between the rated importance of PRO evidence and the number of published PRO studies (p=0.0029); the evidence also suggests a positive association between the stated importance of burden/cost of illness evidence and the number of such publications, though the association is not statistically significant (p=0.1069). There is no evidence of an association between the stated and revealed choices for the other HEOR types.

Discussion

The findings of this survey suggest that HEOR executives in pharmaceutical companies discriminate as to the amount of HEOR investment required for different products based on the product-market scenario. The respondents to our survey clearly and consistently differentiated the products that were most and least likely to benefit from HEOR, and these stated choices were substantiated by literature reviews of the total number of published HEOR studies. For those products that fall between the most and least likely to benefit from HEOR, however, there was some divergence of opinions as to whether HEOR would have a positive impact on payer decisions. The product and market attributes that were significantly associated with the stated likelihood that HEOR would have a positive impact on payer decisions were: trial comparator, relative efficacy, years until generic entry to the market, and relative pricing. While the other product and market attributes did not reach the level of statistical significance, it is possible that this is due to the small sample size of our survey.

With respect to the specific types of HEOR evidence that were selected as important investments to optimize U.S. payers' reimbursement decisions, budget impact evidence, indirect treatment comparisons, and resource utilization/treatment pattern studies were selected most frequently. However,

we did not find a significant association between the stated importance of these types of evidence and the number of publications in the literature. On the other hand, disease incidence/prevalence studies were infrequently selected as a top priority: this may be a consequence of the fact that disease incidence/prevalence studies are often conducted by epidemiology functions and do not always fall under the remit of HEOR organizations. A significant association between stated and revealed choices was found only for PROs studies. Those companies that invested in PRO evidence for a product typically published multiple studies in this category, as supporting evidence is required to establish the validity of PRO instruments prior to their use. This is exemplified by the number of PRO-related publications identified for Toviaz, the majority of which were focused on the development and validation of related PRO instruments.

It is important to note that in some instances the number of publications may not reflect the level of actual investment: for instance, it is possible that budget impact and cost-effectiveness evidence are developed for the U.S. market but are supplied to payers within the framework of the AMCP dossier and are not published in peer-reviewed journals. If these types of evidence are less relevant to other audiences, e.g., physicians and patients, there may be less motivation to publish. Additionally, companies may be hesitant to publish such evidence, as the conclusions of these studies depend on an assumed product price, and often the net price of a product varies across payers/purchasers due to confidentially negotiated discounts and rebates.

The lack of association between stated and revealed choices may also be attributed to other nuances of the process undertaken to identify HEOR publications. The sensitivity our literature search may be impaired due to challenges in identifying studies that were funded by the pharmaceutical company that developed/commercialized the product but where the authors listed on the publication did not include any individuals affiliated with the company. We attempted to mitigate this risk by also searching the text of the funding section of HEOR publications. Another potential source of under-identification of HEOR publications is our exclusion of non-U.S. studies. While this is aligned with our interest in focusing on the U.S. market, it is possible that studies from other countries, particularly developed, English-speaking countries, may be leveraged with U.S. payers. However, the findings of our literature review, summarized in Chapter 1, indicate that a key concern of U.S. payers is whether

evidence from other study populations translates to their own covered populations; thus, we felt exclusion of non-U.S. studies was warranted. Finally, it is possible that the timeframe of publications that we examined was not inclusive of all studies that were completed prior to submission of evidence to payers' for their review and initial formulary decisions. We included all studies published within two years of FDA approval: however, given the delays between approval and launch, and between study completion and publication, it is possible that some studies were completed in the relevant timeframe but published after this two-year period. Additionally, we included studies that were published up to five years prior to FDA approval; while this was driven by our findings in Chapter 2 that most HEOR is conducted in Phase 3, we acknowledge that some HEOR studies may be conducted earlier in development and may have not been captured in our literature review.

Other drivers of the level of HEOR investment may also have affected the association between stated and revealed choices. For two of the ten products that we conducted literature reviews for, the companies that developed or commercialized the product had other products for the same indication on the market simultaneously. It was evident in our literature reviews that in these scenarios, the number of publications is substantially greater, and often, it was difficult to delineate whether a disease-specific (and product-agnostic) study was conducted to support one or both products. Further, it is likely that companies with multiple products for a single indication may invest more in disease-specific studies that can be leveraged for both products. Additionally, we identified two products that were not developed in-house but were licensed during the clinical development phase. In these instances, it is expected that the level of investment in HEOR may be less, given the shorter time period to conduct and disseminate research. Finally, it is possible that actual investment decisions are affected by the existing literature and the publications related to competitors' products. If much disease-related literature already exists, it may be less important for a company to duplicate these efforts and independently develop and publish such research. For product-specific studies, we may observe greater actual investment versus stated importance of such evidence in the event that manufacturers invest for the purpose of creating a literature base for their product that is parallel to that which exists for competitors' products. For instance, a company may be more likely to conduct a study of PRO impact if such literature exists for competing products.

We did not identify any previous studies that examined pharmaceutical companies' perceptions of the importance of HEOR by type of HEOR study that compared stated and revealed choices. The findings of this study are consistent with previous studies that have found that U.S. HEOR research scientists believe their work is important to payers.[37,45,46] However, a study by Nichol et al. in 2007 reported that five out of seven members of the Pharmaceutical Research and Manufacturers of America (PhRMA) Foundation's Health Outcomes Committee indicated their companies always included an economic model in the AMCP Dossier submitted to payers; the other two respondents indicated that their companies included economic models in the AMCP Dossier 50-85% of the time.[37] The findings of our literature reviews identified few BIMs and CEAs in the literature. This difference in findings may be indicative of a changing trend in the level of investment in economic models and perhaps and growing interest in other types of HEOR evidence, or this may be evidence to suggest that economic models are often developed but are not published in peer-reviewed journals.

The findings of our research are limited by the small sample size of respondents completing the survey. We attempted to mitigate this by asking each respondent to evaluate 20 product profiles. In addition to the limitations due to the sample size, it is important to note the potential biases introduced in these results due to the process of sample selection. The respondents to our survey included members of our project Steering Committee, who are self-selected, highly motivated individuals in leadership positions for large, mostly multi-national pharmaceutical companies. Given their positions of leadership, their responses are likely representative of the HEOR investment decision-making process undertaken by their respective companies and individuals within their companies; however, it is possible that their investment choices differ from those of other, smaller pharmaceutical companies, potentially reducing the generalizability of our findings.

While the decision-makers we surveyed are in agreement as to when HEOR evidence is important information for U.S. payer decision-making, they are less consistent in their responses as to when specific types of HEOR evidence are important. Further, the stated importance of specific HEOR studies is often at odds with the number of published studies. With this in mind, in a follow-on study described in the next chapter, we seek to conduct a broader and more generalizable survey of pharmaceutical HEOR scientists and formulary decision-makers for U.S. payer organizations to

understand when specific types of HEOR evidence are important and to assess the alignment between the two groups. This research may help guide companies in the prioritization of HEOR research investments such that evidence generated is aligned with payers' preferences, potentially optimizing formulary placement for new pharmaceutical products.

Table 3-1. Model Variables and Coding.

Variables	Variable Type	Coding
HEOR Impact *(Survey Q2)*	Categorical	*('Unsure' treated as missing)* 0 – Very unlikely 1 – Somewhat unlikely 2 – Somewhat likely 3 – Very likely
Respondent	Categorical	1-11 – Respondent identifier
Compound Type	Categorical	0 – NME 1 – New biologic 2 – New indication 3 – New combination
Trial Comparator	Categorical	0 – Placebo 1 – None 2 – Active/Constituents 3 – Active/Competitor
Relative Efficacy	Categorical	0 – Comparable 1 – Worse 2 – Unclear 3 – Better
Market Position	Continuous	Market entry position based on FDA approval date (≥1)
Time to Generic	Continuous	Years until key competitor loses patent protection (≥0)
Relative Pricing	Categorical	0 – Parity 1 – Discount 2 – Premium
Disease Severity	Categorical	0 – No/Limited impact on life expectancy 1 – Reduced life expectancy 2 – Life-threatening
Familiarity	Categorical	0 – Unfamiliar with this market and prefer not to respond 1 – Unfamiliar with this market but able to respond based on the information provided 2 – Moderately familiar with this market 3 – Very familiar with this market

Table 3-2. Frequency of Responses of the Likelihood that HEOR Evidence Would Have a Positive Impact on Reimbursement in the U.S.

Drug	Compound	Approval Type	Indication (Original Indication)	Frequency (%)				Median	Mode
				Very Likely (4)	Somewhat Likely (3)	Somewhat Unlikely (2)	Very Unlikely (1)		
Gilenya	Fingolimod	NME	Multiple sclerosis	5 (56%)	4 (44%)	0 (0%)	0 (0%)	4	4
Dulera	Formoterol Fumarate, Mometasone Furoate	New Combination	Asthma	4 (40%)	4 (40%)	2 (20%)	0 (0%)	3	4,3
Pradaxa	Dabigatran Etexilate Mesylate	NME	Atrial fibrillation	4 (40%)	6 (60%)	0 (0%)	0 (0%)	3	3
Votrient	Pazopanib Hydrochloride	NME	RCC	2 (20%)	6 (60%)	2 (20%)	0 (0%)	3	3
Afinitor	Everolimus	NME	RCC	2 (22%)	3 (33%)	4 (44%)	0 (0%)	3	2
Actemra	Tocilizumab	Biologic	Rheumatoid arthritis	1 (10%)	9 (90%)	0 (0%)	0 (0%)	3	3
Effient	Prasugrel Hydrochloride	NME	Thrombotic CV events	1 (9%)	8 (73%)	1 (9%)	1 (9%)	3	3
Arzerra	Ofatumumab	Biologic	CLL	1 (10%)	7 (70%)	2 (20%)	0 (0%)	3	3
Jalyn	Dutasteride, Tamsulosin Hydrochloride	New Combination	Hyperplasia	1 (14%)	4 (57%)	2 (18%)	0 (0%)	3	3
Treximet	Naproxen Sodium, Sumatriptan Succinate	New Combination	Migraines	0 (0%)	6 (67%)	3 (33%)	0 (0%)	3	3
Cymbalta	Duloxetine Hydrochloride	New Indication	FM (depression)	0 (0%)	5 (63%)	3 (38%)	0 (0%)	3	3
Zortress	Everolimus	New Indication	Organ rejection (RCC)	0 (0%)	5 (56%)	3 (33%)	1 (11%)	3	3
Promacta	Eltrombopag Olamine	NME	Thrombocytopenia	0 (0%)	5 (63%)	2 (25%)	1 (13%)	3	3
Adcirca	Tadalafil	New Indication	PAH (ED)	1 (13%)	3 (38%)	1 (13%)	3 (38%)	2.5	3,1
Pristiq	Desvenlafaxine Succinate	NME	MDD	1 (10%)	3 (30%)	5 (50%)	1 (10%)	2	2
Toviaz	Fesoterodine Fumarate	NME	Overactive bladder	1 (10%)	3 (30%)	5 (50%)	1 (10%)	2	2
Intelence	Etravirine	NME	HIV	1 (11%)	3 (33%)	4 (44%)	1 (11%)	2	2
Lastacaft	Alcaftadine	NME	Allergic conjunctivitis	0 (0%)	2 (33%)	4 (67%)	0 (0%)	2	2
Fanapt	Iloperidone	NME	Schizophrenia	0 (0%)	1 (9%)	5 (45%)	5 (45%)	2	2,1
Nucynta	Tapentadol Hydrochloride	NME	Pain	1 (13%)	2 (25%)	2 (25%)	3 (38%)	2	1

CV = cardiovascular; CLL = chronic lymphocytic leukemia; MDD = major depressive disorder; HIV = human immunodeficiency virus; PAH = pulmonary arterial hypertension; ED = erectile dysfunction; FM = fibromyalgia; RCC = renal cell carcinoma.

Table 3-3. Which Attributes are Predictors of the Perceived Impact of HEOR?

Variable	Odds Ratio	95% CI		P-Value	Combined P-Value
Compound Type: New Biologic	0.27	0.05	1.46	0.127	0.154
Compound Type: New Indication	0.96	0.36	2.53	0.935	
Compound Type: New Combination	0.55	0.09	3.56	0.531	
Trial Comparator: None	2.43	0.25	23.44	0.443	**<0.001**
Trial Comparator: Active/Competitor	0.06	0.01	0.25	**<0.001**	
Relative Efficacy: Worse	0.17	0.04	0.66	**0.011**	**<0.001**
Relative Efficacy: Unclear	1.94	0.45	8.43	0.377	
Relative Efficacy: Better	0.91	0.30	2.76	0.874	
Market Position	0.85	0.65	1.11	0.238	0.238
Time to Generic	0.80	0.71	0.91	**<0.001**	**<0.001**
Relative Pricing: Discount	0.16	0.04	0.62	**0.008**	**0.028**
Relative Pricing: Premium	0.80	0.40	1.61	0.525	
Disease Severity: Reduced Life Expectancy	1.84	0.19	17.36	0.596	0.277
Disease Severity: Life-Threatening	0.61	0.06	6.56	0.681	
Familiarity: Unfamiliar/Able to Respond	0.39	0.12	1.29	0.122	0.116
Familiarity: Moderately Familiar	0.35	0.13	0.94	**0.038**	

Table 3-4. Assessment of Agreement Across Respondents Using Inter-Rater Reliability.

Evidence Type	κ	Z	Prob > Z
Likely/Unlikely Positive Impact of HEOR Evidence	**0.1721**	**4.68**	**<0.0001**
Adherence/Compliance	0.0283	0.78	0.2180
Budget Impact	0.0716	1.97	**0.0245**
Burden or Cost of Illness	-0.0677	-1.86	0.9687
CEA / CUA	-0.0059	-0.16	0.5644
Disease Incidence or Prevalence	-0.0563	-1.55	0.9389
Indirect Treatment Comparison	0.0160	0.44	0.3300
PRO Impact	0.0631	1.74	**0.0413**
Resource Utilization / Treatment Patterns	-0.0353	-0.97	0.8345

Table 3-5. How Do Revealed and Stated Choices Compare for Specific Types of Investments?

Product Name	Stated vs. Revealed Choice Method	A/C	BI	BCOI	CEA	Inc/Prev	ITC	PRO	RU/TX	OVERALL
Gilenya	Survey % Who Prioritized	33%	89%	22%	44%	11%	67%	56%	67%	100%
	# of Publications	2	0	1	2	0	2	11	3	21
Pradaxa	Survey % Who Prioritized	50%	90%	40%	70%	20%	30%	10%	80%	100%
	# of Publications	1	0	10	1	0	3	0	7	21
Actemra	Survey % Who Prioritized	10%	70%	30%	50%	20%	90%	60%	40%	100%
	# of Publications	2	0	0	0	0	3	5	3	13
Afinitor	Survey % Who Prioritized	0%	89%	44%	11%	33%	56%	33%	67%	55%
	# of Publications	1	1	1	1	1	1	4	3	12
Cymbalta	Survey % Who Prioritized	13%	88%	25%	38%	38%	63%	50%	38%	63%
	# of Publications	5	0	5	0	0	0	0	1	13
Toviaz	Survey % Who Prioritized	40%	70%	30%	20%	10%	40%	80%	70%	40%
	# of Publications	1	0	8	0	10	0	25	2	42
Lastacaft	Survey % Who Prioritized	50%	83%	17%	33%	17%	67%	50%	17%	33%
	# of Publications	0	0	0	0	0	0	3	0	3
Adcirca	Survey % Who Prioritized	13%	38%	25%	38%	38%	63%	50%	38%	51%
	# of Publications	0	0	0	0	0	0	1	1	2
Nucynta	Survey % Who Prioritized	13%	50%	25%	13%	13%	38%	50%	63%	38%
	# of Publications	0	0	0	1	0	1	2	2	6
Fanapt	Survey % Who Prioritized	36%	36%	18%	27%	9%	36%	9%	45%	9%
	# of Publications	0	0	0	0	0	2	0	1	3

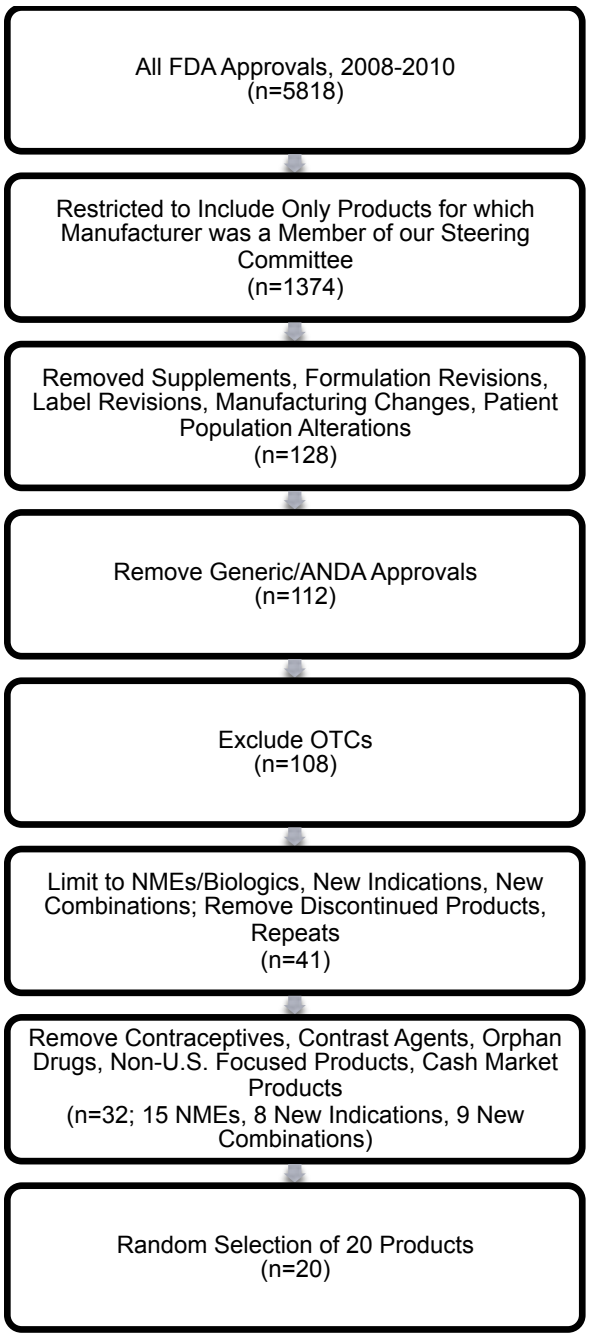
A/C = adherence/compliance; BI = budget impact; BCOI = burden/cost of illness; CEA = cost-effectiveness analysis; Inc/Prev = incidence/prevalence; ITC = indirect treatment comparisons; PRO = patient-reported outcomes; RU/TX = resource utilization/treatment patterns.

Table 3-6. Correlation Between Stated Choices and Revealed Choices.

Evidence Type	Spearman's ρ	P-Value
Adherence/Compliance	-0.2872	0.4210
Budget Impact	0.3503	0.3211
Burden or Cost of Illness	0.5402	0.1069
CEA / CUA	0.0070	0.9848
Disease Incidence or Prevalence	-0.1392	0.7012
Indirect Treatment Comparison	-0.1461	0.6871
PRO Impact	0.8305	**0.0029**
Resource Utilization / Treatment Patterns	0.4069	0.2433
Overall HEOR	0.5926	0.0710

CEA = cost-effectiveness analysis; CUA = cost-utility analysis; PRO = patient-reported outcomes; HEOR = health economics and outcomes research.

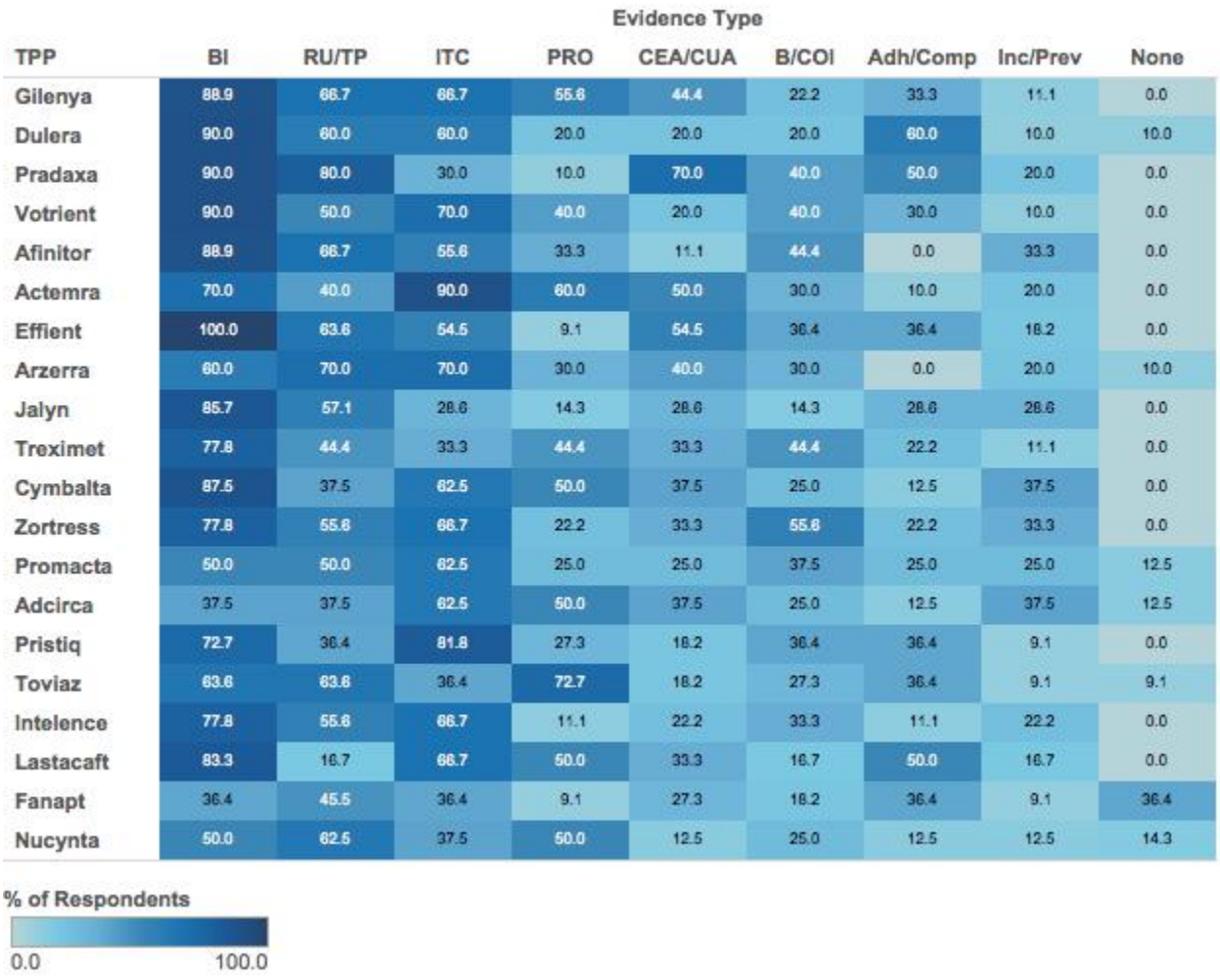
Figure 3-1. Identification of Products for the Target Product Profiles.
Note: Numbers in parentheses indicate the number of products remaining after the reduction step.



FDA = Food and Drug Administration; ANDA = Abbreviated New Drug Application; OTC = over the counter; NME = new molecular entity.

Figure 3-2. What Types of HEOR Evidence Would be Valuable Investments to Optimize U.S. Payer Reimbursement Decisions?

Priority HEOR Investments
(% of Respondents Selecting Evidence Type)



BI = budget impact; RU/TP = resource utilization/treatment patterns; PRO = patient-reported outcomes; CEA = cost-effectiveness analysis; CUA = cost-utility analysis; B/COI = burden/cost of illness; Adh/Comp = adherence/compliance; Inc/Prev = incidence/prevalence.

Figure 3-3. Number of Times Each Evidence Type was Selected as a 1st, 2nd, 3rd, 4th or Lesser Priority.

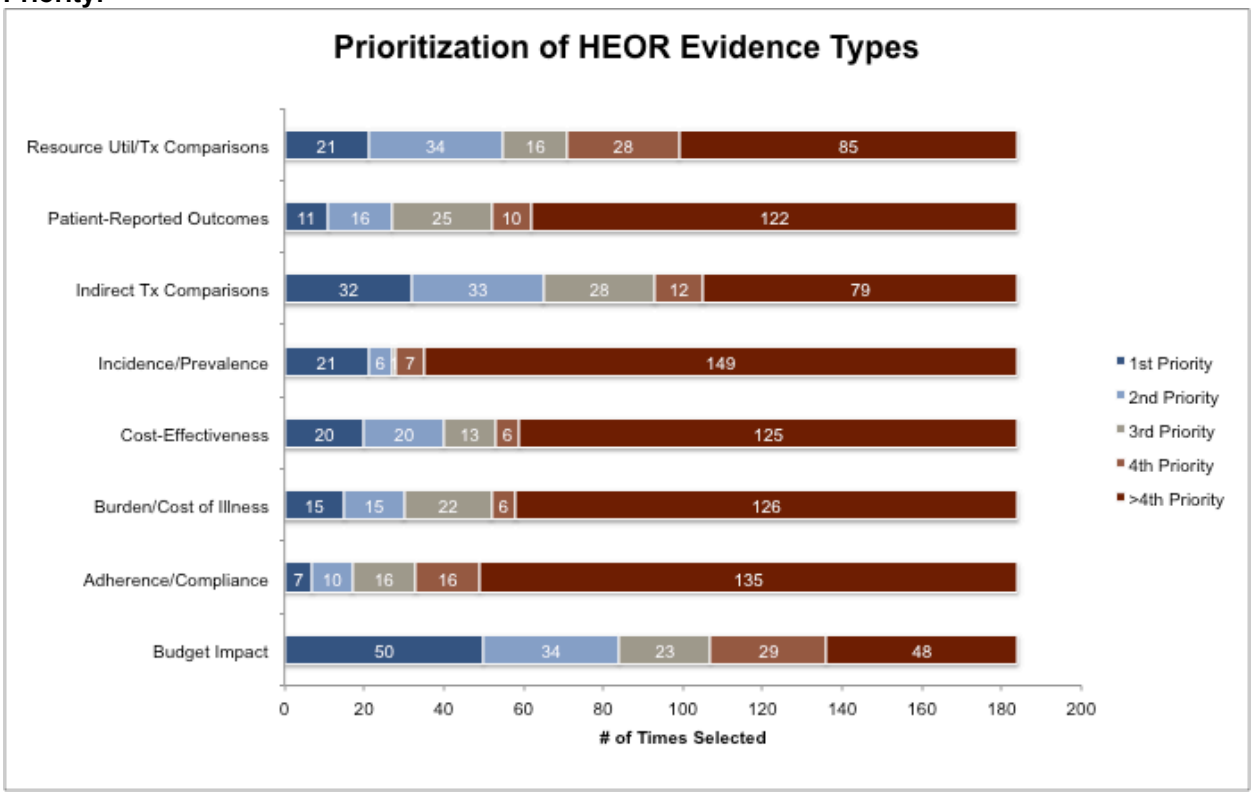
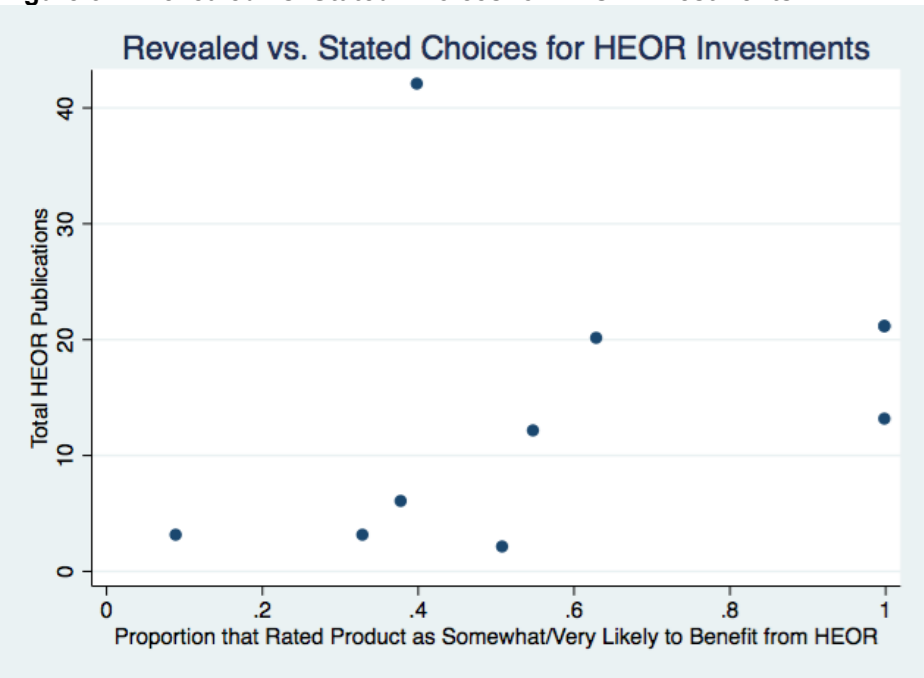


Figure 3-4. Revealed vs. Stated Choices for HEOR Investments.



CHAPTER 4

The Impact Of Health Economics And Outcomes Research On Formulary Decisions In The U.S. And Alignment Between Pharmaceutical And Payer Stakeholders

Abstract

Objectives: Pharmaceutical companies are increasingly investing in health economics and outcomes research (HEOR) evidence to demonstrate the value of their products to reimbursement agencies. As the scope of evidence produced by HEOR units in pharmaceutical companies has grown, it is important to consider how payers use this broader base of evidence when making formulary decisions. The aim of this study was to identify the scenarios where payers value specific types of HEOR evidence and to assess whether pharmaceutical decision-makers and formulary decision-makers are aligned in their assessment of which specific types of HEOR evidence are important in what circumstances.

Methods: We conducted a survey of formulary decision-makers for payer organizations and HEOR decision-makers for pharmaceutical companies, consisting of general questions around the importance of HEOR and specific questions related to hypothetical product scenarios. We asked respondents to rate the importance of seven types of HEOR evidence to support formulary decisions for each product scenario. The product scenarios were developed based on specific hypotheses. We used frequencies and means to analyze responses to the general questions and binary logistic regression to test the association between product and market scenarios and importance ratings.

Results: We received 63 responses from pharmaceutical decision-makers and 31 responses from payer decision-makers. Among payers, 81% stated HEOR evidence is an explicit consideration in the formulary decision-making process, and 55% indicated their organization develops its own HEOR evidence internally. Payers indicated they consider budget impact evidence most frequently, followed by data on the unmet need/adherence/compliance to the standard of care, and resource utilization/cost-offset data. With the exception of indirect treatment comparisons, payers indicate they consider all other types of evidence at least half of the time. Pharmaceutical respondents indicated they most often develop budget impact evidence, followed by cost-effectiveness/cost-utility evidence, and burden/cost of illness evidence. Based on mean responses, pharmaceutical companies generate all of the seven types of HEOR evidence for at least half of their products. With respect to the product profiles, payers seem to value all

seven types of HEOR evidence to be important considerations in their formulary decision, and rarely rate HEOR evidence to be not at all important or not needed. Adjusting for product and market attributes, payers rate the importance of health-related quality of life evidence significantly higher than pharmaceutical respondents; on the other hand, they rate the importance of budget impact evidence significantly lower.

Conclusions: HEOR evidence has a substantial role in payers' formulary decision-making processes and its role is expected to grow in the future. The scope of HEOR evidence produced by pharmaceutical companies has increased, and payers generally find all evidence types useful in decision-making. There is some evidence of misalignment as to when specific types of evidence are important; understanding when payers value each type of evidence will allow pharmaceutical companies to make more efficient investment decisions in the future.

Introduction

The discipline of health economics and outcomes research (HEOR) encompasses a set of accepted methodologies and standards derived from the fields of epidemiology, statistics, economics, and the social sciences that are used to measure the clinical, economic, and humanistic impacts of pharmaceutical and other healthcare interventions. While clinical trials are used to establish the efficacy and safety of new drugs in order to achieve regulatory approval, pharmaceutical companies are increasingly investing in HEOR evidence to demonstrate the value of their products to reimbursement agencies.

HEOR evidence, and more specifically cost-effectiveness analysis (CEA), is required in some major markets to obtain market access, but the use of such evidence in the U.S. is less explicit.[5] Payer organizations in the U.S. have historically been reluctant to deny coverage for drugs that have met the evidentiary requirements of the Food and Drug Administration (FDA). Instead, in recent years payers have leveraged tiered formularies with differential copayments and other restrictions, including step therapy and prior authorization requirements, to control the use of pharmaceutical products.[34] Thus, while it is generally true that HEOR evidence does not inform the decision to approve or deny heath plan coverage, it can play a role in the formulary placement of pharmaceutical products, which directly affects uptake by patients and thus market share. The growth of HEOR departments in the U.S. and the development and uptake of the Academy of Managed Care Pharmacy (AMCP) Format for Formulary Submissions, which encourages formal requests for dossiers of clinical and economic evidence from pharmaceutical companies by health plans, is further indication that economic evidence is playing some role in the commercial success of pharmaceutical products in the U.S.[13,14,46]

Previous studies that have examined the impact of HEOR evidence (somewhat narrowly construed) on formulary decision-making in the U.S. have found that payers' understanding of HEOR methodologies and metrics has increased and their interest in such evidence is growing.[17,37,39,40] Still, the role of HEOR evidence varies across payers and is used in a different fashion by different organizations. Barriers to the use of HEOR evidence that have been identified include: the perception that pharmaceutical companies present a biased selection of evidence, the provision of analyses that answer questions that are not pertinent to payers, clinical trial populations that do not translate to payer

populations, and the separation of rebating and value assessment which results in rebates holding more weight.[17] However, previous studies have largely focused on the use of CEAs and, to some extent, the use of patient-reported outcomes (PROs) to measure health-related quality of life (HRQOL) and utility. As the scope of evidence produced by HEOR units in pharmaceutical companies has grown, it is important to consider how payers use this broader base of evidence when making formulary decisions.

We hypothesize that the overall importance of HEOR evidence and the types of HEOR evidence that are pertinent to payers vary based on attributes of the product and the market. As described in Chapter 3, in previous work with HEOR executives representing various U.S. pharmaceutical companies, we have identified a set of product and market attributes that play some role in influencing the decision to invest in HEOR evidence on the part of pharmaceutical companies. In addition, we have developed a set of specific hypotheses as to which scenarios are likely to make different, specific types of HEOR evidence most pertinent to payer decision-makers. The purpose of this research is to better understand how pharmaceutical decision-makers make investment decisions, to identify the product-market scenarios where payers value specific types of HEOR evidence, and to assess whether pharmaceutical decision-makers and formulary decision-makers are aligned in their assessment of which specific types of HEOR evidence are important in what circumstances.

Methods

Approach

To assess the importance of HEOR evidence to U.S. formulary decision-makers and the alignment between drug companies and payer organizations, we set out to design a stated choice survey that would allow us to identify the product and market scenarios for which various types of HEOR evidence are considered important. We elected to study this question using stated choice survey methods, as it was a believed an empirical approach to this question would be difficult to employ on a large scale given (a) the confidential nature of the formulary decision-making process, (b) our inability to identify the types of HEOR evidence presented to payers (in previous work we found that not all HEOR evidence generated by pharmaceutical companies is published and AMCP dossiers are not publicly available), and (c) that a significant level of confounding is expected in real-world decisions, including the impact of discounts and

rebates, that we would be unable to measure and account for. As such, we sought to design a study that would allow us to estimate the importance of HEOR in a more controlled fashion.

Design

To inform the survey approach and design, we conducted phone and in-person interviews with ten individuals working for payer organizations as employees or consultants in order to understand the formulary decision-making processes, if and how payers currently use HEOR evidence, and more practical considerations about survey audience and length. The findings from these discussions were used to ensure our survey was reasonable and applicable to a range of payer audiences.

We designed a survey with a set of thirteen product profiles and asked payers to review the profiles and respond to the questions as if the profiles represented recently approved products. We asked payers to consider the data provided as if they were making an initial coverage/reimbursement decision for the products with only commercial (non-Medicare/non-Medicaid) formularies in mind. For each profile, we asked payers to rate the importance for each of the seven types of HEOR evidence listed below. Specifically, we asked payers: "For the product described, how important would it be to receive each type of HEOR evidence below in order to support your formulary placement decision (in terms of tiering, utilization management, etc.)".

- Budget impact
- Burden/cost of illness
- Cost-effectiveness/cost-utility
- Indirect treatment comparisons
- Patient health-related quality of life/utility
- Resource utilization/cost-offsets
- Unmet need – adherence/compliance of standard of care

The categories of HEOR evidence were defined in previous work, described in Chapter 2.

Respondents were asked to rate the importance of each type of evidence on a scale of 1 to 5 (1 = not at all important/not needed, 5 = extremely important/absolutely essential). Respondents also had an option to indicate they were unsure or required more information. Sample questions for both surveys are provided in Appendix 4-1.

To assess the alignment between pharmaceutical companies and payers, we designed the pharmaceutical survey congruently to the payer survey. We leveraged the same thirteen product profiles, and instructed respondents to review each scenario as if it were a target product profile for a product in development and asked them, “For the product described, how important would it be to conduct and disseminate each type of HEOR evidence in order to achieve formulary placement with commercial payers in the U.S. (in terms of tiering, restrictions, etc.)?”.

We selected the product profile question format, as it was our hypothesis that the full set of product and market attributes would be necessary to accurately assess the importance of HEOR, and without providing this detailed context, we may not elicit answers that reflect real-world decision-making. The product profiles spanned five disease areas (metastatic colorectal cancer, rheumatoid arthritis, hypertension, herpes simplex virus, and hepatitis C virus) to capture any differences across diseases and therapeutic areas. We varied the product and market attributes such that each level of each attribute was tested at least once; however, we were cautious not to vary the attributes in an irrational or contradictory manner that would generate unlikely profiles (e.g., one in which a product’s relative efficacy is inferior to the standard of care and the product is priced at a premium relative to the standard of care). Additionally, we tried to limit the number of attributes that were varied for profiles in a given disease area and highlighted the attributes that changed within a disease area to reduce the overall cognitive burden of the survey. A summary of the scenarios tested in the survey is described in Table 4-1. The profiles were grouped into blocks by disease area, and the order of blocks was randomized for each participant in attempt to reduce any bias due to respondent fatigue.

In addition to the scenarios, participants were asked more general questions about their role, previous training, years of experience, the perceived current and future importance of HEOR evidence, and the frequency with which each type of HEOR evidence is considered in their evaluation (payers) or planned for products in development (pharmaceutical companies).

We conducted a small pilot (n=6) prior to broad distribution of the survey, which resulted in a reduction in the number of profiles (originally, 20 profiles were planned) and highlighting of the changing attributes across profiles to reduce the cognitive burden of the survey.

Setting

The survey was conducted online using Qualtrics® survey software and required approximately 20-30 minutes to complete.

Participants

The study was designed for administration with the appropriate decision-makers within payer organizations and pharmaceutical companies. For payers the target audience included individuals involved in the formulary decision-making process for private/commercial U.S. payers and pharmacy benefit managers (PBMs). This included those responsible for evidence review/monograph preparation, Pharmacy & Therapeutics (P&T) committee members, Value Assessment (or similar) committee members, formulary managers, and pharmacy directors. For pharmaceutical companies, the target audience included individuals involved in the decision to invest in U.S. HEOR for pharmaceutical companies and familiar with payers' preferences for evidence, including those employed in the HEOR and market access functions, and managed care liaisons.

Analysis

General Questions

We asked three general questions of both stakeholder groups with respect to the importance of HEOR evidence for formulary-decision making and trends in the generation and consumption of HEOR evidence. Responses to these questions are summarized using means and frequencies.

Hypothesis Tests

In our pre-specified hypotheses, we identified scenarios where pharmaceutical companies and/or payers may find more value in the generation/consumption of HEOR evidence. To test our pre-specified hypotheses, the product and market attributes of each TPP were categorized into factors of each variable (Table 4-2). We conducted multivariate analyses using binary logistic regression to test each hypothesis to increase the power of the regression analyses. The dependent variable for each regression was the importance rating for one of the seven types of HEOR evidence, as specified in each hypothesis test (0 = not at all important/not needed, unsure, somewhat important; 1 = very important, extremely important/absolutely essential). The independent variables included all product and market attributes, many of which were collapsed into binary variables to reduce the degrees of freedom; in addition, we

adjusted for respondents' stated level of familiarity with the disease area and accounted for clustering at the respondent level, as each participant responded to thirteen product profiles. Separate models were assessed for each hypothesis and for each stakeholder group (pharmaceutical and payer respondents). A large proportion of responses to the pharmaceutical survey were from individuals who worked for the same company (26 of 63 responses, or 41.3%). To account for this, we included a binary indicator variable in our analysis of the pharmaceutical survey data to reflect whether individuals worked for this company. To test each hypothesis, the coefficient of interest was evaluated using the Wald test.

As additional, exploratory analyses, we also tested hypotheses using an ordinal logistic model and, where possible, non-parametric Wilcoxon signed rank sum tests. Seven ordinal logistic regression models were analyzed, with importance ratings for each HEOR evidence type as the dependent variable. The independent variable was limited to the key product or market attribute of interest using the original categorization (not collapsed). Because ordinal logistic regression results in less power, we did not adjust for all product and market attributes. We did adjust for respondents' familiarity with the disease area, organization (for the pharmaceutical survey), and clustering at the respondent level. In some cases, the product profiles (scenarios) allow us to test our hypotheses directly by comparing responses to two profiles. To evaluate whether there is a difference in the stated importance of specific evidence types between two scenarios, we used the Wilcoxon signed rank sum test to test our hypotheses. The Wilcoxon signed rank sum test is a suitable choice because, as a non-parametric test, it can be used with our outcome of interest, which is ordinal in nature (Likert scale). Additionally, each respondent answered both scenarios that used to test each scenario, and the Wilcoxon signed ranks test accounts for the paired nature of the data.

Alignment Between Pharmaceutical Company and Payer Organization Stakeholders

To evaluate whether payers and pharmaceutical companies are aligned in their preferences, we conducted a binary logistic regression for each evidence type. The ordinal importance rankings for each evidence type were collapsed into binary variables (0 = not at all important/not needed, unsure, somewhat important; 1 = very important, extremely important/absolutely essential). In total, seven models were assessed – one for each dependent variable, or evidence type. The independent variables in each model included the product and market attributes, an indicator for the type of respondent (pharmaceutical

versus payers), an adjustment variable for the respondents' stated level of familiarity with each disease, and a binary indicator variable for the respondent's organization (pharmaceutical survey only). In addition, we accounted for clustering at the respondent level. To test whether a significant difference exists between payer and pharmaceutical respondents' preferences, we tested the significance of the regression coefficient for each interaction term using the Wald test.

More details on the methods of analysis are provided in Appendix 4-2.

Results

We received 63 complete responses to the survey of pharmaceutical HEOR decision-makers and 31 complete responses to the survey of formulary decision-makers. Respondents to the pharmaceutical company survey represented at least 16 unique companies (17 respondents did not provide the name of their organization). Respondents to the payer survey represented at least 23 unique companies that cover over 150 million lives in total (4 respondents did not provide the name of their organization).

Respondent Characteristics

Key respondent characteristics are summarized in Table 4-3. All payer respondents were employed by a commercial/private payer or pharmacy benefit manager (PBM), and the majority were Pharmacy and Therapeutics (P&T) Committee members, Value Access (or similar) Committee members, formulary managers, or evidence reviewers/monograph preparers. The vast majority were pharmacists, had more than one year of experience, were involved in the formulary decision-making process for more than one organization, and were involved in the formulary decision-making process for more than one formulary. All of the respondents to the pharmaceutical survey were employed by pharmaceutical or biotechnology companies. Most respondents were employed in HEOR functions of their companies and had 6 or more years of experience.

General Questions

In addition to the demographic questions summarized above, we asked payers high-level questions about the formulary decision-making process for the organizations which they are involved with. When asked if HEOR evidence was an explicit consideration in the formulary decision-making process, 81% said yes, 13% said no, and 7% were unsure. With respect to whether a separate committee, apart from the P&T Committee, existed that was tasked with reviewing HEOR evidence for new products, 77% said a

separate committee did not exist, 19% indicated a separate committee did exist, and 3% were unsure. Additionally, 55% of respondents indicated the organization for which they were involved in the formulary decision-making process developed its own HEOR evidence internally.

We asked respondents to both surveys to indicate how frequently, in terms of percentages, each of the types of HEOR evidence are considered in their evaluation (payer respondents) or planned for products in development (pharmaceutical respondents). The results are presented in Figure 4-1. Payer respondents indicated they considered budget impact evidence most frequently (mean: 68.68%), followed by data on the unmet need/adherence/compliance to the standard of care (mean: 62.48%) and resource utilization/cost-offset data (mean: 60.81%). With the exception of indirect treatment comparisons, payer respondents that they consider all other types of evidence at least half of the time. Pharmaceutical respondents indicated they most often develop budget impact evidence (mean: 87.98%); though this seems to be more often than payers are interested in budget impact evidence, it is consistent in that it is the most frequently produced or considered type of evidence for both stakeholders. Following budget impact evidence, pharmaceutical respondents indicated that they develop cost-effectiveness/cost-utility evidence 78.43% of the time, on average, and burden/cost of illness evidence 77.38% of the time, on average. Based on mean responses, pharmaceutical companies generate all of the seven types of HEOR evidence for at least half of their products.

We also asked both groups of respondents to what degree they think HEOR evidence affects formulary decisions in the U.S. (Figure 4-2). Approximately one-third of respondents in both groups felt that HEOR has a major impact on formulary decisions (36.51% and 32.26% of pharmaceutical respondents and payer respondents, respectively). The majority of respondents believed that HEOR evidence has a minor impact (57.14% and 61.29% of pharmaceutical and payer respondents, respectively). Only one pharmaceutical respondent felt that HEOR evidence has no impact on formulary decisions (1.59%); none of the payer respondents selected this option.

Finally, we asked respondents to both surveys how they believe the impact of HEOR evidence on U.S. formulary decisions would change in the five to ten years (Figure 4-3). The majority of all respondents stated they believe that the impact of HEOR evidence will increase (84.13% and 96.77% of pharmaceutical and payer respondents, respectively). A minority believed that the impact of HEOR

evidence would stay the same (15.87% and 3.23% of pharmaceutical and payers respondents, respectively), and none of the respondents indicated they believed the impact of HEOR evidence would decrease.

Hypothesis Tests

The frequency of responses across all profiles is presented in Figures 4-4 and 4-5. In Figure 4-4, we see that payers generally rated each HEOR evidence type to be important. Indirect treatment comparison evidence was most frequently rated as "not important" by payers, but still only in 11% of cases. Budget impact and cost-effectiveness evidence were rated as extremely important most frequently by payers, in 28% and 24% of scenarios, respectively. Pharmaceutical respondents also most frequently rated indirect treatment comparisons as the evidence type that is not at all important (18%), followed by HRQOL/utility evidence (15%) and cost-effectiveness/cost-utility evidence (14%). Budget impact evidence and resource utilization/cost-offset evidence were the types of evidence most frequently rated as extremely important by pharmaceutical respondents (41% and 29%, respectively).

The results of the binary logistic regression analyses for the pharmaceutical and payer surveys are presented in Table 4-4 and Table 4-5, respectively. To reduce the risk of type I errors due to multiple testing, we evaluated the significance of coefficients for those attributes specified in our hypotheses. The pre-specified hypotheses and results of the regression analyses are listed in Table 4-6. In addition to the primary tests of significance using the binary logistic regression analyses, we tested the hypotheses using ordered logistic regression and non-parametric methods; however these secondary analyses are presented for exploratory purposes and to assess the robustness of the results of our primary analyses.

Budget Impact

With respect to budget impact evidence, the results suggest that both pharmaceutical and payer decision-makers believe budget impact evidence is less important for products with a narrow scope of indication compared to those with a broader scope of indication (OR=0.40 and OR=0.82, respectively). However, these trends did not reach the level of statistical significance (p=0.167 and p=0.345, respectively). Pharmaceutical respondents felt the importance of budget impact evidence was significantly less when the product's relative price was at parity or discount with respect to the standard of care than when the product was priced at a premium (OR=0.09, p=0.031). This relationship was reversed

for payer respondents: payers were almost three times as likely to rate budget impact evidence as important when product price was at parity or discount compared to the standard of care than when it was a premium (OR=2.81), suggesting misalignment between pharmaceutical and payer decisions-makers. However, this finding was not statistically significant (p=0.236). Pharmaceutical and payer respondents were in a agreement as to the importance of budget impact evidence when a product's safety profile is worse than that of the standard of care compared to when it is better or comparable: both groups tended to rate the importance of budget impact evidence lower when safety was worse compared to the standard of care than when it was comparable or better (OR=0.54 and OR=0.41, respectively). These trends were not significant (p=0.353 and p=0.223, respectively).

Burden/Cost of Illness

The results for the regression analyses of the importance of burden/cost of illness evidence suggest that pharmaceutical and payer respondents both believe burden/cost of illness evidence is less important when a product is a "me too" drug versus when it is first-in-class or a fast-follower (OR=0.61 and OR=0.74, respectively). These findings were not statistically significant for either group (p=0.108 and p=0.152, respectively). Pharmaceutical respondents indicated burden/cost of illness information is more important when the product's indication is narrow versus when it is broad (OR=1.22, p=0.567). Payers, however, did not differentiate the need for HEOR evidence (OR=1.00, p=1.00). Both pharmaceutical and payer respondents indicated that burden/cost of evidence is less important when a product is an add-on therapy than when it is a monotherapy (OR=0.41 and OR=0.46, respectively); however, this trend was only significant for pharmaceutical respondents (p=0.024 and p=0.116 respectively).

Cost-Effectiveness/Cost-Utility

Both pharmaceutical and payer respondents rated the importance of cost-effectiveness information higher when the trial endpoint was mortality/survival versus when the trial endpoint was a surrogate endpoint (OR=1.41 and OR=1.53, respectively). These trends were not significant (p=0.148 and p=0.151, respectively). There was some indication that pharmaceutical respondents believe cost-effectiveness evidence to be more important when the trial endpoint is a morbidity endpoint versus a surrogate endpoint as well, but this trend was also not significant (OR=1.41, p=0.157). Payer respondents did not assign different levels of importance to cost-effectiveness evidence when the trial endpoint was a

morbidity endpoint versus a surrogate endpoint (OR=1.00, p=1.000). With respect to disease severity, there is evidence of disagreement between pharmaceutical and payer respondents. Pharmaceutical respondents rated the importance of cost-effectiveness evidence significantly higher when diseases severity was substantial versus minimal or moderate (OR=2.57, p=0.005). On the other hand, payer respondents generally rated the importance of cost-effectiveness lower when disease severity was substantial versus minimal or moderate: however, this was not a significant finding (OR=0.70, p=0.536). Trends in pharmaceutical respondents survey responses indicated a trend towards higher ratings of importance for "me too" products compared to first in class products and fast followers (OR=1.21, p=0.407). Responses from payers indicated the opposite trend: cost-effectiveness evidence was rated as less important for "me too" products compared to first in class and fast follower products (OR=0.85, p=0.660). However, these trends were not statistically significant for either group. We were unable to test the fourth hypothesis due to multicollinearity.

Indirect Treatment Comparisons

There is some evidence of discordance between pharmaceutical and payer decision-makers with respect to the importance of indirect treatment comparisons as related to the study comparator used in clinical trials. Pharmaceutical respondents' responses suggest they perceive indirect treatment comparisons to be less important when the trial is conducted versus an active comparator; however, this difference was not significant (OR=0.87, p=0.708). Payer respondents generally rated the importance of indirect treatment comparisons as higher when for products where clinical trials were conducted versus an active comparator compared to those where it was conducted versus placebo, though the differences in ratings were also not significant (OR=1.30, p=0.586). We were unable to test the second hypothesis due to multicollinearity.

Health-Related Quality of Life / Utility

The results indicate that pharmaceutical and payer respondents differ in their ratings of the importance of health-related quality of life/utility evidence based on disease severity. Pharmaceutical respondents tended to rate the importance of health-related quality of life/utility evidence lower when disease severity was substantial compared to when disease severity was minimal or moderate; this finding was not significant (OR=0.59, p=0.120). Payers, on the other hand, tended to rate the importance higher when disease severity was substantial compared to when disease severity was minimal or moderate; this finding also did not reach the level of statistical significance (OR=1.51, p=0.584).

Resource Utilization/Cost-Offsets

Both pharmaceutical and payer respondents rated the importance of resource utilization/cost-offset evidence higher for disease that are of substantial severity compared to those of minimal/moderate severity (OR=1.85 and OR=2.30, respectively). The odds ratios were not significant for either group, however (p=0.295 and p=0.214, respectively). There was little evidence that place in therapy was associated with the ratings of importance; both groups rated the importance similarly for add-on therapies compared to monotherapies (OR=1.00, p=0.993 for pharmaceutical respondents; OR=1.08, p=0.849 for payer respondents).

Unmet Need – Adherence/Compliance of the Standard of Care

With respect to the importance of unmet need (adherence/compliance of the standard of care) evidence, pharmaceutical respondents rated the importance significantly lower for acute therapies versus chronic therapies (OR=0.22, p=0.009). Responses from payers were directionally similar but were not statistically significant (OR=0.75, p=0.689). Pharmaceutical respondents also rated the importance of unmet need evidence lower for cures compared to chronic therapies (OR=0.52, p=0.097). Payers rated the importance of unmet need evidence slightly higher for cures versus chronic therapies, but this was not a statistically significant difference (OR=1.09, p=0.881). Overall, there was a significant association between treatment type and the importance of unmet need evidence among pharmaceutical respondents (p=0.0190) but not among payer respondents (p=0.8145).

Alignment Between Pharmaceutical and Payer Respondents

The findings with respect to the alignment between pharmaceutical and payer respondents are presented in Table 4-7. The results suggest a significant difference in the overall ratings of importance of budget impact evidence between pharmaceutical and payer decision-makers. Specifically, payers generally rated the importance of budget impact evidence significantly lower than pharmaceutical respondents (OR=0.44, p=0.039). On the other hand, payer respondents rated the importance of health-related quality of life/utility evidence higher, overall, than pharmaceutical respondents (OR=2.69, p=0.011).

We did not find another statistically significant differences in the importance ratings between the two groups of respondents. The odds ratios indicate that payers rated the importance of burden/cost of illness evidence, cost-effectiveness evidence, and adherence/compliance evidence for the standard of care higher than pharmaceutical respondents (OR=1.14, p=0.738; OR=1.20, p=0.687; OR=1.67, p=0.180). On the other hand, payers generally rated the following types of evidence to be less important than pharmaceutical respondents: indirect treatment comparisons (OR=0.74, p=0.424) and resource utilization/cost-offsets (OR=0.53, p=0.135).

Discussion

This study adds a new assessment to the body of literature that has attempted to characterize the evolving importance and use of HEOR evidence by U.S. payer organizations. Our survey of payers suggests an increasing role of HEOR in formulary decision-making: the vast majority (81%) of respondents indicate that HEOR evidence plays an explicit role in their decisions – an increase from a 2010 survey that found that 74-77% percent of decision-makers leverage HEOR evidence.[39] Further, more than half of respondents indicate that their organizations develop HEOR evidence internally – also suggestive of an increase in the use of HEOR evidence by payers, as a survey conducted in 2004-2005 reported that 40% of respondents said their organizations develop their own economic models to support formulary decisions.[37] Additionally, we found that close to 20% of payer respondents report that their organization has a separate committee specifically charged with evaluating economic evidence.

We also assessed the importance of seven types of HEOR evidence in the formulary decision-making process, from the perspectives of both pharmaceutical and payer decision-makers. We found that payers state they most frequently consider budget impact evidence when making formulary decisions,

followed by evidence of unmet need related to adherence or compliance to the standard of care, and resource utilization/cost-offset evidence. Indirect treatment comparisons were rated as least frequently considered by payers, somewhat surprisingly given the increasing focus on comparative effectiveness research. On the other hand, respondents from the pharmaceutical sector indicate they most frequently produce budget impact evidence, cost-effectiveness/cost-utility evidence and burden/cost of illness evidence. In general, this reflects definitive interest in and consideration of HEOR evidence by payers, beyond traditional cost-effectiveness and patient-reported outcomes evidence that has been the focus of previous research. This also is indicative of the growing scope and remit of HEOR organizations in pharmaceutical companies.

Based on the frequency with which pharmaceutical and U.S. payer decision-makers state that they produce and consume HEOR evidence, respectively, we observe that pharmaceutical respondents indicate they produce each type of evidence as frequently or more frequently than payers say they consider each evidence type. This apparent over-production of HEOR evidence may be attributable to the different preferences for HEOR evidence by payers in different markets: due to economies of scale, producing cost-effectiveness analyses for the U.S., for instance, may be of modest cost due to the requirement to produce such evidence for the U.K. Additionally, it is important to consider that given the pluralistic and fragmented healthcare payer system in the U.S., a single supplier of HEOR evidence – the pharmaceutical company commercializing a new product – must generate evidence to satisfy the information needs of numerous payers with potentially differing preferences for specific types of HEOR evidence. Thus, the higher frequencies with which pharmaceutical companies state they generate evidence may be necessary to meet the needs of numerous U.S. payers. One exception to this trend of higher frequencies of production of HEOR versus consumption of HEOR is observed for evidence of unmet need (related to adherence/compliance of the standard of care): for this evidence type, payers indicate they consider this type of evidence more frequently compared to the frequency with which pharmaceutical companies produce this type of evidence.

In general, with respect to the product profiles, payers seem to value all seven types of HEOR evidence to be important considerations in their formulary decision, and rarely rate HEOR evidence to be not at all important or not needed. Of all the evidence types, payers most frequently rate indirect

treatment comparisons to be not important; however, this is only in 11% of all cases. Pharmaceutical respondents rate indirect treatment comparisons as not needed slightly more frequently than payers (18% of all cases). Across all product profiles, the evidence types that are rated as not important more frequently by payers compared to pharmaceutical respondents, although only slightly, include burden/cost of illness, budget impact, and resource utilization/cost-offset evidence. Conversely, payers rate unmet need, cost-effectiveness/cost-utility, indirect treatment comparisons, and HRQOL/utility evidence to be not important less frequently than pharmaceutical companies, with respect to the product profiles. While the absolute differences between the ratings are small, there is some suggestion of misalignment between payer and pharmaceutical decision-makers. Adjusting for product and market attributes, payers rate the importance of HRQOL evidence significantly higher than pharmaceutical respondents; on the other hand, they rate the importance of budget impact evidence significantly lower. It is important to note the product profiles tested in this survey are not a random or representative sample of newly approved products in the U.S., and therefore the frequency with which each type of evidence is rated as important may differ from the generalized frequencies presented above.

An understanding of when HEOR evidence is important may help pharmaceutical companies to select investments, and ultimately increase alignment between these two stakeholders groups. Our evaluation of the product and market attributes, though limited by the small sample size of this survey, provides some suggestion as to when each type of HEOR evidence is considered to be important. For instance, our findings suggest that burden/cost of illness may be less important for products that are later entrants to the market and are not first in class or fast-followers. This seems plausible, as such evidence may already exist, and burden/cost of illness may be fairly well understood by the time a later entrant receives regulatory approval.

A more puzzling trend is the association between the importance of cost-effectiveness/cost-utility evidence and the endpoint measured in clinical trials. The results of our regression analysis suggest that payer and pharmaceutical decision-makers tend to rate the importance of cost-effectiveness evidence higher when the trial endpoint is a mortality/survival endpoint compared to when it is a surrogate endpoint. Further, pharmaceutical respondents rate cost-effectiveness as more important when the trial endpoint is a morbidity endpoint compared to when it is a surrogate endpoint. We hypothesized that cost-

effectiveness evidence may be more important when a product measures a surrogate outcome, as modeling allows extrapolation of surrogate measures to clinical outcomes. While the survey findings were not significant, they are suggestive of the opposite relationship between trial endpoint and the importance of cost-effectiveness evidence.

We also observed an interesting relationship between the importance of HRQOL evidence and disease severity. Our results suggest that pharmaceutical respondents believe that HRQOL evidence is more important when a product is indicated for a disease of minimal or moderate severity than when it is indicated for a disease of substantial severity. The rationale may be to demonstrate patient impact for diseases that are not perceived to be serious or severe. Payers, however, rated HRQOL evidence higher for products indicated for substantially severe diseases compared to those indicated for diseases of minimal or moderate severity.

While we were able to identify some significant associations between product and market attributes and the importance of specific types of HEOR evidence, our ability to do so was limited by the small sample size of both surveys. In addition, due to the use of convenience sampling methods, we acknowledge the potential for selection bias that may reduce the generalizability of our findings. However, the participants to our survey are involved in decision-making for at least 16 pharmaceutical companies and 23 payer organizations, increasing our confidence that these findings are representative of a broad range of organizations. Further, there are limited means to reduce these sources of error given the challenges in identifying members of our population of interest. Because we required responses to all thirteen profiles, and the analysis includes only complete survey responses, item nonresponse is not a significant source of error among respondents who completed the survey. There is some potential for measurement error, as survey methods introduce the possibility of varying interpretation of questions by participants. This survey targeted a niche audience that is highly familiar with the commercialization and reimbursement of pharmaceutical product in the U.S., and we do not expect that significant error has been introduced due to misunderstanding of survey instructions or terms. However, it is possible, for instance, that participants may interpret questions differently. For example, while we avoided introducing concepts related to payer concerns about biased evidence, it is possible that some payers rated the importance of HEOR evidence to be lower than other because they implicitly adjusted for perceived bias

in the evidence provided by pharmaceutical companies. Social desirability of responses may also come into play, as in the U.S. there is hesitance on the part of payers to admit that drug price may be a factor in the decision to include a medicine on the formulary and give patients access to it. We attempted to mitigate this risk by presenting participants with a more comprehensive set of product and market attributes, of which price was only one.

To our knowledge, this study is the first to attempt to understand the importance of specific types of HEOR evidence. The results of these surveys indicate the importance of HEOR evidence beyond the hallmark cost-effectiveness analyses and suggest that investment in HEOR evidence by pharmaceutical companies and consideration of such evidence by U.S. payers is nuanced and varies based on the product-market scenarios. As the use of HEOR evidence grows, as is expected by our study participants, it will be increasingly important for pharmaceutical companies to understand when and what kinds of HEOR evidence are valuable in different contexts. This study can be seen as a first step in helping to inform future HEOR investment decisions.

Table 4-1. Summary of Survey Scenarios.

Scenario	Disease	Disease Severity	Market Position	Treatment Type	Scope of Indication	Place in Therapy	Relative Efficacy	Relative Safety	Relative Pricing	Trial Comparator	Trial Endpoint
A	mCRC	Substantial	First in Class	Acute	Broad	1L Mono	Better	Comparable	Premium	Active/SOC	PFS
B	mCRC	Substantial	First in Class	Acute	Broad	1L Mono	Better	Comparable	Premium	Active/SOC	OS
C	mCRC	Substantial	First in Class	Acute	*RAS*+	1L Mono	Comparable	Better	Premium	Active/SOC	PFS
D	mCRC	Substantial	First in Class	Acute	Broad	2L Mono	Worse	Comparable	Parity	Placebo	PFS
E	HCh	Moderate	First in Class	Chronic	Broad	1L Add-On	Better	Comparable	Premium	Active/SOC	Surrogate
F	HCh	Moderate	First in Class	Chronic	Broad	1L Add-On	Comparable	Comparable	Parity	Active/SOC	Surrogate
G	HCh	Moderate	Me Too	Chronic	Broad	1L Add-On	Comparable	Comparable	Discount	Active/SOC	Surrogate
H	HCh	Moderate	First in Class	Chronic	Familial HCh	1L Add-On	Better	Comparable	Premium	Active/SOC	Surrogate
I	HCh	Moderate	Fast Follower	Chronic	Broad	1L Add-On	Better	Comparable	Premium	Active/SOC	Morbidity
J	RA	Moderate	First in Class	Chronic	Broad	1L Mono	Better	Comparable	Premium	Active/SOC	Morbidity
K	RA	Moderate	First in Class	Chronic	Broad	1L Mono	Better	Worse	Premium	Placebo	Morbidity
L	HSV	Minimal	First in Class	Acute	Broad	1L Mono	Better	Comparable	Premium	Placebo	Morbidity
M	HCV	Moderate	First in Class	Cure	Broad	1L Mono	Better	Better	Premium	Active/SOC	Surrogate

mCRC = metastatic colorectal cancer, HCh = hypercholesterolemia, RA = rheumatoid arthritis, HSV = herpes simplex virus, HCV = hepatitis C virus.

Table 4-2. Regression Model Variables & Coding.

Variables	Variable Type	Coding
HEOR Importance *(Dependent variables)*	Categorical	0 – Not at all important/not needed 1 – Unsure/more information needed 2 – Somewhat important 3 – Important 4 – Very important 5 – Extremely important/absolutely essential *Recoded to binary: 0=0-2, 1=3-5*
Disease *(Omitted from analysis due to collinearity)*	Categorical	0 – Metastatic colorectal cancer 1 – Hypercholesterolemia 2 – Rheumatoid arthritis 3 – Herpes simplex virus 4 – Hepatitis C virus
Disease Severity	Categorical	0 – Moderate 1 – Minimal 2 – Substantial *Recoded to binary: 0=0/1, 1=2*
Market Position	Categorical	0 – First in class 1 – Me too 2 – Fast follower *Recoded to binary: 0=0/2, 1=1*
Treatment Type	Categorical	0 – Chronic 1 – Acute 2 – Cure
Scope of Indication	Categorical	0 – Broad 1 – Narrow
Place in Therapy	Categorical	0 – 1st Line Monotherapy 1 – 1st Line Add-on Therapy 2 – 2nd Line Monotherapy *Recoded to binary: 0=0/2, 1=1*
Relative Efficacy	Categorical	0 – Comparable 1 – Better 2 – Worse *Recoded to binary: 0=1, 1=0/2*
Relative Safety	Categorical	0 – Comparable 1 – Better 2 – Worse *Recoded to binary: 0=0/1, 1=2*
Relative Price	Categorical	0 – Premium 1 – Parity 2 – Discount *Recoded to binary: 0=0, 1=1/2*
Trial Comparator	Categorical	0 – Placebo 1 – Active/SOC
Trial Endpoint	Categorical	0 – Surrogate 1 – Morbidity/Progression-Free Survival 2 – Mortality/Survival
Familiarity	Categorical	0 – Not at all familiar 1 – Somewhat familiar 2 – Very familiar
Company X *(Included for Pharma only)*	Categorical	0 – Non-Company X respondent 1 – Company X respondent

Table 4-3. Respondent Characteristics.

	Payer Respondents (n = 31)			Pharmaceutical Respondents (n=63)		
Organization Type *(Note: multiple responses were allowed)*	Commercial/Private Payer	21	(68%)	Pharmaceutical	54	(86%)
	Pharmacy Benefit Manager	11	(35%)	Biotechnology	9	(14%)
	Other	2	(6%)	Medical Devices	2	(3%)
				Other	2	(3%)
Role/Function *(Note: multiple responses were allowed)*	P&T Committee Chair	3	(10%)	HEOR	52	(83%)
	P&T Committee Member	14	(45%)	Market Access	13	(21%)
	Value Access (or similar) Committee Chair	0	(0%)	Other	1	(2%)
	Value Access (or similar) Committee Member	5	(16%)			
	Formulary Manager	9	(29%)			
	Evidence Reviewer	16	(52%)			
	Other	3	(10%)			
Years Experience	<1 year	1	(3%)	<1 year	0	(0%)
	1-5 years	10	(32%)	1-5 years	10	(16%)
	6-10 years	7	(23%)	6-10 years	19	(30%)
	>10 years	13	(42%)	>10 years	34	(54%)
Discipline *(Note: multiple responses were allowed)*	Clinician	3	(10%)	N/A		
	Pharmacist	29	(94%)			
	Other	1	(3%)			
Involved in Formulary Decision-Making for More than One Organization	Yes	8	(26%)	N/A		
	No	20	(65%)			
	No Response	3	(10%)			
Involved in Formulary Decision-Making for More than One Formulary	Yes	25	(81%)	N/A		
	No	6	(19%)			

Table 4-4. Logistic Regression Results: Pharmaceutical Respondents.

	BI OR (p val)	**BCOI** OR (p val)	**CEA** OR (p val)	**ITC** OR (p val)	**HRQOL/U** OR (p val)	**RUCO** OR (p val)	**UN/AC** OR (p val)
Disease Severity:	1.34 (0.658)	0.74 (0.539)	**2.57 (0.005)**	0.65 (0.295)	0.59 (0.120)	1.85 (0.295)	0.92 (0.828)
Market Position	3.15 (0.060)	0.61 (0.108)	1.21 (0.407)	**0.49 (0.001)**	0.65 (0.054)	0.71 (0.206)	0.64 (0.108)
Treatment Type 1	0.34 (0.167)	0.58 (0.370)	**0.29 (0.020)**	0.85 (0.729)	1.74 (0.192)	**0.11 (0.006)**	**0.22 (0.009)**
Treatment Type 2	0.33 (0.184)	1.04 (0.951)	1.33 (0.437)	0.76 (0.521)	1.32 (0.427)	0.72 (0.783)	0.52 (0.097)
Scope of Indication	0.40 (0.167)	1.22 (0.567)	1.00 (1.000)	**0.63 (0.048)**	**1.83 (0.001)**	0.58 (0.421)	0.60 (0.055)
Place in Treatment	0.99 (0.987)	**0.41 (0.024)**	1.07 (0.819)	0.96 (0.895)	**0.38 (0.000)**	1.00 (0.993)	0.59 (0.134)
Relative Efficacy	2.51 (0.177)	1.37 (0.438)	0.70 (0.299)	1.49 (0.077)	0.60 (0.126)	2.15 (0.343)	1.57 (0.258)
Relative Safety	0.54 (0.353)	0.71 (0.508)	0.44 (0.077)	1.57 (0.331)	**2.55 (0.027)**	0.23 (0.072)	0.46 (0.111)
Relative Price	**0.09 (0.031)**	0.48 (0.155)	0.51 (0.167)	0.48 (0.077)	2.06 (0.095)	**0.08 (0.046)**	0.45 (0.159)
Trial Comparator	0.64 (0.471)	1.41 (0.380)	0.72 (0.348)	0.87 (0.708)	**2.55 (0.008)**	0.40 (0.165)	0.75 (0.487)
Trial Endpoint 1	0.47 (0.266)	0.77 (0.367)	1.41 (0.157)	1.24 (0.407)	**1.71 (0.009)**	1.00 (1.000)	0.70 (0.206)
Trial Endpoint 2	0.35 (0.174)	0.71 (0.256)	1.41 (0.148)	1.09 (0.800)	1.01 (0.965)	0.82 (0.834)	0.61 (0.159)
Familiarity 1	0.89 (0.740)	0.58 (0.104)	1.45 (0.233)	1.75 (0.053)	0.82 (0.540)	0.88 (0.713)	0.77 (0.359)
Familiarity 2	0.55 (0.163)	0.55 (0.174)	1.37 (0.484)	2.30 (0.053)	0.58 (0.168)	0.80 (0.626)	1.23 (0.555)
Company X	0.80 (0.591)	1.52 (0.282)	0.68 (0.329)	0.91 (0.808)	1.85 (0.078)	0.88 (0.755)	1.46 (0.281)
Constant	**43.82 (0.002)**	**8.40 (0.003)**	2.90 (0.089)	1.28 (0.675)	0.58 (0.346)	**59.81 (0.003)**	**8.48 (0.003)**

BI = budget impact; BCOI = burden/cost of illness; CEA = cost-utility analysis; ITC = indirect treatment comparison; HRQOL/U = health-related quality of life/utility; RUCO = resource utilization/cost-offsets; UNAC = unmet need – adherence/compliance of standard of care.

Table 4-5. Logistic Regression Results: Payer Respondents.

	BIM OR (p val)	**BCOI** OR (p val)	**CEA** OR (p val)	**ITC** OR (p val)	**HRQOL/U** OR (p val)	**RUCO** OR (p val)	**UN/AC** OR (p val)
Disease Severity	0.98 (0.975)	1.08 (0.879)	0.70 (0.536)	1.17 (0.748)	1.51 (0.584)	2.30 (0.214)	1.71 (0.261)
Market Position	1.00 (1.000)	0.74 (0.152)	0.85 (0.660)	0.87 (0.569)	1.00 (1.000)	0.86 (0.659)	1.16 (0.569)
Treatment Type 1	0.40 (0.262)	1.11 (0.897)	1.32 (0.694)	1.24 (0.753)	2.00 (0.346)	1.37 (0.712)	0.75 (0.689)
Treatment Type 2	1.22 (0.710)	0.75 (0.637)	0.96 (0.926)	0.84 (0.751)	1.17 (0.742)	1.22 (0.763)	1.09 (0.881)
Scope of Indication	0.82 (0.659)	1.00 (1.000)	1.22 (0.569)	1.00 (1.000)	1.82 (0.261)	0.80 (0.710)	0.69 (0.322)
Place in Treatment	1.26 (0.485)	0.46 (0.116)	**0.41 (0.024)**	0.71 (0.486)	0.91 (0.798)	1.08 (0.849)	0.60 (0.153)
Relative Efficacy	1.65 (0.351)	1.63 (0.406)	0.82 (0.569)	1.00 (1.000)	0.55 (0.401)	1.25 (0.710)	1.77 (0.169)
Relative Safety	0.41 (0.223)	0.68 (0.617)	0.97 (0.938)	1.30 (0.652)	1.20 (0.793)	1.65 (0.569)	0.40 (0.188)
Relative Price	2.81 (0.236)	1.63 (0.546)	0.98 (0.968)	1.15 (0.783)	0.76 (0.792)	2.70 (0.344)	4.11 (0.058)
Trial Comparator	1.02 (0.973)	2.00 (0.266)	**2.78 (0.006)**	1.30 (0.586)	2.64 (0.201)	2.42 (0.280)	1.08 (0.879)
Trial Endpoint 1	1.00 (1.000)	1.18 (0.659)	1.00 (1.000)	0.75 (0.312)	1.19 (0.659)	1.00 (1.000)	0.69 (0.321)
Trial Endpoint 2	1.60 (0.329)	2.66 (0.070)	1.53 (0.151)	0.86 (0.551)	0.76 (0.522)	0.76 (0.616)	0.84 (0.685)
Familiarity 1	**0.38 (0.043)**	0.81 (0.734)	1.36 (0.622)	0.99 (0.981)	3.43 (0.080)	2.19 (0.228)	1.27 (0.731)
Familiarity 2	0.30 (0.078)	1.93 (0.278)	3.75 (0.088)	3.19 (0.179)	**6.01 (0.022)**	**4.92 (0.035)**	2.63 (0.218)
Constant	3.71 (0.114)	0.95 (0.959)	0.96 (0.967)	0.63 (0.654)	0.29 (0.157)	**0.17 (0.048)**	0.66 (0.672)

BI = budget impact; BCOI = burden/cost of illness; CEA = cost-utility analysis; ITC = indirect treatment comparison; HRQOL/U = health-related quality of life/utility; RUCO = resource utilization/cost-offsets; UNAC = unmet need – adherence/compliance of standard of care.

Table 4-6. Hypotheses Tested.

#	Hypothesis	Rationale	Regression Test	Adjusted Binary Logit Results: Pharma[1]	Adjusted Binary Logit Results: Payers[1]	Unadj. Ordinal Logistic Results: Pharma[2]	Unadj. Ordinal Logistic Results: Payers[2]	Non-Parametric Test of Scenarios	Non Parametric Results: Pharma	Non-Parametric Results: Payers
Budget Impact (BI)										
1	BI evidence is more important for diseases/indications with higher prevalence.	Payers may be concerned about the budget impact when large patient populations are targeted.	β(scope of indication)	OR = 0.40 (0.167)	OR = 0.82 (0.659)	OR = 0.95 (0.629)	OR = 1.13 (0.415)	E vs. H	z = 1.087, (0.2768)	z = 0.143, (0.8863)
2	BI evidence is more important when the relative price of the product is higher.	When price is higher, payers may be more interested in the total budgetary impact of the product.	β(relative price)	**OR = 0.09 (0.031)**	OR = 2.81 (0.236)	**OR1 = 0.52 (0.000)** OR2 = 1.20 (0.402) **p = 0.0002**	OR1 = 0.65 (0.076) OR2 = 0.99 (0.951) p = 0.1861	Not Tested		
3	BI evidence is more important when a product has a worse adverse event profile.	Payers may be interested to see how the costs of AEs affect the total cost of treatment.	β(relative safety)	OR = 0.54 (0.353)	OR = 0.41 (0.223)	OR1 = 1.13 (0.351) OR2 = 1.03 (0.827) p = 0.6201	**OR1 = 1.54 (0.008)** OR2 = 0.60 (0.062) **P = 0.0243**	Not Tested		
Burden/Cost of Illness (BCOI)										
4	BCOI evidence is more important when a product is an earlier (first) vs. later entrant to market.	BCOI may be less well established for products that are first in class.	β(market position)	OR = 0.61 (0.108)	OR = 0.74 (0.152)	**OR1 0.39 (0.000)** OR2 = 0.93 (0.671) **p = 0.0002**	**OR1 = 0.57 (0.018)** OR2 = 0.70 (0.126) **p = 0.0464**	Not Tested		

#	Hypothesis	Rationale	Regression Test	Adjusted Binary Logit Results: Pharma[1]	Adjusted Binary Logit Results: Payers[1]	Unadj. Ordinal Logistic Results: Pharma[2]	Unadj. Ordinal Logistic Results: Payers[2]	Non-Parametric Test of Scenarios	Non Parametric Results: Pharma	Non-Parametric Results: Payers
5	BCOI evidence is more important when the disease treated is rare, a less well-known disease, or when subpopulations of a disease are targeted.	Rare diseases may have less well-understood consequences. Targeted subgroups may have a different risk profile or treatment pattern than the larger population.	β(scope of indication)	OR = 1.22 (0.567)	OR = 1.00 (1.000)	OR = 1.17 (0.260)	OR = 1.24 (0.188)	E vs. H	z = -0.504 (0.6140)	z = 0.714 (0.4751)
6	BCOI evidence is more important when the drug is indicated as an add-on therapy.	Quantifying the residual BCOI may justify the need for an add-on treatment.	β(place in treatment)	**OR = 0.41 (0.024)**	OR = 0.46 (0.116)	**OR1 = 0.65 (0.000)** **OR2 = 0.35 (0.000)** **P < 0.0001**	OR1 = 0.65 (0.101) OR2 = 0.59 (0.149) P = 0.0654	Not Tested		
Cost-Effectiveness/Cost-Utility (CEA/CUA)										
7	CEA/CUA evidence is more important when the trial endpoint is a surrogate.	CEA/CUA evidence attempts to extrapolate the impact on length/quality of life.	β(trial endpoint)	OR1 = 1.41 (0.157) OR2 = 1.41 (0.148) p = 0.3387	OR1 = 1.00 (1.000) OR2 = 1.53 (0.151) p = 0.1512	OR1 = 1.09 (0.381) OR2 = 1.35 (0.061) P = 0.1537	OR1 = 1.12 (0.448) **OR2 = 1.90 (0.011)** **P = 0.0106**	A vs. B	z = -0.401 (0.6885)	z = 0.059 (0.9533)
8	CEA/CUA evidence is more important for more severe diseases.	For more severe diseases, the impact on quality of life may be more important.	β(disease severity)	**OR = 2.57 (0.005)**	OR = 0.70 (0.536)	OR1 = 0.75 (0.147) OR2 = 0.92 (0.521) P = 0.3487	OR1 = 0.88 (0.713) OR2 = 1.32 (0.293) P = 0.2269	A vs. J	z = 0.076 (0.9391)	z = -1.012 (0.3117)

#	Hypothesis	Rationale	Regression Test	Adjusted Binary Logit Results: Pharma[1]	Adjusted Binary Logit Results: Payers[1]	Unadj. Ordinal Logistic Results: Pharma[2]	Unadj. Ordinal Logistic Results: Payers[2]	Non-Parametric Test of Scenarios	Non Parametric Results: Pharma	Non-Parametric Results: Payers
9	CEAs/CUAs evidence is more important when a drug is first in class.	When 1st in class, the drug is setting the benchmark; CEA/CUA evidence may be less useful for followers that get benchmarked to the 1st in class drug.	β(market position)	OR = 1.21 (0.407)	OR = 0.85 (0.660)	**OR1 = 0.54 (0.014)** **OR2 = 1.34 (0.025**) **p = 0.0001**	**OR1 = 0.60 (0.040)** OR2 = 0.96 (0.838) p = 0.1215	Not Tested		
10	CEA/CUA evidence is more important when a product's price is higher and efficacy is better than the standard of care.	CEA/CUA is necessary to justify the cost.	β(relative price x relative efficacy)	(collinearity)	(collinearity)	(collinearity)	(collinearity)	E vs. F	z = 2.982, p = 0.0029	z = 0.849, p = 0.3959
Indirect Treatment Comparisons / Network Meta-Analyses (ITC)										
11	ITCs are more important to payers when trials are conducted versus placebo.	ITCs are less important when trials are conducted versus the relevant SOC.	β(Trial Comparator)	OR = 0.87 (0.708)	OR = 1.30 (0.586)	**OR = 0.62 (0.004)**	OR = 1.13 (0.663)	Not Tested		
12	ITCs are more important when a product's efficacy or safety relative to the SOC is unclear.	A formal analysis is required to assess relative efficacy/safety.	β(relative efficacy x trial comparator) β(relative safety x trial comparator)	(collinearity)	(collinearity)	**OR[3] = 1.82 (0.019)** (collinearity)	OR[3] = 0.73 (0.408) (collinearity)	Not Tested	TBD	TBD

#	Hypothesis	Rationale	Regression Test	Adjusted Binary Logit Results: Pharma[1]	Adjusted Binary Logit Results: Payers[1]	Unadj. Ordinal Logistic Results: Pharma[2]	Unadj. Ordinal Logistic Results: Payers[2]	Non-Parametric Test of Scenarios	Non Parametric Results: Pharma	Non-Parametric Results: Payers
Health-Related Quality of Life/Utility (HRQOL/U)										
13	HRQOL/U evidence is more important when the drug is indicated for a severe or life threatening disease.	Assessing patient impact for severe diseases is most important.	β(disease severity)	OR = 0.59 (0.120)	OR = 1.51 (0.584)	OR1 = 1.35 (0.125) **OR2 = 1.45 (0.028)** p = 0.0514	OR1 = 0.90 (0.773) **OR2 = 1.83 (0.042)** **p = 0.0305**	A vs. J	z = -0.423 (0.6726)	z = 1.159 (0.2466)
Resource Utilization/Cost-Offsets (RU/CO)										
14	RU/CO evidence is more important for less severe diseases.	Demonstrating cost-offsets provides value arguments for products for less severe disease.	β(disease severity)	OR = 1.85 (0.295)	OR = 2.30 (0.214)	**OR1 = 0.64 (0.028)** **OR2 = 0.49 (0.000)** **p = 0.0001**	OR1 = 0.99 (0.970) OR2 = 1.46 (0.203) p = 0.3617	A vs. J	z = -2.538 (0.0111)	z = 0.145 (0.8849)
15	RU/CO evidence is more important for add-on versus monotherapies.	RU/CO evidence may be important for add-on therapies to demonstrate value.	β(place in therapy)	OR = 1.00 (0.993)	OR = 1.08 (0.849)	OR1 = 1.03 (0.849) **OR2 = 0.39 (0.001)** **p = 0.0012**	**OR1 = 0.60 (0.041)** **OR2 = 0.42 (0.030)** **p = 0.0125**	Not Tested		
Unmet Need – Adherence/Compliance of SOC (UNAC)										
16	UNAC evidence is more important for chronic diseases.	Adherence/compliance tend to be lower for chronic diseases.	β(treatment type)	**OR1 = 0.22 (0.009)** OR2 = 0.52 (0.097) **p = 0.0190**	OR1 = 0.75 (0.689) OR2 = 1.09 (0.881) p = 0.8145	**OR1 = 0.41 (0.000)** OR2 = 1.30 (0.241) **P<0.0001**	OR1 = 1.68 (0.105) **OR2 = 2.61 (0.000)** **P = 0.0001**	Not Tested		

[1]Binary logistic regression (0=0-2; 1=3-5) with all predictors (collapsed into binary variables where possible), and adjusted for respondent familiarity and clustering at the respondent level. Pharma analyses also adjusted for Company X.
[2]Ordered logistic regression with key predictor of interest only (not collapsed), and adjusted for respondent familiarity and clustering at the respondent level. Pharma analysis also adjusted for Company X. None of the analyses are adjusted for predictors that are not of interest.
[3]Efficacy was recoded as a binary variable for these analyses.

Table 4-7. Alignment Between Pharmaceutical and Payer Decision-Makers.

Evidence Type	Binary Logit Odds Ratio[1] (p-value)
Budget Impact	**0.44 (0.039)**
Burden/Cost of Illness	1.14 (0.738)
Cost-Effectiveness/Cost-Utility	1.20 (0.687)
Indirect Treatment Comparisons	0.74 (0.424)
Patient Health-Related QOL / Utility	**2.69 (0.011)**
Resource Utilization / Cost-Offsets	0.53 (0.135)
Unmet Need: Adherence/Compliance of SOC	1.67 (0.180)

[1]Odds ratio: payer vs. pharmaceutical respondents.

Figure 4-1. Frequency With Which Evidence is Developed (Pharmaceutical Respondents) and Considered (Payer Respondents) for New Products.

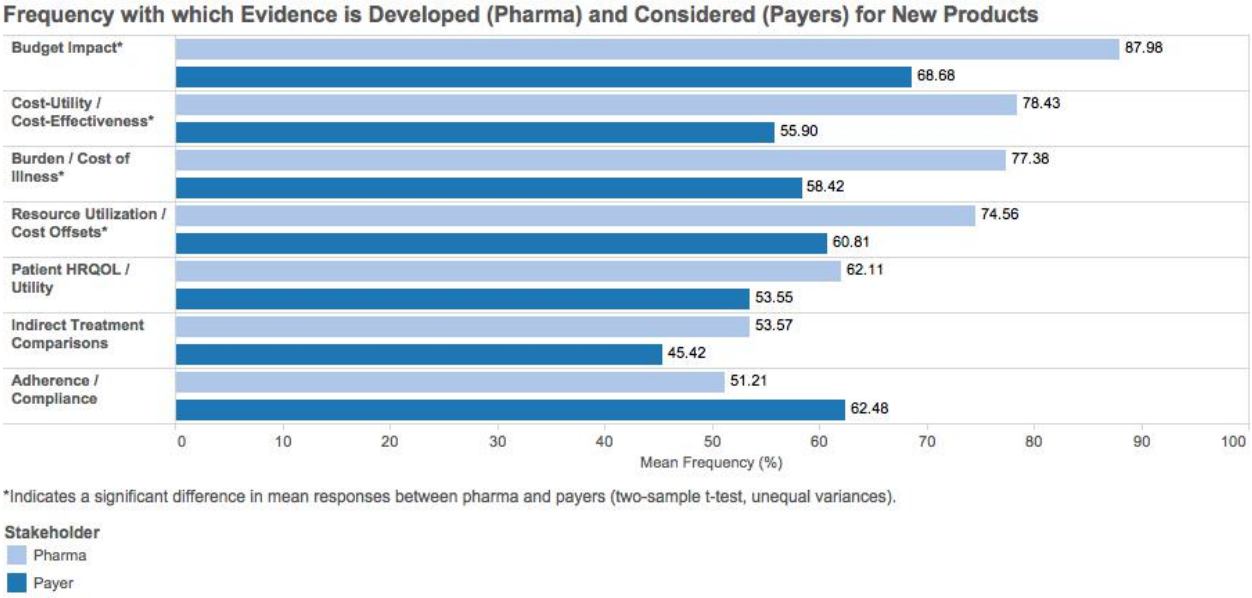


Figure 4-2. To What Degree Does HEOR Evidence Impact Formulary Decisions in the U.S.?

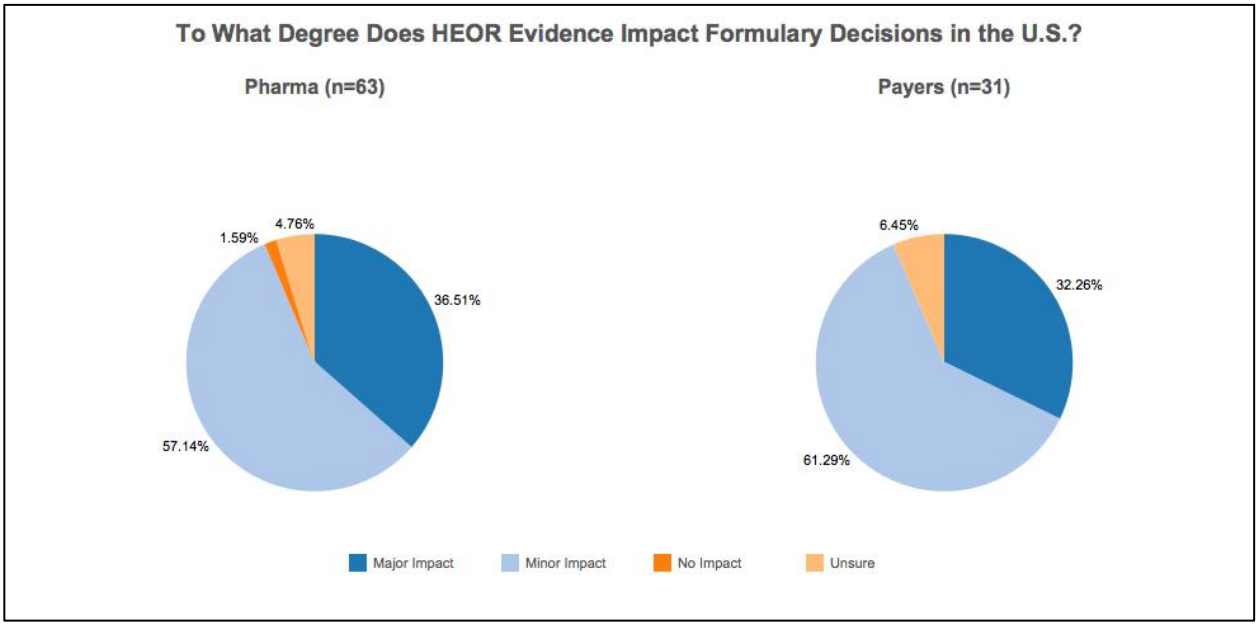


Figure 4-3. How Will the Impact of HEOR Evidence on U.S. Formulary Decisions Change in the Next 5-10 Years?

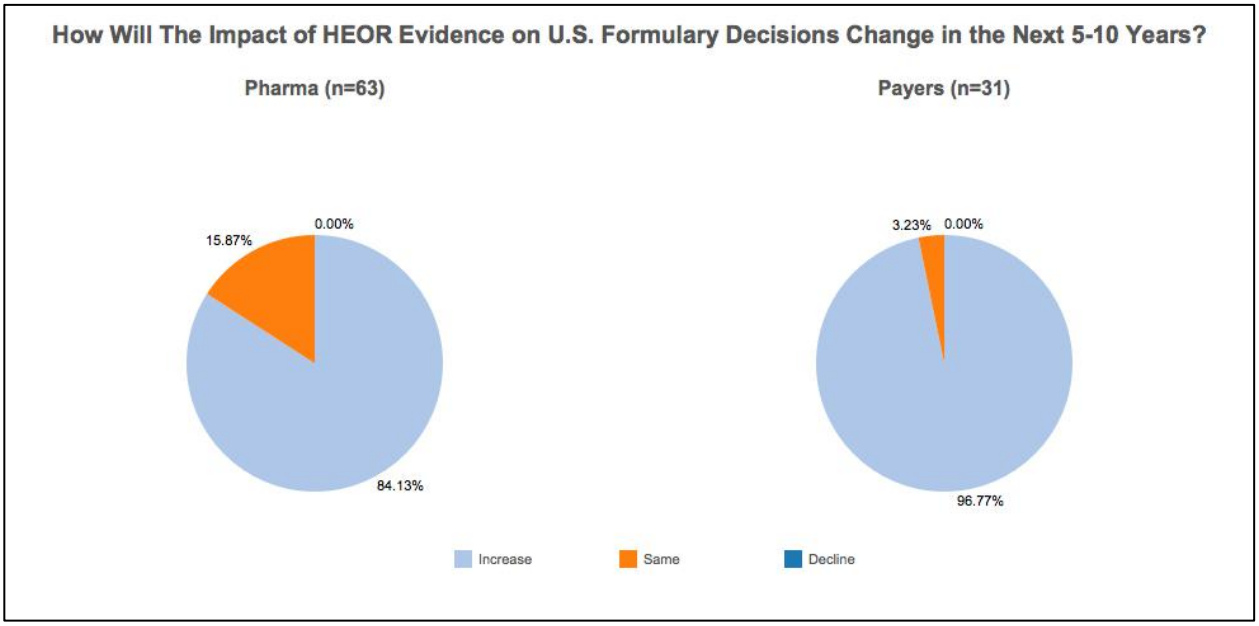
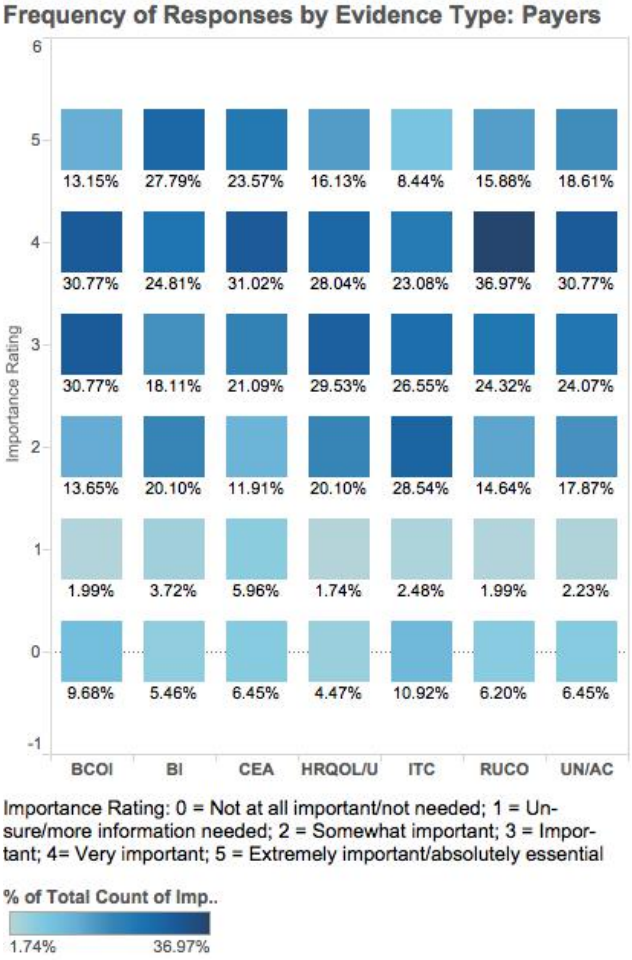
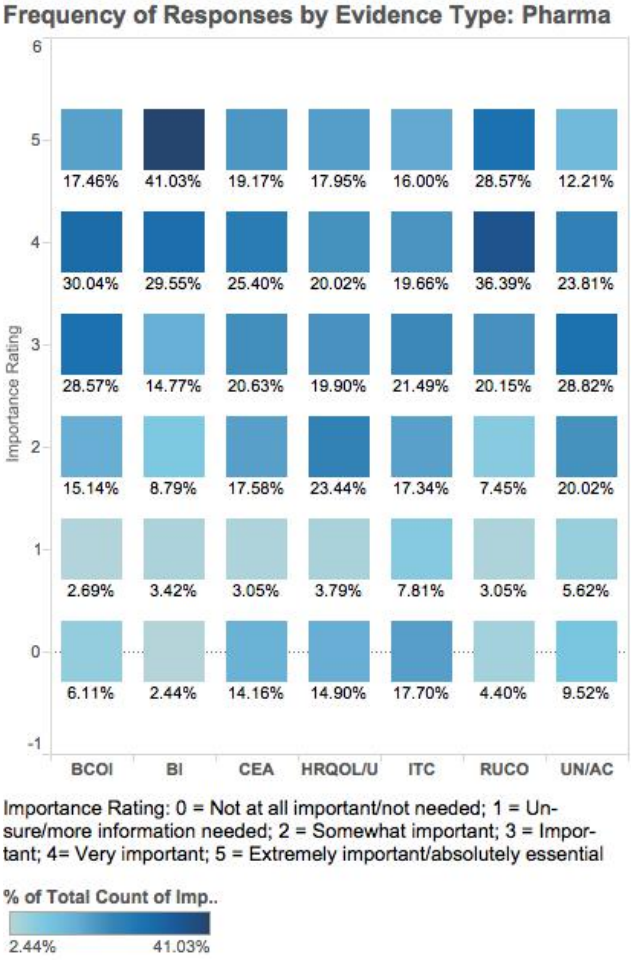


Figure 4-4. Frequency of Responses by Evidence Type: Payer Respondents.



BCOI = burden/cost of illness; BI = budget impact; CEA = cost-effectiveness analysis; HRQOL/U = health-related quality of life/utility; ITC = indirect treatment comparisons; RUCO = resource utilization/cost-offsets; UN/AC = unmet need – adherence/compliance of standard of care.

Figure 4-5. Frequency of Responses by Evidence Type: Pharmaceutical Respondents.



BCOI = burden/cost of illness; BI = budget impact; CEA = cost-effectiveness analysis; HRQOL/U = health-related quality of life/utility; ITC = indirect treatment comparisons; RUCO = resource utilization/cost-offsets; UN/AC = unmet need – adherence/compliance of standard of care.

CHAPTER 5

Overall Research Implications

While health economics and outcomes research (HEOR) plays an explicit and sometimes critical role in the success of pharmaceutical products in select markets, the impact of HEOR evidence on a product's success in the U.S. is less well understood. Given the increasing focus on costs in the U.S. health care market, there is reason to believe that HEOR evidence may have a significant role in the reimbursement success of new products. Thus, we sought to assess the impact of HEOR evidence on reimbursement decisions in the U.S.

The literature review conducted in Chapter 1 provided evidence of more frequent submission of HEOR evidence to U.S. payers by pharmaceutical companies, and increased understanding and review of HEOR evidence by U.S. payers. However, the existing literature is largely focused on cost-effectiveness analyses, and to some extent, health-related quality of life studies. We did not identify any studies that considered a broader, more comprehensive scope of HEOR. Additionally, only one study, conducted a decade ago, assessed the importance of HEOR from both the payer and pharmaceutical company perspectives.

In Chapter 2, we evaluated the perspectives, goals, incentives, strategy, and tactics of both payer and pharmaceutical stakeholders. Based on this, we drew the conclusion that while U.S. payers have historically been reluctant to deny coverage of new medicines on the basis of price, tiered copayments and restrictions on use are mechanisms by which they control costs, and therefore, HEOR evidence may inform decisions about the implementation of these cost-control mechanisms. Further, we hypothesized that it is probable that HEOR evidence is not always important; specific types of evidence may have greater value in informing U.S. private payer reimbursement decisions under certain product-market scenarios.

In our focus group sessions and planning surveys, we identified eight types of HEOR evidence that fall into the scope of investments an HEOR function might undertake during a product's development to demonstrate its value for the purposes of reimbursement. These include: budget impact, burden/cost of illness, cost-effectiveness/cost-utility, disease incidence/prevalence, indirect treatment comparisons, patient health-related quality of life/utility, resource utilization/cost-offsets, and unmet need (adherence/compliance of the standard of care). In our focus group sessions, we also identified 21 product attributes, market attributes, data quality attributes, and exogenous factors that HEOR executives

felt were important considerations when assessing the importance of HEOR. We then developed more nuanced hypotheses as to when specific types of HEOR evidence may be important, described in terms of product-market scenarios.

Our survey of HEOR executives in Chapter 3 allowed us to better understand the supply side of the market by assessing general trends in HEOR investments, level of agreement across decision-makers, the product and market attributes that drive investment decisions, and the correlation between stated importance and actual levels of investment. Our findings suggested that there are certain scenarios where HEOR evidence is believed to be more impactful to payers: respondents clearly and consistently differentiated the products that were most and least likely to benefit from HEOR, and these stated choices were substantiated by literature reviews of the total number of published HEOR studies. However, respondents rarely indicated that they would not invest in any type of HEOR evidence.

We found that budget impact evidence is generally believed to be important to payers for all products. While the decision-makers we surveyed were in agreement as to when HEOR evidence is important information for U.S. payer decision-making, they were less consistent in their responses as to when specific types of HEOR evidence are important. This suggests that a better understanding of when payers value specific types of HEOR evidence could help to guide HEOR investment decisions by pharmaceutical companies.

In Chapter 4, our survey findings suggest that HEOR is an explicit consideration in the formulary decision-making process for most payers. In addition, approximately one in five payers have a separate committee in place to review HEOR evidence, and approximately half develop their own HEOR evidence. Taken in context with previous research, these findings suggest an increase in the uptake of HEOR evidence by U.S. payers.

In general, payers seem to value all types of HEOR evidence to be important considerations in their formulary decisions, and rarely rate HEOR evidence to be not at all important or not needed. Payers stated they most frequently consider budget impact evidence when making formulary decisions, followed by evidence of unmet need related to adherence or compliance to the standard of care, and resource utilization/cost-offset evidence. Indirect treatment comparisons were stated by payers to be the least frequently considered type of evidence. On the other hand, respondents from the pharmaceutical sector

indicated they most frequently produce budget impact evidence, cost-effectiveness/cost-utility evidence, and burden/cost of illness evidence. There is evidence of some misalignment between payer and pharmaceutical decision-makers as to when specific types of HEOR evidence are important.

Overall, this research contributes to the body of literature that characterizes the evolving importance and use of HEOR evidence by U.S. payers. The importance of HEOR evidence appears to have increased in recent years, and we expect use of this information to continue to grow with the increasing cost pressures in the health care industry. As decision-makers in the U.S. look beyond safety and efficacy and become more interested in value, HEOR evidence will be a critical factor in resource allocation decisions.

Our research also suggests an increase in the scope of the types of HEOR evidence produced by pharmaceutical companies. Understanding payer preferences and the scenarios in which the various types of evidence are important will help companies to select and prioritize investments in HEOR. This study can be seen as a first step in helping to inform future HEOR investment decisions.

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APPENDICES

Appendix 2-1. Steering Committee Questionnaire on the Scope of HEOR.

HTF Steering Committee Survey

As the University of Washington team develops a detailed project plan for the Health Tech Fund project, we would like to pose a few questions to the Steering Committee for clarity and help with our thought process. The following brief survey includes questions on the scope and role of HEOR, as well as the availability of and your ability to provide data from your organization.

Note: Because some members are located in a US HEOR function and others in Global HEOR function, and some have experience in both, we have structured the questionnaire to reflect this distinction.

1. **What is the geographical jurisdiction of your HEOR function within your company?**

   □ US HEOR
   □ Global HEOR
   □ Other: _____

2. **Where is your HEOR function located organizationally within your company currently? *(Select all that apply.)***

   □ R&D
   □ Medical Affairs
   □ Commercial
   □ Other: _____

   What is the role of your HEOR unit?

3. **For purposes of this project, how would you define an HEOR study?**

4. **For purposes of this project, how would you define "commercial success"?**

5. **Which of the following are types of HEOR studies conducted (either internally or externally) by the HEOR function at your company, or another function at your company (e.g., Epidemiology)?**

   In the fourth column, please provide an estimate of the average cost of each of the studies selected, <u>when conducted externally</u>. *(To the nearest $10,000 US Dollars)*

	Conducted by HEOR Function in my Company	Conducted by Other Function in my Company	External Avg. Study Cost (To nearest $10,000 USD)
Burden of illness studies	□	□	_____
Determination of disease incidence or prevalence	□	□	_____
Collection of utilization data alongside Phase 3 trials	□	□	_____
Cost-effectiveness model development	□	□	_____
Budget impact model development	□	□	_____
Global value dossiers	□	□	_____
Adherence / compliance studies	□	□	_____
Patient-reported outcomes instrument development and validation	□	□	_____
Patient-reported outcomes studies	□	□	_____
Assessment of treatment patterns	□	□	_____
Assessment of treatment costs / health care utilization	□	□	_____
HEOR studies alongside Phase 3B/4 trials	□	□	_____
Registry studies	□	□	_____
Observational database research pre-launch	□	□	_____
Observational database research post-launch	□	□	_____
Comparative effectiveness research *(Please specify: _____)*	□	□	_____
Evidence synthesis (e.g., meta-analysis, indirect treatment comparisons)	□	□	_____
Other HEOR Study:	□	□	_____
Other HEOR Study:	□	□	_____

6. **Looking over your entire portfolio in the past year, how would you approximate the distribution of spend for HEOR activities in each phase? *(Please feel free to respond with US only, Global only, or both—if you are comfortable doing that.)***

US		Global	
Phase 1:	_____ %	Phase 1:	_____ %
Phase 2:	_____ %	Phase 2:	_____ %
Phase 3:	_____ %	Phase 3:	_____ %
Post-Launch:	_____ %	Post-Launch:	_____ %

7. **Looking over your entire portfolio in the past 5 years, how would you approximate the distribution of spend for HEOR activities in each phase? *(Please feel free to respond with US only, Global only, or both—if you are comfortable doing that.)***

US		Global	
Phase 1:	_____ %	Phase 1:	_____ %
Phase 2:	_____ %	Phase 2:	_____ %
Phase 3:	_____ %	Phase 3:	_____ %
Post-Launch:	_____ %	Post-Launch:	_____ %

8. **At a broader industry level, how would you approximate the distribution of spend for HEOR activities in each phase across pharmaceutical companies? *(Please feel free to respond with US only, Global only, or both—if you are comfortable doing that.)***

US		Global	
Phase 1:	_____ %	Phase 1:	_____ %
Phase 2:	_____ %	Phase 2:	_____ %
Phase 3:	_____ %	Phase 3:	_____ %
Post-Launch:	_____ %	Post-Launch:	_____ %

9. **If requested, would you be able to provide the following historical data on a product-by-product basis, for products launched by your company between, for example, 2005 and 2007? All data would be treated as confidential by the UW study team. *(Select all that apply.)***

	US	Global
Types of product-specific HEOR studies conducted	□	□
Actual cost of each product-specific HEOR study conducted	□	□
Total cost of all HEOR studies conducted for a given product	□	□
Timing of HEOR study completion	□	□
HEOR publications, abstracts and presentations	□	□
Time elapsed from regulatory submission to approval	□	□
Number of regulatory submissions prior to approval	□	□

If not, why not? Is this data only available after a certain year?

10. **To what extent is the above information available for drugs that were submitted for regulatory approval, between for example 2005 and 2007, but were not approved?**

11. **Do you have any other suggestions as to relevant data that we should consider or that would be available on a product-by-product basis? *(E.g., competitive intelligence information, benchmarking data)***

Other comments and questions:

Appendix 2-2. Focus Group Discussion Guide / Questionnaire.

1. Do you/your company invest in HEOR differentially for the following types of products?

   □ Yes □ No

   New molecular entities _____
   New indications _____
   New dosage forms _____
   New combinations _____

   If yes, please rank the level of investment (5 = largest investments on average; 1 = smallest investments on average) by the product types above.

2. Are there any HEOR studies that are conducted for all products in development? If so, please list:

   _____

3. Please indicate which, if any, of the following **market attributes** affect your likelihood to invest in HEOR for a given product.

   □ Unmet need
   □ Market position (1st in class, fast follower, crowded market)
   □ Intended patient population (broad, targeted)
   □ Lifestyle versus life-threatening diseases
   □ Other(s): _____

4. Please indicate which, if any, of the following **product attributes** affect your likelihood to invest in HEOR for a given product.

   □ Effectiveness
   □ Safety
   □ Trial endpoints
   □ Convenience
   □ Cost of treatment / expected product price
   □ Quality of life impacts
   □ Other(s): _____

5. Please indicate which, if any, of the following **company-level investment behaviors** affect your likelihood to invest in HEOR for a given product.

   □ Leadership attitudes towards HEOR
   □ Studies conducted by competitors for products with the same indication
   □ Probability of favorable findings
   □ Other(s): _____

Appendix 2-3. Definitions of "HEOR Study" Provided by Steering Committee Members.

Respondent 1: **"**A study, either prospective or retrospective in nature, examining the healthcare resource utilization and costs associated with a particular medical condition, therapeutic area, class of drugs or interventions or an individual intervention. These include burden of illness, cost consequence, budget impact or cost effectiveness analyses."

Respondent 2: "One with the primary objective of generating evidence to support pricing, reimbursement and access - piggyback studies don't count. Study may or may not collect economic outcomes, but likely collects patient-reported outcomes."

Respondent 3: "Non-interventional – Prospective or retrospective study using existing or new data. Evaluates clinical, economic and / or humanistic outcomes. Studies may be conducted using a range of methodologies: Literature Reviews and Meta-Analyses - Systematic literature reviews, network meta-analyses, MTC/ITC, etc. Models - CEA, CMA, CUA, Budget Impact. Interventional - RCT and PCTs may include HCRU/Economic/PRO endpoints which also may be classified as HEOR studies in the context of interventional studies."

Respondent 4: **"**Any study that is specifically developed for the purposes of supporting a population based health care decision."

Respondent 5: **"**An study the ties together the clinical, patient reported and economic outcomes of a given asset or treatment intervention to facilitate a determination of value and appropriate formulary placement."

Respondent 6: **"**A economic endpoint/analysis in a Phase 2 through Phase 4 clinical trial, a prospective observational study, a retrospective study, a post-hoc analyses of sub-populations and other variables from Phase 2 – Phase 4 clinical trials, a patient reported survey instrument/questionnaire study in Phase 2 – Phase 4 clinical study."

Respondent 7: **"**I would focus solely on projects where new evidence is generated in support of a product or disease state, which is done with the intent to communicate this information to external stakeholders. This would help eliminate more market research based projects, where we conduct research on payers and other stakeholders to determine evidence expectations which help inform internal decisions. Also, there may be some desire to apply this to new instrument development for claims – but I would suggest limiting the focus on types of activities for the first attempt, and then seeing how we can expand to other situations once we have a workable approach for a more focused group of projects."

Respondent 8: **"**Almost any project that generates data/evidence outside of a clinical trial."

Respondent 9: **"**A study to generate and/or communicate evidence to support the payer and customer value propositions, typically involving health economic, PRO, or other non-clinical endpoints or study methods."

Appendix 2-4. Definitions of "Commercial Success" Provided by Steering Committee Members.

Respondent 1: **"**Open or adequate formulary access for those patients for which the product is clinically appropriate."

Respondent 2: **"**Product achieves its forecast in terms of volume and price."

Respondent 3: **"**Commercial success would be defined as obtaining formulary access at predefined targets and achieving sales goals."

Respondent 4: **"**Achieving desired access and reimbursement upon first submission to payer/authority."

Respondent 5: **"**Appropriate formulary placement that is consistent with the clinical, patient reported, and economic outcomes associated with a given asset."

Respondent 6: **"**Optimal payer access for the maximum number of medically appropriate patients allowing for the most efficient use of resources in patient care and producing the greatest amount of patient health outcomes."

Respondent 7: **"**For me, commercial success for our activities would be based on being able to reduce uncertainty on our current predictions and projections. So instead of, we improved the NPV! We could say, our confidence in the estimate is improved and our access filter on the model which may be at 10-20%, is now reduced."

Respondent 8: **"**Sales."

Respondent 9: **"**Generally by improvement of short-term or long-term revenue, typically by achievement or facilitation of market access for our products, and/or positive impact on price or market share, and/or, more indirectly, by positive impacts on company reputation or credibility."

Appendix 3-1. Stated Choice Survey: Sample Target Product Profile.

Note: Complete set of twenty profiles available upon request from authors.

Interleukin-6 Receptor Antagonist for Rheumatoid Arthritis		
Product Information	**Chemical Type**	New biologic
	Indication	For adults with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies
	Drug Class	Disease-modifying anti-rheumatic drugs (DMARDs)
	Mechanism of Action	Recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody specific for interleukin-6 (IL-6) receptor
	Dosage and Administration	Intravenous infusion; Starting dose is 4 mg per kg every 4 weeks followed by an increase to 8 mg per kg every 4 weeks based on clinical response
Clinical Data	**Trial Comparator(s)**	Placebo
	Primary Trial Endpoint(s)	Proportion of patients with 20% improvement in signs and symptoms of rheumatoid arthritis according to American College of Rheumatology criteria (ACR20 response) at week 24
	Efficacy	Relative Risk for improvement vs. Placebo: 4.0 [95% CI: 2.6 – 6.1]
	Safety[1]	Skin or subcutaneous disorder (18% vs. 7%)
Competitive Landscape	**Market Position[2]**	4th
	Key Competitor	Non-TNF inhibitors – e.g., Rituxan® (rituximab)[4]
	Time on Market until 1st Key Competitor's Patent Expires	3 years
Pricing	**Pricing vs. Selected Key Competitor[3]**	Price Premium

[1]Adverse events occurring at a rate 5% greater than seen in the study comparator group. Rates listed are for drug vs. study comparator.
[2]Market position based on expected launch relative to other products in the same class with the same mechanism of action.
[3]"Price Premium" reflects a price that is >10% more than the key competitor's price; "Price Parity" reflects a price within 10% of the key competitor's price; "Price Discount" reflects a price that is >10% less than the key competitor's price. Price comparisons are based on branded drug prices.
[4]Rituxan® is a biologic, administered as an intravenous infusion. Pivotal studies were conducted versus placebo. Relative risk for ACR20 improvement vs. placebo: 2.8.

Appendix 3-2. Stated Choice Survey: Target Product Profile Questions.

Question1: Please rate your familiarity with this market (drug class and/or disease area):

□ Very familiar with this market.
□ Moderately familiar with this market.
□ Unfamiliar with this market but able to respond based on the information provided.
□ Unfamiliar with this market and prefer not to respond.

Question 2: What is the likelihood that HEOR evidence for this product would have a positive impact on reimbursement decisions in the U.S.?

□ Very likely □ Somewhat likely □ Somewhat unlikely □ Very unlikely □ Unsure

Question 3: What types of HEOR evidence, if any, would be valuable investments to optimize U.S. payer reimbursement decisions for this product? *Please select and prioritize up to four evidence types.*

	1st Priority	2nd Priority	3rd Priority	4th Priority
Adherence / compliance	□	□	□	□
Budget impact	□	□	□	□
Burden or cost of illness	□	□	□	□
Cost-effectiveness / Cost-utility	□	□	□	□
Disease incidence or prevalence	□	□	□	□
Indirect treatment comparisons	□	□	□	□
PRO impact	□	□	□	□
Resource utilization / Treatment patterns	□	□	□	□
None of these HEOR evidence types would be valuable	□	□	□	□

Question 4: What factors in the TPP are most influential to your response? *Please enter text:*

Appendix 3-3. What Types of HEOR Evidence Would be Valuable Investments to Optimize U.S. Payer Reimbursement Decisions?

Product Name	Approval Type	Indication	% of Respondents Who Selected Evidence Type as a Priority								
			Adherence/ Compliance	Budget Impact	Burden/Cost of Illness	CEA/CUA	Disease Incidence / Prevalence	Indirect Tx. Comparisons	PRO Impact	Resource Util / Tx Patterns	None
Gilenya	NME	Multiple sclerosis	33%	89%	22%	44%	11%	67%	56%	67%	0%
Dulera	New Combo	Asthma	60%	90%	20%	20%	10%	60%	20%	60%	10%
Pradaxa	NME	Atrial fibrillation	50%	90%	40%	70%	20%	30%	10%	80%	0%
Votrient	NME	RCC	30%	90%	40%	20%	10%	70%	40%	50%	0%
Afinitor	NME	RCC	0%	89%	44%	11%	33%	56%	33%	67%	0%
Actemra	Biologic	RA	10%	70%	30%	50%	20%	90%	60%	40%	0%
Effient	NME	Thrombotic CV	36%	100%	36%	55%	18%	55%	9%	64%	0%
Arzerra	Biologic	CLL	0%	60%	30%	40%	20%	70%	30%	70%	10%
Jalyn	New Combo	Hyperplasia	29%	86%	14%	29%	29%	29%	14%	57%	0%
Treximet	New Combo	Migraines	22%	78%	44%	33%	11%	33%	44%	44%	0%
Cymbalta	New Indication	FM	13%	88%	25%	38%	38%	63%	50%	38%	0%
Zortress	New Indication	Organ rejection	22%	78%	56%	33%	33%	67%	22%	56%	0%
Promacta	NME	Thrombocytopenia	25%	50%	38%	25%	25%	63%	25%	50%	13%
Adcirca	New Indication	PAH	13%	38%	25%	38%	38%	63%	50%	38%	13%
Pristiq	NME	MDD	40%	80%	40%	20%	10%	90%	30%	40%	0%
Toviaz	NME	Overactive bladder	40%	70%	30%	20%	10%	40%	80%	70%	10%
Intelence	NME	HIV	11%	78%	33%	22%	22%	67%	11%	56%	0%
Lastacaft	NME	Allergic conjunct.	50%	83%	17%	33%	17%	67%	50%	17%	0%
Fanapt	NME	Schizophrenia	36%	36%	18%	27%	9%	36%	9%	45%	36%
Nucynta	NME	Pain	13%	50%	25%	13%	13%	38%	50%	63%	13%
Total # of Times Evidence Type was Selected			**49**	**136**	**58**	**59**	**35**	**105**	**62**	**109**	**7**

RA = rheumatoid arthritis; RCC = renal cell carcinoma; CLL = chronic lymphocytic leukemia; FM = fibromyalgia; HIV – human immunodeficiency virus; MDD = major depressive disorder; PAH = pulmonary arterial hypertension

Appendix 4-1. Sample Survey Questions.

Pharma Profile

Product 1 for Metastatic Colorectal Cancer		
Market Attributes	**Disease Severity**	Substantial impact on morbidity/mortality
	Market Position	First in Class
Product Attributes	**Treatment Type**	Acute
	Scope of Indication[1]	Broad
	Place in Therapy	1st Line Monotherapy
	Relative Efficacy[2]	Better (vs. expected standard of care)
	Relative Safety[2]	Comparable (vs. expected standard of care)
	Relative Pricing[2]	Price Premium (vs. expected standard of care)
Data Attributes	**Trial Comparator**	Active (Expected Standard of Care)
	Trial Endpoint	Progression-Free Survival

[1]Indicates whether the product's indication is intended for a broad population (all patients inflicted with the disease), or a narrow population (e.g., patients refractory to the standard of care or selected based on a diagnostic test result).
[2]For first-in-class drugs, relative to expected standard of care for the same place in therapy. For fast-follower and me-too drugs, relative to the best-in-class drug for the same place in therapy.

Payer Profile

Product 1 for Metastatic Colorectal Cancer		
Market Attributes	**Disease Severity**	Substantial impact on morbidity/mortality
	Market Position	First in Class
Product Attributes	**Treatment Type**	Acute
	Scope of Indication[1]	Broad
	Place in Therapy	1st Line Monotherapy
	Relative Efficacy[2]	Better (vs. standard of care)
	Relative Safety[2]	Comparable (vs. standard of care)
	Relative Pricing[2]	Price Premium (vs. standard of care)
Data Attributes	**Trial Comparator**	Active (Standard of Care)
	Trial Endpoint	Progression-Free Survival

[1]Indicates whether the product's indication is intended for a broad population (all patients inflicted with the disease), or a narrow population (e.g., patients refractory to the standard of care or selected based on a diagnostic test result).
[2]For first-in-class drugs, relative to standard of care for the same place in therapy. For fast-follower and me-too drugs, relative to the best-in-class drug for the same place in therapy.

Pharma: For the product described, how important would it be to conduct and disseminate each type of HEOR evidence in order to achieve formulary placement with commercial payers in the U.S. (in terms of tiering, restrictions, etc.)?

Payer: For the product described, how important would it be to receive each type of HEOR evidence below in order to support your formulary placement decision (in terms of tiering, utilization management, etc.)?

	Not At All Important / Not Needed	Somewhat Important	Important	Very Important	Extremely Important / Absolutely Essential	Unsure / Need More Information
Budget Impact	○	○	○	○	○	○
Cost-Effectiveness/ Cost-Utility	○	○	○	○	○	○
Resource Utilization/ Cost-Offsets	○	○	○	○	○	○
Patient Health-Related Quality of Life/Utility	○	○	○	○	○	○
Indirect Treatment Comparison (Network Meta-Analysis)	○	○	○	○	○	○
Burden/Cost of Illness with Current Treatments	○	○	○	○	○	○
Adherence/Compliance of Current Treatments	○	○	○	○	○	○

Appendix 4-2. Analysis Details.

Regression Analysis

To identify the product and market attributes that are associated with the importance of HEOR evidence and test our pre-specified hypotheses, the product and market attributes of each TPP were categorized into factors of each variable. We conducted a binary logistic regression to assess the association of product and market attributes (independent variables) on the perceived importance of each type of HEOR evidence (dependent variables), accounting for clustering at the individual levels.

Pharma:

$$\text{logit}\,[\pi(Y_i)] = \alpha + \beta_{1i}X_1 + \beta_{2i}X_2 + \beta_{3i}X_3 + \beta_{4i}X_4 + \beta_{5i}X_5 + \beta_{6i}X_6 + \beta_{7i}X_7 + \beta_{8i}X_8 + \beta_{9i}X_9 + \beta_{10i}X_{10} + \beta_{11i}X_{11} + \beta_{12i}X_{12} + \varepsilon_i$$

Y_i = Importance rating for evidence type i

X_1 = disease severity
X_2 = market position
X_3 = treatment type
X_4 = scope of indication
X_5 = place in therapy
X_6 = relative efficacy
X_7 = relative safety
X_8 = relative pricing
X_9 = trial comparator
X_{10} = trial endpoint
X_{11} = familiarity with disease area
X_{12} = company X

i = (budget impact, burden/cost of illness, cost-effectiveness/cost-utility, indirect treatment comparisons, health-related quality of life/utility impact, resource utilization/cost-offsets, unmet need – adherence/compliance of SOC)

Payers:

$$\text{logit}\,[\pi(Y_i)] = \alpha + \beta_{1i}X_1 + \beta_{2i}X_2 + \beta_{3i}X_3 + \beta_{4i}X_4 + \beta_{5i}X_5 + \beta_{6i}X_6 + \beta_{7i}X_7 + \beta_{8i}X_8 + \beta_{9i}X_9 + \beta_{10i}X_{10} + \beta_{11i}X_{11} + \varepsilon_i$$

X_1 = disease severity
X_2 = market position
X_3 = treatment type
X_4 = scope of indication
X_5 = place in therapy
X_6 = relative efficacy
X_7 = relative safety
X_8 = relative pricing
X_9 = trial comparator
X_{10} = trial endpoint
X_{11} = familiarity with disease area

i = (budget impact, burden/cost of illness, cost-effectiveness/cost-utility, indirect treatment comparisons, health-related quality of life/utility, resource utilization/cost-offsets, unmet need – adherence/compliance of SOC)

Note: 'Company' is not included as a variable here as most respondents to the payer survey represented unique companies.

A binary logit model was selected for analysis, as the data currently available (n=63 for pharmaceutical respondents, n= 31 for payers with each individual providing 13 observations) may not generate enough observations within each outcome category.

To test our specific hypotheses, the coefficient of interest was tested using the Wald test, e.g.:

Hypothesis: Burden/cost of illness evidence may be preferred if subpopulations of a disease are targeted with a different risk profile or treatment pattern than the larger population.

For this scenario, and other scenarios where possible, we will test the significance of the relevant regression coefficient using the Wald test. E.g.:

$$H_0: \beta_{5i} = 0 \text{ and } H_a: \beta_{5i} \neq 0 \text{ for i = burden/cost of illness}$$

Analysis Consideration: Collinearity in independent variables

We have a few collinear variables because we did not vary the levels of the variables at random / irrationally in the scenarios (e.g., we did not expect that a company would price a new drug at premium if the drug is inferior to the standard of care in terms of efficacy, and therefore did not test this scenario). To remediate this collinearity, we have dropped and recoded certain variables.

Collinear Variables	*Corrective Actions*
Disease & Disease severity collinear	Omit disease
Disease severity & Treatment type collinear	Recode 'Disease severity' as binary
Place in therapy (1) & Disease collinear	Recode 'Market position' as binary
Relative efficacy (2) & Scope of indication collinear (?)	Recode 'Place in therapy' as binary
Relative price & Place in therapy collinear (?)	Recode 'Relative efficacy' as binary
Trial comparator (1) & Relative efficacy collinear	Recode 'Relative safety' as binary
Trial endpoint (2) & disease severity collinear	Recode 'Relative price' as binary

Non-Parametric Analysis

In our pre-specified hypotheses, we identified scenarios where pharmaceutical companies and/or payers may find more value in the generation/consumption of HEOR evidence. In some cases, the product profiles (scenarios) were designed to allow us to test our hypotheses directly. For example:

Burden/cost of illness evidence may be preferred if subpopulations of a disease are targeted with a different risk profile or treatment pattern than the larger population.

Two scenarios were defined to be able to test this hypothesis (disease: hypercholesterolemia):

Scenario	Disease Severity	Market Position	Treatment Type	Scope of Indication	Place in Treatment	Relative Efficacy	Relative Safety	Relative Pricing	Trial Comp.	Trial Endpoints
E	Moderate	First in class	Chronic	Broad	1L Add-On	Better	Comparable	Premium	Active/SOC	Surrogate
H	Moderate	First in class	Chronic	Familial HCh	1L Add-On	Better	Comparable	Premium	Active/ SOC	Surrogate

To evaluate whether there is a difference in the stated importance of burden/cost of illness studies for these two scenarios, we will use the Wilcoxon signed rank sum test to test the following hypothesis:

> H_0: The median importance ranking for burden/cost of illness studies does not differ between the two scenarios (i.e., $Md_E = Md_H$).
>
> H_a: The median importance ranking for burden/cost of illness studies is greater for scenario H vs. scenario E (i.e., $Md_E < Md_H$).

Tests will be performed for hypotheses where scenarios that are suitable to testing exist, and will be performed separately for respondents from payer organizations and pharmaceutical companies. The Wilcoxon signed rank sum test is appropriate because it is a non-parametric test, which is necessary as our outcome of interest is ordinal in nature (Likert scale). Additionally, each respondent answered both scenarios that are being tested, and the Wilcoxon signed ranks test accounts for the paired nature of the data.

Q3: Evaluate whether payers and pharmaceutical companies are aligned in their preferences.

Regression Analysis

To evaluate whether payers and pharmaceutical companies are aligned in their preferences, a single model with an indicator for the type of respondent was analyzed, and the significance of the respondent variable was assessed.

$$\text{logit}\,[P(Y_i)] = \alpha + \beta_{1i}X_1 + \beta_{2i}X_2 + \beta_{3i}X_3 + \beta_{4i}X_4 + \beta_{5i}X_5 + \beta_{6i}X_6 + \beta_{7i}X_7 + \beta_{8i}X_8 + \beta_{9i}X_9 + \beta_{10i}X_{10} + \beta_{11i}X_{11} + \beta_{12i}X_{12} + \beta_{13i}X_{13} + \beta_{13i}X_{13} + \varepsilon_i$$

Y_i = Importance rating for evidence type i
X_1 = disease
X_2 = disease severity
X_3 = market position
X_4 = treatment type
X_5 = scope of indication
X_6 = place in therapy
X_7 = relative efficacy
X_8 = relative safety
X_9 = relative pricing
X_{10} = trial comparator
X_{11} = trial endpoint
X_{12} = company
X_{13} = familiarity with disease area
X_{14} = payer

i = [budget impact models, burden/cost of illness, cost-effectiveness/cost-utility, indirect treatment comparisons, quality of life/PRO impact, resource utilization/cost-offsets, unmet need – adherence/compliance of SOC]

To test whether a significant difference exist between responses from payer organizations and pharmaceutical companies, we will test the significance of the regression coefficient for the pharma/payer indicator using the Wald test:

$$H_0: \beta_{14i} = 0 \text{ and } H_a: \beta_{14i} \neq 0, \text{ for each value of 'I'}$$

While a more nuanced understanding of the alignment between pharmaceutical and payer respondents would involve an interaction term between each product/market attribute and the 'payer' indicator variable, the power required for such an analysis is greater than permitted by our sample size.

Non-Parametric Analysis

As an exploratory analysis, we also assessed differences in the importance ratings between the two stakeholder groups (pharmaceutical and payer respondents) for each evidence type using the Wilcoxon-Mann-Whitney test. This non-parametric test allows us to maintain the ordinal nature of the data without a significant loss in power.

H_0: There is no difference between the pharmaceutical and payer respondents with regard to their median importance rankings for each type of HEOR evidence.

H_a: Pharma and payer respondents will have different median importance rankings for each type of HEOR evidence.

It is important to note that two assumptions of the Wilcoxon-Mann-Whitney test are violated. First, the observations within each group do not represent randomly selected observations, as the respondents are from a convenience sample. Second, the observations within each group are not independent, as we have repeated observations (13 observations from the 13 profiles) from each respondent. Thus the results of the Wilcoxon-Mann-Whitney test should be interpreted with caution.

The results suggest that there is a statistically significant difference between the underlying distributions of the importance ratings between pharmaceutical and payer respondents with respect to the importance of budget impact evidence ($p<0.0001$), cost-effectiveness/cost-utility evidence ($p<0.0001$), patient health-

related quality of life/utility evidence ($p=0.0003$), resource utilization/cost-offset evidence ($p<0.0001$), and unmet need – adherence/compliance evidence for the standard care ($p<0.0001$).

For budget impact evidence, we see that the observed rank sum is greater than expected for pharmaceutical respondents, indicating that pharmaceutical respondents generally rated the importance of budget impact evidence higher than payer respondents.

For cost-effectiveness/cost-utility evidence, we see that the observed rank sum is greater than expected for pharmaceutical, indicating that pharmaceutical respondents generally rated the importance of cost-effectiveness/cost-utility evidence higher than payer respondents.

For patient HRQOL/utility evidence, we see that the observed rank sum is greater than expected for payers, indicating that payer respondents generally rated the importance of patient HRQOL/utility higher than pharmaceutical respondents.

For resource utilization/cost-offset evidence, we see that the observed rank sum is greater than expected for pharmaceutical respondents, indicating that pharmaceutical respondents generally rated the importance of resource utilization/cost-offset evidence higher than payer respondents.

For unmet need-adherence/compliance of the standard of care evidence, we see that the observed rank sum is greater than expected for payers, indicating that payer respondents generally rated the importance of unmet need-adherence/compliance of the standard of care evidence higher than pharmaceutical respondents.

Appendix 4-3. Frequencies of Observations in Each Group: Payers.

Code	Label	UN/AC	BI	BCOI	CEA	ITC	HRQOL/U	RUCO
0	Not at all important/Not needed	26	22	39	26	44	18	25
1	Somewhat important	72	81	55	48	115	81	59
2	Important	97	73	124	85	107	119	98
3	Very important	124	100	124	125	93	113	149
4	Extremely important/ Absolutely essential	75	112	53	95	34	65	64
5	Unsure/More information needed	9	15	8	24	10	7	8

UN/AC = Unmet need – adherence/compliance of standard of care; BI = budget impact; BCOI = burden/cost of illness; CEA = cost-effectiveness analysis; ITC = indirect treatment comparisons; HRQOL/U = health-related quality of life / utility; RUCO = resource utilization/cost-offsets.

Appendix 4-4. Frequency of Observations in Each Group: Pharma.

Code	Label	UN/AC	BI	BCOI	CUA	ITC	HRQOL/U	RUCO
0	Not at all important/Not needed	78	20	50	116	145	122	36
1	Somewhat important	164	72	124	144	142	192	61
2	Important	236	121	234	169	176	163	165
3	Very important	195	242	246	208	161	164	298
4	Extremely important/ Absolutely essential	100	336	143	157	131	147	234
5	Unsure/More information needed	46	28	22	25	64	31	25

UN/AC = Unmet need – adherence/compliance of standard of care; BI = budget impact; BCOI = burden/cost of illness; CEA = cost-effectiveness analysis; ITC = indirect treatment comparisons; HRQOL/U = health-related quality of life / utility; RUCO = resource utilization/cost-offsets.

Appendix 4-5. Wilcoxon-Mann-Whitney Test Results: Pharma vs. Payers.

HEOR Evidence Type	Group	Observations	Rank Sum	Expected	Z	P-Value
Budget Impact	Pharma	791	501079.5	466690	6.548	**<0.0001**
	Payer	388	194530.5	228920		
Burden/Cost of Illness	Pharma	797	485303.5	475410.5	1.829	0.0674
	Payer	395	225724.5	235617.5		
Cost-Effectiveness/Cost-Utility	Pharma	794	442129	466078	-4.526	**<0.0001**
	Payer	379	246422	222473		
Indirect Treatment Comparisons	Pharma	755	439961.5	433747.5	1.193	0.2330
	Payer	393	219564.5	225778.5		
Patient Health-Related QOL / Utility	Pharma	788	447484	466890	-3.579	**0.0003**
	Payer	396	254036	234630		
Resource Utilization / Cost-Offsets	Pharma	794	502713.5	472430	5.664	**<0.0001**
	Payer	395	204741.5	235025		
Unmet Need: Adherence/ Compliance of SOC	Pharma	773	430672	451432	-3.924	**0.0001**
	Payer	394	250856	230096		

Appendix 4-6. Regression Results for Alignment Between Pharmaceutical and Payer Decision-Makers.

Evidence Type	Ordered Logit Odds Ratio[1] (p-value)
Budget Impact	0.50 (0.059)
Burden/Cost of Illness	0.95 (0.870)
Cost-Effectiveness/Cost-Utility	1.19 (0.641)
Indirect Treatment Comparisons	0.75 (0.374)
Patient Health-Related QOL / Utility	**2.08 (0.023)**
Resource Utilization / Cost-Offsets	**0.50 (0.034)**
Unmet Need: Adherence/Compliance of SOC	1.62 (0.148)

[1]Odds ratio: payer vs. pharmaceutical respondents.