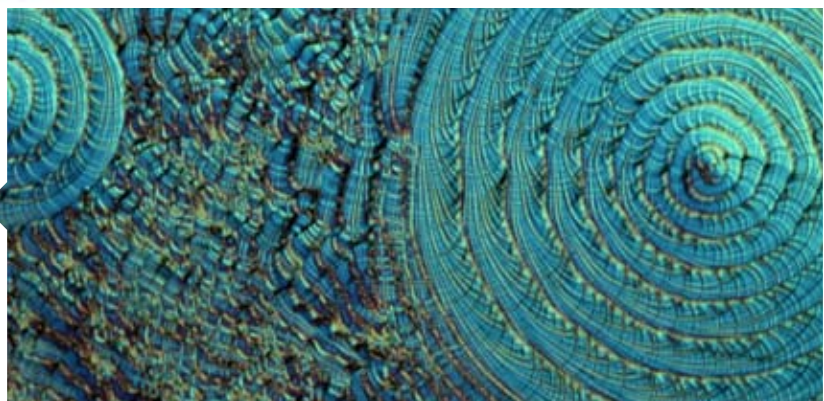


# Rewarding Innovation and Value: What is the Role of Comparative Effectiveness Research?

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## Executive Summary

Recent cases of high-profile failures of products in late-stage pharmaceutical development have clearly highlighted the need for transformational change. Today, new drugs cost as much as \$2 billion to develop over eight years or more, with severe attrition at each stage of development. Even those products that gain regulatory approval must often prove their value in health technology assessments (HTAs) or other elements of Comparative Effectiveness Research (CER) by public and private payers.

CER is increasingly in the public spotlight as a promising way to help improve the productivity and efficiency of healthcare systems in the United States and abroad. Recent decisions to provide substantial federal funding for CER – \$1.1 billion under the 2009 economic stimulus package, and a further \$800 million under the 2010 healthcare reform legislation – serve to underline the increasing interest in this approach. In future, CER will change pre-market experimental research design to reflect the requirements of multiple healthcare stakeholders. It will also drive increased investment in post-market observational research on the real-world performance of marketed products.

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In its response to the cacophony of demands for cost-effective, innovative medicines, the biopharmaceutical industry has a unique chance to influence the U.S. health care landscape. The traditional model of pharmaceutical R&D in which a steady stream of broadly indicated blockbusters gave market-based rewards is a rapidly fading memory. While products are becoming more targeted to smaller patient populations, companies are simultaneously under pressure to demonstrate the relative value of their products.

Current market factors and policy debates provide industry a chance to take the lead in establishing a valuation system that compensates innovation fairly. The proposed approach would build on and extend the concept of Comparative Effectiveness Research (CER), a health care policy issue that has been brought to the forefront since being allocated \$1.1 billion out of the \$787.2 billion budget of the economic stimulus bill. \$300 million was allocated specifically for CER by the AHRQ Effective Health Care Program.<sup>1</sup>

CER is developing at a rapidly accelerating rate. Companies and trade groups should move quickly to play an increasing role, helping to drive the establishment of a product valuation system that compensates innovation fairly.

### Background: Drivers for Comparative Effectiveness Research

Calls for innovative treatments to be cost-effective are louder than ever, coming from politicians, public and commercial payers, providers and patients. Indeed, in August 2009 the *New England Journal of Medicine* featured an article authored by a Stanford University-based research team who proposed that the FDA require CER data to be included in a product's label in order to separate products that truly improve outcomes versus those that do not.<sup>2</sup> To respond to these calls, industry needs to demonstrate the benefits of its products in terms that are meaningful for these audiences. High-value innovation is not merely to introduce new medicines, but to introduce better ones – pharmaceuticals and devices that are proven to provide greater therapeutic benefit, safety, improved quality of life and/or convenience for patients or providers. The overall treatment process or outcome must be shown to be a significant improvement; and for commercial viability, innovation must adapt to market realities.

CER allows the relative value of products to be evaluated in a true-to-life setting against the current standard of care. As defined in June 2009 by the Federal Coordinating Council for Comparative Effectiveness Research, CER is “the conduct and synthesis of research comparing the benefits and harms of different

<sup>1</sup> <http://www.effectivehealthcare.ahrq.gov/index.cfm/what-is-the-effective-health-care-program/history-of-the-effective-health-care-program/>

<sup>2</sup> Stafford RS, et al. New, but Not Improved? Incorporating Comparative-Effectiveness Information into FDA Labeling. *N Engl J Med*. 2009 Aug 12.[Epub ahead of print]

*The Patient-Centered Outcomes Research Institute<sup>4</sup>*

*Under the recent healthcare reform, a Patient-Centered Outcomes Research Institute (PCORI) is being set up to spearhead efforts to prioritize and fund comparative effectiveness research (CER) using a largely stakeholder-driven process. This initiative builds on the total of \$1.1 billion in funding for CER in the American Recovery and Reinvestment Act (ARRA) of 2009.*

*The Institute will:*

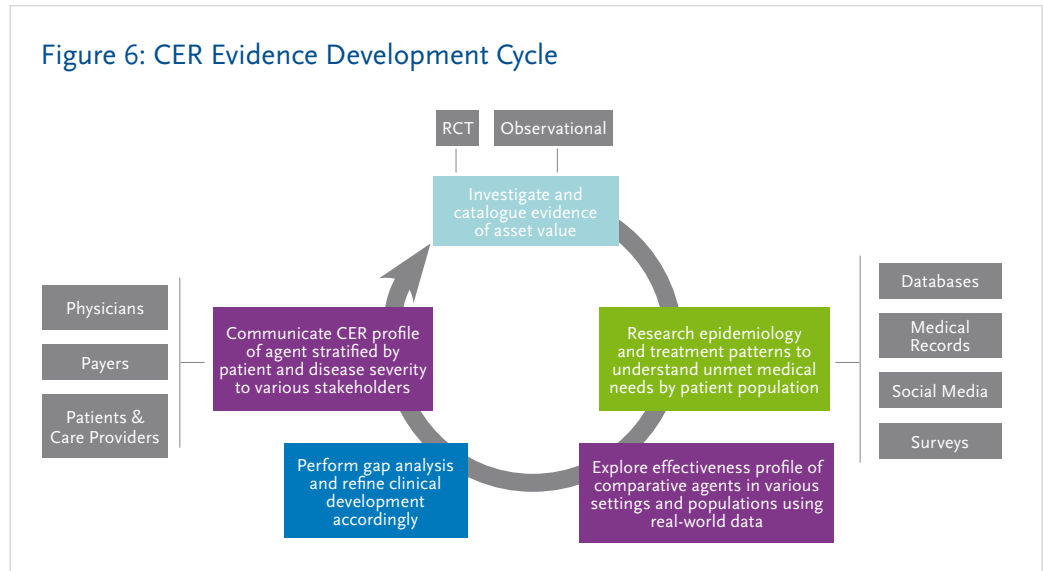
- *Establish an objective research agenda*
- *Develop research methodological standards*
- *Contract with eligible entities to conduct the research*
- *Ensure transparency by requesting public input*
- *Disseminate the results to patients and healthcare providers.*

*Efforts to identify and refine standards for CER study designs – such as pragmatic clinical trials, randomized controlled trials, and patient registries – will be led by a 15-member standing methodology committee. This committee is required to start issuing methodological standards for CER within 18 months.*

*The law allows CMS to use CER evidence in coverage and/or reimbursement decisions as long as the coverage process is an iterative one – a standard that the current CMS national coverage determination process meets. CMS may also use CER to establish differential copayments, which could be used in a value-based insurance design program.*

*The Office of Communications and Knowledge Transfer at AHRQ*

interventions and strategies to prevent, diagnose, treat and monitor health conditions in ‘real world’ settings.”<sup>3</sup> There may be no explicit evaluation of cost-effectiveness, but CER invariably includes an implicit appraisal of value in areas such as safety, effectiveness, quality of life and convenience. Various elements involved in developing evidence of value are illustrated below:



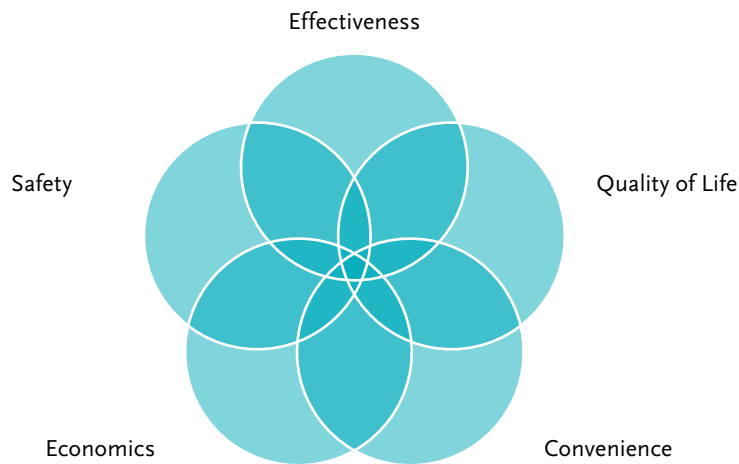
A form of CER known as a Healthcare Technology Assessment (HTA) – a structured analysis that often is based on a retrospective review of evidence – is emerging globally as a tool to help payers, providers, and policy-makers make informed decisions on coverage, payment and patient care. HTAs are already well known from their use by organizations such as the U.K. National Institute for Health and Clinical Excellence (NICE).

In addition to their impact in the U.K., NICE rulings also are influential in other European countries, and, increasingly, in the U.S. As such, increasing use of HTAs is raising concerns within the biopharmaceutical industry about the need for transparent decision-making on drug reimbursement.

<sup>3</sup> *The Pink Sheet*, July 13, 2009

<sup>4</sup> <http://www.cmtptnet.org/comparative-effectiveness/overview-of-the-patient-centered-outcomes-research-institute>

Figure 1



Comparative effectiveness considers overlapping product attributes and aims to determine each therapy's relative strengths and weaknesses for an overall value assessment.

### Current Status: Economic Stimulus Package and Legislative Approaches

CER has been in the spotlight since being allocated \$1.1 billion in funding from the \$787.2 billion budget of the economic stimulus bill signed into law by President Obama in February 2009. Of this figure, \$400 million will go to the National Institutes of Health (NIH), \$300 million to the Agency for Healthcare Research and Quality (AHRQ), and the remaining \$400 million will be allocated by the Department of Health and Human Services (DHHS). The bill also called for the creation of the Federal Coordinating Council for Comparative Effectiveness Research<sup>3</sup> “to reduce duplication of [CER] activities within the Federal government,” coordinate CER and advise the President and Congress.

will facilitate the wide dissemination of findings, with assistance from NIH. This will include consultation with medical and clinical associations to ensure that findings are translated into clinical decision support tools.

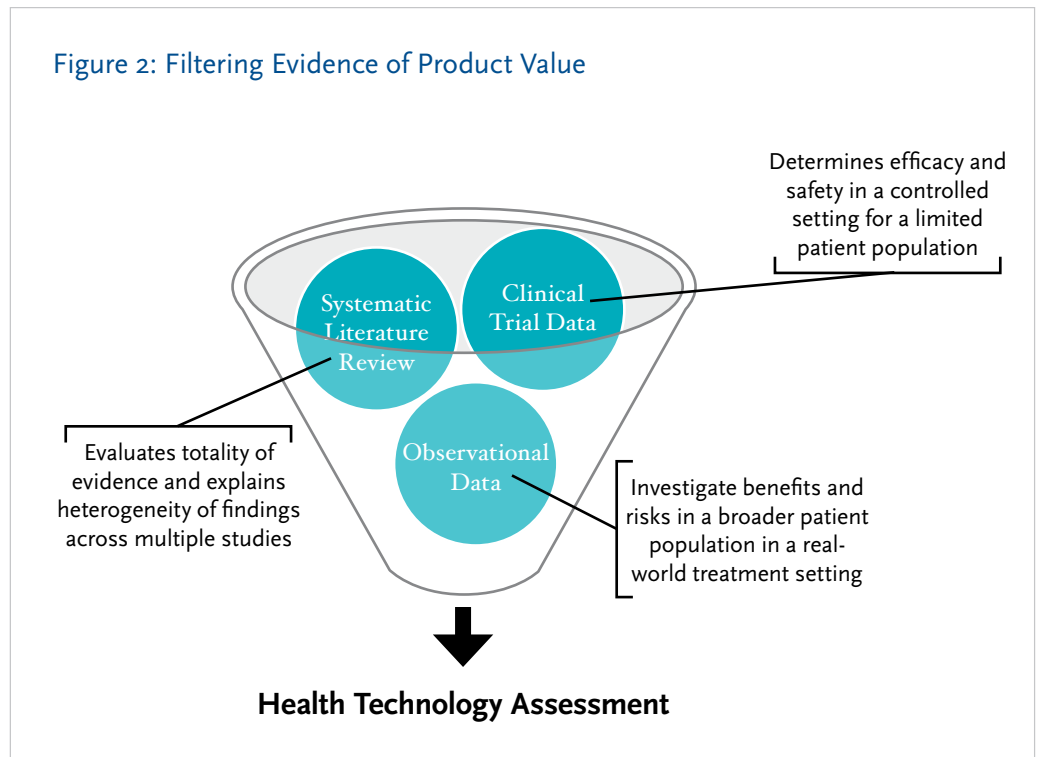
### Health Technology Assessments

*Comparative Effectiveness Research (CER) involves a review of a product in which performance is evaluated in a true-to-life setting relative to the current standard of care. CER may use a variety of methodologies, including prospective trials, retrospective analyses and modeling techniques (see Figure 2). Health Technology Assessment (HTA) is considered a specialized method of CER.*

*HTA is a structured analysis conducted to provide input to a policy decision. It brings together information on the clinical, economic and humanistic qualities of a production a systematic, transparent, unbiased and robust manner. The aim is to inform the adoption of safe, effective and cost-effective health policies. HTAs typically use a blend of retrospective and modeling practices. Although often used interchangeably with CER, HTA, in fact, defines a more formal process. Many agencies exist globally to conduct HTA analyses, often to guide coverage and health care policy decisions.*

<sup>3</sup> <http://www.pharmatimes.com/WorldNews/article.aspx?id=15292>

Figure 2: Filtering Evidence of Product Value



The boost in funding to the AHRQ should continue the agency's work in performing, organizing and communicating health technology assessments through its Centers for Education and Research on Therapeutics. The Centers for Medicare and Medicaid Services (CMS) already implicitly includes the value of technology in its designation of six classes of products as "medically essential" for Part D benefits. Going forward, CMS also should create an evidence-based formulary giving preferred status on Medicare Advantage Plans and Prescription Drug Plans for new drugs that demonstrate significant therapeutic benefit over the existing standard of care.

As part of the 2010 U.S. healthcare reform legislation, a non-profit Patient-Centered Outcomes Research Institute (PCORI) is being established with \$800 million in funding for the period up to 2019. PCORI will help the new legislation transform the healthcare system. By advancing CER, the Institute will highlight value and drive real-world studies on pharmaceuticals, medical devices and procedures in the private sector. PCORI will establish a national agenda for CER, and will develop standards for study designs.

This market-driven CER methodology would be designed to ensure universally accepted, standardized techniques, with transparency, independence, objectivity and credible findings.

Further support for CER was expressed in an Institute of Medicine (IOM) report to Congress in June 2009, which prioritized initiatives for the DHHS.<sup>6</sup> At the top of the IOM's recommendations for primary research was "health care delivery systems," with an emphasis on examining "how or where services are provided, rather than which services are provided." The message this sends to the biopharmaceutical industry is a compelling demand for not only outcomes data, but treatment process data as well. CER may be applied to not only evaluate the "effectiveness" of innovation, but also the "efficiency." This wider working definition of CER opens the door to a new channel of research dedicated to measuring how a new technology impacts the treatment process, perhaps by streamlining care and optimizing the allocation of health care systems. Intuitively, enhancing treatment process may lead to direct and indirect improvement in treatment outcomes.

### Current Status: Decentralized Initiatives

There is ongoing debate on whether broader use of CER may be imposed by Washington or whether it may become decentralized and market driven.

Contributing to the debate are the issues of the lack of resources and expertise to manage a centralized function, as well as the segmented structure of the U.S. health care system with its complex web of distributors, payers and providers.

Managed care organizations are also beginning to demand a formal demonstration of value when considering a new product for formulary placement. For example, in May 2010, WellPoint, Inc. became the first health benefits company to develop standardized CER guidelines for formulary decision making.<sup>7</sup> The WellPoint Outcomes-Based Formulary aims to use "real world" data to make formulary decisions that will help improve clinical health outcomes; quality of life; productivity at work, school, and leisure activities; and will reduce the total cost of pharmacy and medical care.<sup>8</sup> WellPoint's guidelines explicitly state that "a more expensive medication can be less expensive overall if the member's health is improved, resulting in use of fewer healthcare resources."<sup>9</sup>

Another example of a managed care organization initiative is the Blue Cross and Blue Shield Association Technology Evaluation Center (BCBSA Tec). This is charged with providing "health care decision makers with timely, objective and scientifically rigorous assessments that synthesize the available evidence on the diagnosis, treatment, management and prevention of disease."<sup>10</sup> In one landmark evaluation,

<sup>6</sup> Institute of Medicine, Initial National Priorities for Comparative Effectiveness Research, June 2009

<sup>7</sup> WellPoint press release, May 19, 2010: <http://www.prnewswire.com/news-releases/wellpoint-is-first-health-benefits-company-to-release-cer-guidelines-for-use-in-evaluating-pharmaceuticals-94274639.html>

<sup>8</sup> [https://www.wellpointnextrx.com/shared/noapplication/f1/so/to/pw\\_b145032.pdf](https://www.wellpointnextrx.com/shared/noapplication/f1/so/to/pw_b145032.pdf)

<sup>9</sup> [https://www.wellpointnextrx.com/shared/noapplication/f1/so/to/pw\\_b145032.pdf](https://www.wellpointnextrx.com/shared/noapplication/f1/so/to/pw_b145032.pdf)

<sup>10</sup> <http://www.bcbs.com/blueresources/tec/>

the TEC found no “clinically significant difference between epoetin and darbepoetin in the treatment of anemia.” The CMS in turn deemed the two products “functionally equivalent,” effectively limiting the level of reimbursement for the newer agent, darbepoetin. A public backlash ensued and ultimately the Medical Modernization Act prohibited CMS from explicitly evaluating “functional equivalence” in their coverage and reimbursement decisions. The question remains, however: how will CMS implicitly consider comparative effectiveness (see Figure 3)?

Figure 3: CER – A Historical Case

### Procrit vs. Aranesp

The publication of a BCBSA Tec CER announcing therapeutic equivalence between Procrit and Aranesp prompted policy changes in the form of mandatory substitutions

Situation	CER Activity
<ul style="list-style-type: none"> <li>Two erythropoietic stimulants were available commercially in the United States, Procrit (epoetin alfa) and Aranesp (darbepoetin alfa), a newer and longer acting drug</li> <li>Aranesp is the less costly option for the management of anemia in patients undergoing cancer treatment as it requires less frequent dosing and is priced slightly lower than Procrit</li> <li>However, because it was unknown whether the two drugs were equally effective, the higher-priced market incumbent Procrit continued to be reimbursed</li> </ul>	<ul style="list-style-type: none"> <li>The 2006 CER: “Comparative Effectiveness of Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment,” conducted by BCBSA Tec highly influenced coverage decisions</li> <li>The report concluded, “The evidence does not show any clinically significant difference between epoetin and darbepoetin in hemoglobin response, transfusion reduction, and thromboembolic events.”</li> <li>Other studies have shown darbepoetin alfa delivers added patient convenience with fewer injections per month and cost-savings potential</li> </ul>

### Coverage and Reimbursement Impact

- The CMS determined that the treatments were “functionally equivalent” because they “use the same biological mechanism to produce the same clinical result,” and thus warranted the same payment; both drugs would be reimbursed at the lower Procrit rate
- Several private payers followed suit and announced policy changes around the implementation of a therapeutic interchange, substituting Aranesp for Procrit
- CMS’s decision prompted a range of responses from the industry, manufacturers (Amgen filed suit against CMS, J&J endorsed the decision), and politicians
- In the 2003 Medicare Prescription Drug, Improvement, and Modernization Act, lawmakers prohibited future use of the “functional equivalence” approach, while retaining the existing decision for Aranesp
- In 2005, CMS reversed its “functionally equivalent” decision and began reimbursing each drug individually based on ASP

Note: BCBSA Tec: Blue Cross and Blue Shield Association’s Technology Evaluation Center; CER: Comparative Effectiveness Review  
 Source: <http://www.effectivehealthcare.ahrq.gov/repFiles/EPO%20Final.pdf>; *Oncologist* 2004;9:696-707. <https://www.clevelandclinicmeded.com/medicalpubs/pharmacy/julyaug2004/interchange.htm>; <http://www.upa-llc.com/guidelines/Humility%20of%20Mary%20Health%20Partners%20-%20TI.pdf>; [http://professional.cancerconsultants.com/reim\\_news.aspx?id=34664](http://professional.cancerconsultants.com/reim_news.aspx?id=34664); *Health Affairs* 25, no. 5 (2006): 1260–1269

Other pioneers in reviewing cost-effectiveness and comparative effectiveness of various therapies include national provider organizations such as United Healthcare and Aetna, staff model HMOs such as Kaiser Permanente, and integrated health care networks such as Pennsylvania's Geisinger. Some academic groups also are developing CER expertise, with prestigious universities such as Harvard leading the way. Although these do not have the level of funding that might be available to a federal institution, their independence lends weight to the groups' findings. Another interesting approach under the purview of the AHRQ is the Drug Effectiveness Review Project (DERP) – a self-governing collaboration between public and private organizations, including 14 states. These various groups and initiatives aim to provide “systematic, evidence-based reviews of the comparative effectiveness and safety of drugs in many widely used drug classes and to apply the findings to inform public policy and related activities in local settings.”<sup>11</sup>

In addition to these approaches – which are generally based on retrospective research – there is also mounting pressure for clinical trials to compare a new therapy “head to head” (H2H) to the existing gold-standard. For example, the National Eye Institute has sponsored a H2H comparison of Avastin versus Lucentis in the treatment of age-related macular degeneration.<sup>12,13</sup> Although these types of trials may be illuminating, historically they have had limited influence in changing practice patterns. The ALLHAT (comparing anti-hypertensive agents for the prevention of heart attack) and CATIE (comparing antipsychotic medications for the treatment of schizophrenia) trials, for example, were designed as H2H trials comparing newer branded therapies to older generic products.<sup>14,15</sup> Results showed a benefit to starting patients on older generic products before prescribing branded medications, but were hotly contested in the literature and ultimately fell short in precipitating a significant change in clinical practice. The aftermath of these trials underscores the complexity in influencing health care policy and treatment patterns based on CER.

### The Future: A Role for Pharma in Driving CER?

As comparative effectiveness research gains more influence, pharma can simply not afford to wait passively for policy-makers to dictate comparative effectiveness requirements and not actively participate in the discussions concerning the proper design and use of CER. By supporting the development of a standard set of guidelines, the industry could rightly earn a seat at the table if initiatives are

<sup>11</sup> <http://www.ohsu.edu/drugeffectiveness/>

<sup>12</sup> <http://www.nei.nih.gov/news/pressreleases/o222o8.asp>

<sup>13</sup> <http://www.allaboutvision.com/conditions/lucentis-vs-avastin.htm>

<sup>14</sup> The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. *JAMA*. 2002;288:2981-2997.

<sup>15</sup> The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Project: Schizophrenia Trial Design and Protocol Development. *Schizophr Bull*. 2003;29:15-31.

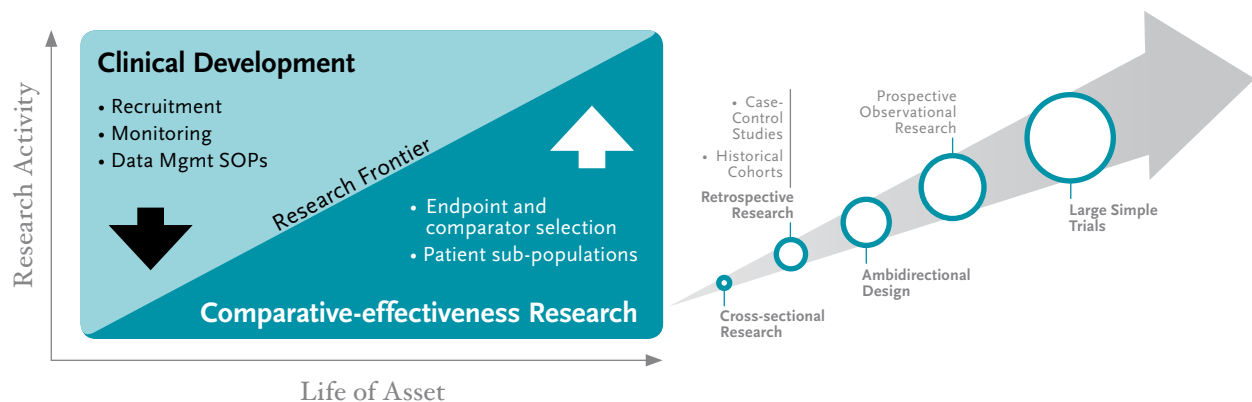
launched at the federal level. A key argument in favor of engaging in these early discussions of CER and HTAs is to gain influence over the form this approach takes as it evolves into a more universally accepted, standardized format which could be used alongside a product's traditional data demonstrations.

More importantly, biopharmaceutical manufacturers need to examine the data which shows exactly how their medicines are being used, and by whom. This will enable decisions to be made all along the development process that are more rooted in real-world data. Furthermore, it can develop new standards for myriad observational techniques to complement traditional clinical development in order to more fully develop the mosaic of comparative evidence supporting the adoption of their product. Although H2H trials may be considered a gold standard for measuring relative differences in efficacy, their impact is limited by the protracted timeline and cost associated with implementing such trials.

Industry should broaden its evidence gathering activities beyond traditional clinical research methods that are focused predominantly on placebo-controlled trials. Complementing the RCT clinical pathway with observational techniques may illuminate the shortcomings of the current gold standard, and also enable biopharmaceutical manufacturers to refine development and product positioning pre-launch. Such evidence gathering techniques would also enable companies to document real-world patient experience post-launch (*see Figure 4*). Retrospective research provides a meaningful window into historical treatment including multiple drug exposures and outcomes, but is limited by the evolution of health care practices. Prospective observational research, such as cohort studies and registries,

**Figure 4: CER Evolution**

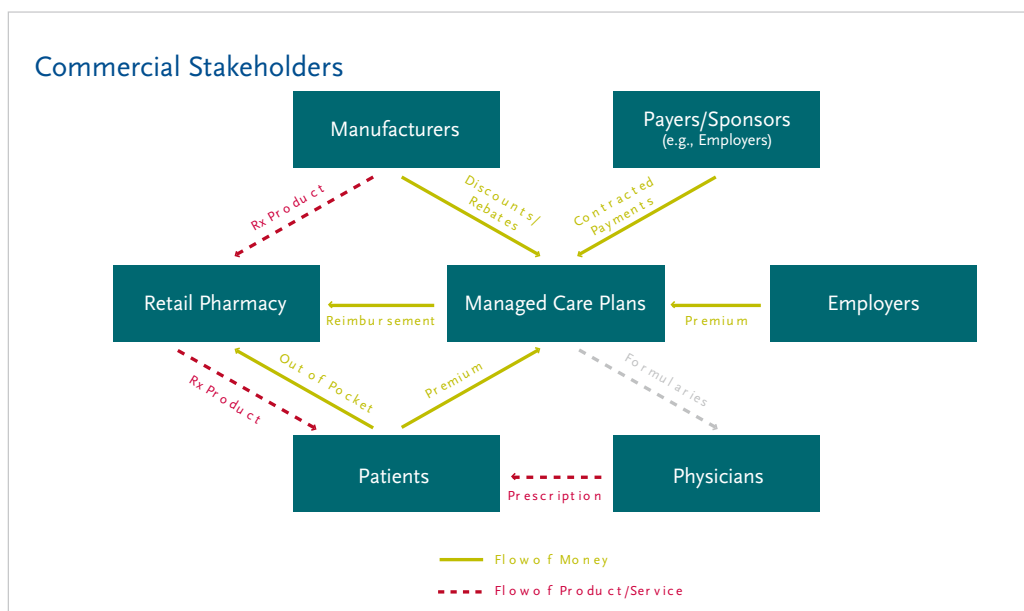
CER is evolving into a fundamental strategy focused on substantiating the proof of a product's value, thereby amplifying and extending the commercial value of an asset.



offer a remarkable channel to collect real-world data on treatment process and outcome, but need to be evaluated carefully to address potential bias and confounding.

It is imperative for the economic efficiency of the health care industry to develop a universally accepted pharmaceutical valuation system based on a standard set of CER principles. Ultimately, every manufacturer must communicate the value of its products to multiple stakeholders – including patients, employers and managed care plans, as well as the traditional physicians and payers – in a manner that allows for comparison to competing agents (*see diagram below*).

With drug development costs reaching new highs each year, the risk of standing on the sideline while comparative effectiveness evolves is untenable. Given the variety



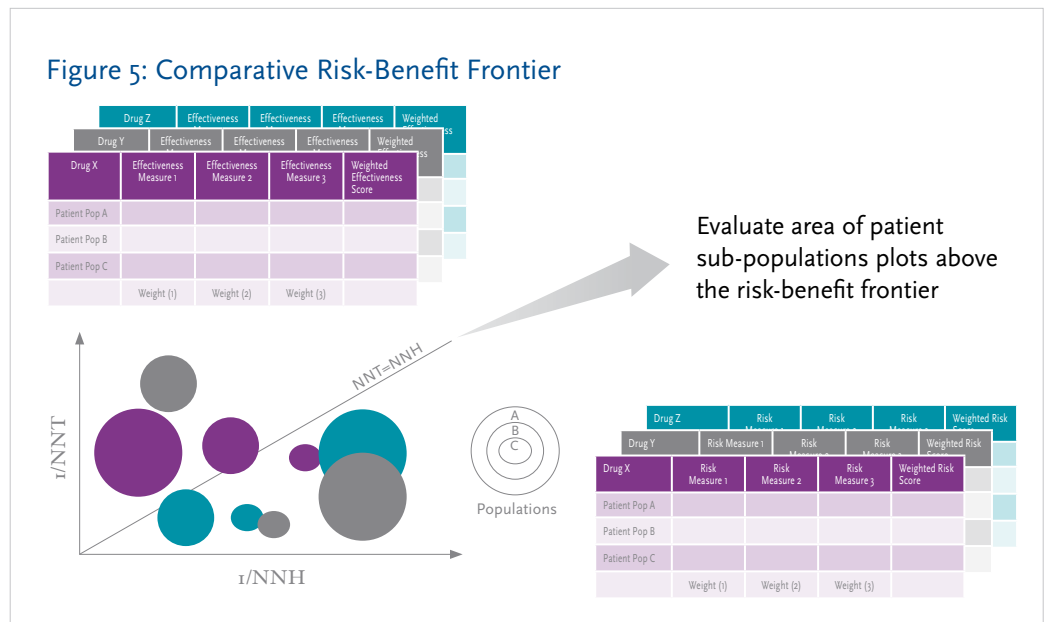
of health care stakeholders, CER guidelines should focus on a holistic notion of value which encompasses a variety of treatment process and outcome metrics measured by an array of research designs. In the end, a variety of techniques that complement each other should be deployed to investigate the comparative benefits and risks of products. Accordingly, the biopharmaceutical industry should propose a standardized process for designing, implementing and reporting this array of study designs.

Under an evidence-based market paradigm, payers would base their recommendations on systematic, unbiased assessments. The “value” concept would ideally be based on a product’s evidence of comparative effectiveness – an incremental improvement in treatment process or outcome conferred to patients

compared with the current standard-of-care in a real world setting. Today, most evidence of value is based on placebo-controlled trials designed to isolate the effect of a product and not necessarily generalize findings to a larger population. Many biopharmaceutical companies, therefore, are wrestling with payer demands for head-to-head data that many times do not match regulatory data requirements for approval.

The responsibility for developing and demonstrating a product’s value rightfully falls to the biopharmaceutical manufacturers. But this should be regarded as a historical market opportunity, not as a burden. Present discussions around the concept of CER have limited metrics, such as explicit measures of effectiveness and implicit measures of cost-effectiveness as well as designs, such as H2H trials. It is in the best interest of all stakeholders in the health care system to broaden these metrics and designs to accurately and fairly appraise the value of pharmaceutical innovation.

Conceivably, effectiveness measurement can be complemented with risk measurement, and both metrics can be compared using a common denominator. For example, number-needed-to-treat to derive an a priori defined threshold for effect can be plotted against the number-needed-to-harm based on an adverse event of interest. This exercise could be replicated in a variety of patient populations across multiple benefit and risk metrics. Ideally, an array of effectiveness metrics should be tested and validated in a variety of patient populations weighing the “battle-tested” metrics higher than the newly introduced (see Figure 5).



As a diversity of data is amassed under CER guidelines that include both observational and experimental research techniques measuring an array of outcomes, pharmaceutical companies should be able to present formidable evidence of their product's value and therefore be properly rewarded for their innovations.

## About the Author



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John Doyle, Ph.D., MPH, is Vice President and Practice Leader for Market Access with the Consulting group at Quintiles. Previously, he was president and a founder of Analytica International, a global reimbursement, outcomes and market access consulting firm. He previously led the Oncology and Immunology Economics Research Group at Bristol-Myers Squibb.

Since 1993, Dr. Doyle has authored over 50 original research articles and abstracts, in a variety of therapeutic areas. As a health economist and epidemiologist, he has lectured on research methodologies for academic and commercial audiences in the U.S., Canada, Europe and Latin America. He has consulted global pharmaceutical and biotech firms on strategic concerns regarding product development, pricing, reimbursement, market valuation and other commercialization issues.

Dr. Doyle received a Bachelor of Science degree in Applied Economics with a concentration in the Life Sciences from Cornell University. He received a Master of Public Health degree and a Doctor of Public Health degree in Epidemiology from the Mailman School of Public Health at Columbia University.

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