

Commentary: The Real-world Convergence of Comparative Effectiveness Research and Risk-Benefit Assessment

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INTRODUCTION

Key drivers in today's biopharma market include the shifting priorities and information requirements of major stakeholders, focused on the following:

- *Safety concerns*, including a heightened need to better understand and manage safety signals and risk-benefit in diverse populations and health care settings after a product is launched. To meet this need, the US Food and Drug Administration is considering creating a new "super office" of drug safety within the Center for Drug Evaluation and Research to oversee FDA's multiple drug safety initiatives (1).
- *Comparative effectiveness*, focused on proof of clinical benefit versus the standard of care in a naturalistic environment outside of randomized clinical trials (RCTs).
- *Real-world value*, entailing a demonstration of incremental economic impact to stakeholders compared with existing therapies.
- *Regulatory acceleration*, with a call for more efficient approaches to approval and a faster time to market, especially in areas of acute unmet medical need. Taking cancer as an example, to date, FDA has granted accelerated approvals to cancer drugs 49 times. Of these, 27 have completed postmarketing studies verifying benefit, four have completed studies and await an FDA decision, five failed to confirm benefits in studies, six have been on the market for more than 2 years and have not com-

pleted studies, and seven have been on the market for less than 2 years (2).

These concerns about safety, value, and outcomes are driving demand for more robust evidence about biopharmaceuticals and other medical interventions. Data generated by traditional premarket clinical development typically do not provide a comprehensive view of a product's ultimate performance to allay these stakeholders' concerns. This de facto data shortfall limits market access. Consequently, a new paradigm of complementing and integrating real-world research with RCTs is on the rise to provide a holistic view of biopharmaceuticals.

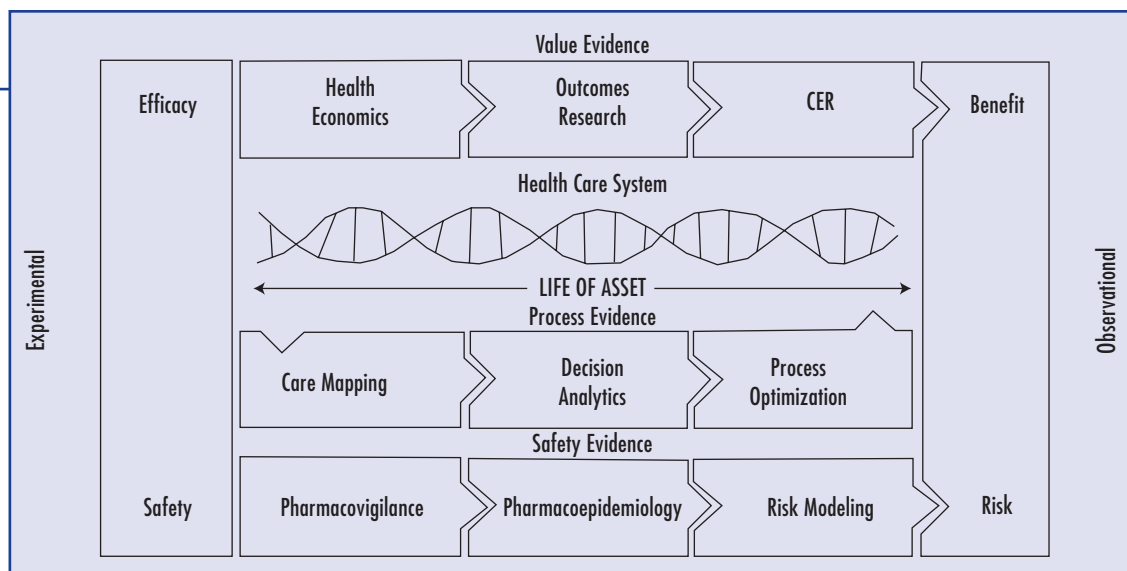
COMPARATIVE EFFECTIVENESS RESEARCH

Reimbursability hinges on comparative effectiveness research (CER), a real-world comparison of the new product with the existing standard of care. CER is defined by the Institute of Medicine as the "comparison of effective interventions among patients in typical patient care settings, with decisions tailored to individual patient needs." CER encompasses observing naturalistic practice patterns, investigating patient populations, comparing the relative effectiveness of products, and communicating the results.

According to a recent study (3), just over half (51%) of new molecular entities had CER data

FIGURE 1

Stakeholders (physicians, patients, policymakers, and payers) will require customized clinical and commercial evidence derived from patient-level analysis of real-world data. Postlaunch, efficacy and safety are translated into benefit and risk.



available at the time of drug approval in the United States over the past decade. Such data were most common for products for diabetes (89% had CER data), followed by infectious diseases (73%), HIV/AIDS (64%), arthritis and rheumatism (60%), and cancer (35%). A confluence of safety concerns and diminishing unmet need due to effective standards of care may have precipitated the comparative research in these therapeutic areas. Logically, as more safety signals are detected for other widely used product categories and competition ratchets up, CER is likely to be included in clinical development programs for a wave of additional therapeutic areas.

CER has the potential to inform decisions throughout a product's life cycle and should be incorporated from early development through to patent expiry and beyond. Overall, the increasing focus on CER will trigger adjustments to research design including:

- More head-to-head comparisons
- Addition of composite endpoints, including cost effectiveness
- Widening of subgroup analysis to identify niches for optimal risk-benefit
- Longer trials to track downstream outcomes
- Larger sample size to accommodate additional endpoints and patient subgroups

CER weighs the benefits and risks of ways of preventing, diagnosing, treating, or monitoring clinical conditions to determine which work best for various patient populations in different circumstances. Figure 1 shows the evidence continuum for a drug. The double helix in Figure 1 symbolizes the dynamics of the health care system—a modulating process that affects biopharmaceutical product use and performance. While the biopharma sector has historically focused single mindedly on regulatory approval, increasing adoption of CER means that a wider set of stakeholders (including physicians, policymakers, patients, and payers) is now demanding data on real-world outcomes and relative benefits. Biopharma firms must now generate information to meet these demands as part of the R&D process. Risk factors that impact a product's effect should be taken into account in all three of the core methodologies for CER—observational studies, experimental trials, and systematic reviews. It should be emphasized that in research that is not randomized and controlled, it is important to consider alternative explanations of observed effects, such as confounding, bias, and chance. Study design and analytic techniques need to be refined on this front to ensure validity and reliability of findings.

Figure 1 can be viewed as information chan-

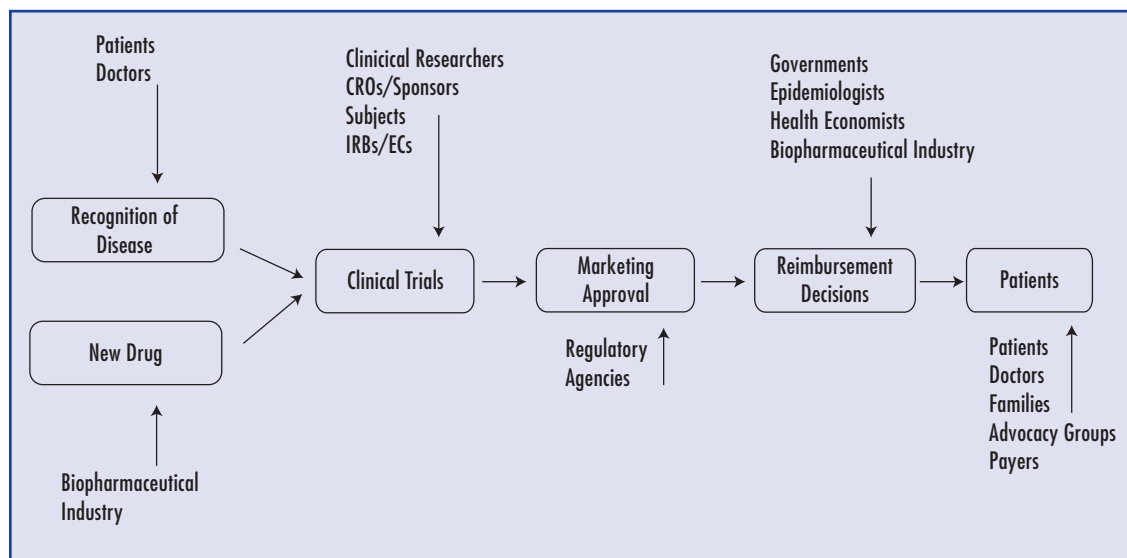


FIGURE 2

Stakeholders involved in risk-benefit assessment during lifecycle drug development. Adapted from “Balancing Benefits and Risks: Sharing Responsibility.” European Biopharmaceutical Enterprises. See www.ebe-biopharma.org.

nels that flow through the health care system. For the value evidence channel, treatment efficiency and effectiveness (including patient-reported outcomes) are evaluated to compare the clinical, economic, and humanistic value to the standard of care. For the process evidence channel, the treatment algorithm is evaluated from a health care systems perspective to understand stakeholder relationships. Key elements include care mapping, decision analytics, and process optimization. For the safety evidence channel, elements include pharmacovigilance, pharmacoepidemiology and risk modeling. From left to right, efficacy is ultimately translated into patient benefit, while safety is translated into risk. All components of this risk-benefit profile must then be clearly communicated to health care stakeholders.

RISK-BENEFIT ASSESSMENT

Risk-benefit assessment (RBA) is defined as the use of quantitative methods for systematically evaluating the risks and benefits of new or existing medical interventions. This process involves multiple stakeholders (Figure 2). These methods evaluate risk-benefit trade-offs to assist regulatory and clinical decision making in the absence of directly comparable metrics. RBA fits under the larger umbrella of risk management, and includes various methods that are not

meant to replace but enhance clinical evaluation. The balanced objective of RBA is to minimize unnecessary patient exposure to adverse events while maximizing the benefits conferred to these patients.

Risk identification is the first step in risk management. However, some side effects may not be evident until a drug has been used for many years or by many patients. Very rare or very late side effects cannot be predicted early in a drug life cycle, and the potential for harm will remain unknown during this time. The second element of risk management is risk assessment, which includes risk perception. Assessing risk relies on some understanding of numerical values and is influenced by the experience, expectations, and behavior of the person facing the risk. The perceived risk may be far from the real risk and can depend greatly on whether or not the person is in control of the situation. The main goal of risk prioritization and communication is to improve collective and individual decision making.

Regulators, clinicians, and patients who routinely make decisions that require trading safety for desired clinical benefits are increasingly demanding better transparency and objectivity in this trade-off analysis. Indeed, the Council for International Organizations of Medical Sciences has called for a standardized definition

for risks and benefits and a universal quantitative approach to RBA. Both the FDA and the European Committee on Proprietary Medicinal Products (CPMP) are increasingly requesting RBA of biopharmaceutical products. In the United States, the FDA currently relies on multiple approaches because no single approach is deemed sufficiently comprehensive to permit full evaluation of all important problems. The agency has recommended analysis of report data and use of large, population-based databases. The CPMP also does not have a standardized method for benefit-risk studies, other than the assessment of risks. The biopharma trade association, European Biopharma Enterprises, has called for shared responsibilities among stakeholders in managing biopharmaceutical risk-benefit.

The present regulatory climate demands RBA, yet there are few formalized methods that contain quantitative syntheses of benefit and risk. In 2010, in conjunction with the New York Academy of Sciences, the FDA issued a draft qualitative framework for RBA (4). This framework provides a high-level view of issues relevant to regulatory decisions, including target populations, patient preference, efficacy in subgroups, trial dropouts, study populations, trial design and conduct, and the clinical relevance of the endpoint. FDA's framework evaluates five areas: severity of condition, unmet medical need, clinical benefit, risk, and risk management. Its main aims are as follows:

- Provide a concise bottom-line description of the evidence on each topic and the benefit-risk implications
- Support more structured discussions of the range of issues involved in benefit-risk assessments
- Improve predictability and consistency through a standardized structure
- Function as a living document, able to be updated based on new information

The industry association PhRMA has a Benefit Risk Action Team (BRAT), which set out in 2009 to develop a structured, transparent benefit-risk framework and integrate it into the regulatory

review process. The six-step BRAT qualitative framework facilitates structured, systematic decision making via customizable tools and processes. This framework can be considered as a set of processes and tools to guide decision makers in structuring, summarizing, and interpreting the information. It does not currently evaluate the use of any particular RBA method but rather applies a communication structure for whichever approach aids in decision making. The adoption and use of this framework will advance the rigor, transparency, and communication of the rationale behind benefit-risk decisions; pilot studies and applications are currently being planned.

There remains a need for an RBA decision tool that aids stakeholders in selecting the most appropriate RBA method for pre- and postapproval decision making. At the development and approval stage, the RBA framework would improve the quality of the discussion between sponsors and regulators and, as a consequence, between providers and patients, particularly with respect to medicines for which the benefit-risk balance is not straightforward. At the postapproval stage, the framework could ensure a more balanced assessment and communication of both benefits and risks, particularly as new data emerge.

CONCLUSION

Currently, the risks and benefits of innovative medical treatments are the subject of intense health policy debate, particularly concerning the methods and approaches. CER and RBA are increasingly following convergent pathways, with both avenues of research following pragmatic designs in pursuit of real-world data on safety and effectiveness. Furthermore, both CER and RBA are increasingly concerned with capturing the patient perspective when appraising treatment process and outcomes. Last, both fields of research are arguably in their nascent stage of development, now focused on standardizing and harmonizing methodologies to ensure valid and reliable findings.

Common denominators between CER and RBA include the need for the following:

- Patient-centric focus
- Evaluation of both safety and effectiveness in the real world
- Multifaceted approach to stakeholders
- Population-level analysis
- Real-world research
- Generalizability to be optimized
- Longitudinal follow-up
- Heterogeneity to be explored
- Superiority to be tested
- The approach to be outcomes oriented

As a result of these common denominators, data collected for CER can also inform RBA, and vice versa. Optimizing the risk-benefit profile of a product—by identifying the appropriate patient population, provider type, concomitant therapies, and treatment duration—purportedly will optimize comparative effectiveness. Collectively, both avenues of research hold the promise of synergistically improving public health.

Recent proposals for a parallel review process between Centers for Medicare and Medicaid Services (CMS) and FDA highlight this recognition of the value of a common data set (5). Under a memorandum of understanding signed on June 25, 2010 (6), the agencies agreed to work together to “promote initiatives related to the review and use of FDA regulated drugs, biologics, medical devices, and foods, including dietary supplements.” In a *New England Journal of Medicine* article titled “Listening to Provenge—What a Costly Cancer Treatment Says About Future Medicare Policy” (7), the authors commented that “in theory, parallel review is appealing. . . . Simultaneous engagement with the CMS and the FDA by product manufacturers during their clinical development programs could provide valuable feedback to companies about the study design and end points needed to justify reimbursement, which could, in turn, improve the predictability of the process.” They concluded that Provenge “raises important questions about prospects for parallel review by the FDA and the CMS. From a health policy standpoint, however, its lasting legacy may be its role in accelerating overdue payment reforms.”

Indeed, Provenge provides an interesting case history of CER in action. The product, based on sipuleucel-T, is a novel cellular immunotherapy for the treatment of asymptomatic or minimally symptomatic, metastatic, hormone-refractory prostate cancer. This was approved in April 2010 based on a pivotal clinical trial showing an increase in median survival of 4.1 months as compared with placebo and fewer side effects than occur with docetaxel. Priced at \$31,000 per treatment, with a usual course of three treatments, sipuleucel-T is one of the most expensive cancer therapies ever to hit the marketplace. CMS opened a national coverage analysis for sipuleucel-T (7). A final decision that Medicare would pay for the product was issued on June 30, 2011 (8).

Major stakeholders in the US health care system are appealing to the biopharmaceutical industry to improve their vigilance around real-world product performance and bolster the evidence base supporting their products' value propositions. Given the commonalities in the means of generating this data, it would be most efficient to accelerate the convergence of methods and sharing of information across CER and RBA to optimize their public health impact. Regardless of whether a formal integrated pathway is mandated, if industry is to pursue access to real-world, longitudinal data across multiple patient subpopulations, it makes good business sense to evaluate these data from multiple angles to increase collective stakeholder return on investment.

REFERENCES

1. Baghdadi R. FDA considering “super office” of drug safety within drug center. *RPM Report*, March 25, 2011; http://therpmpreport.com/Free/9ac0ed7b-3afe-4fe3-b04c-ced675140264.aspx?utm_source=RPMel.
2. Eastman P. ODAC backs FDA's strong stance on need for post-marketing studies on accelerated-approval cancer drugs. *Oncology Times*. February 11, 2011; http://journals.lww.com/oncology-times/Fulltext/2011/02250/ODAC_Backs_FDA_s_Strong_Stance_on_Need_for.3.aspx.
3. Goldberg NH, Schneeweiss S, Kowal MK, Gagne JJ.

- Availability of comparative efficacy data at the time of drug approval in the United States. *JAMA*. 2011;305:1786–1789; <http://jama.ama-assn.org/content/305/17/1786.short>.
4. Jenkins J. A United States regulator's perspective on risk-benefit considerations. FDA presentation, April 23, 2010; <http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM210155.pdf>.
 5. Slotnik J. CMS-FDA proposed premarket parallel review—the devil is in the details. *Value-Based Cancer Care*; <http://valuebasedcancer.com/article/cms-fda-proposed-premarket-parallel-review%E2%80%94devil-details>.
 6. Memorandum of understanding between United States Food and Drug Administration and Centers for Medicare and Medicaid Services. *Fed Register*. 48699, August 11, 2010; <http://www.federalregister.gov/articles/2010/09/17/2010-23252/parallel-review-of-medical-products>.
 7. Chambers JD, Neumann PJ. Listening to Provenge—what a costly cancer treatment says about future Medicare policy. *NEJM*. May 5, 2011; <http://www.nejm.org/doi/full/10.1056/NEJMp1103057>.
 8. Pollack A. Medicare will pay for prostate drug. *New York Times*, June 30, 2011; <http://prescriptions.blogs.nytimes.com/2011/06/30/medicare-will-pay-for-prostate-cancer-drug/>.
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