

PERSPECTIVE

Comparative Effectiveness Research in the United States: A Catalyst for Innovation

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Recent calls for value in the US healthcare system have spurred an increase in comparative effectiveness research, which generates evidence on competing treatment options to inform healthcare stakeholders. As a large healthcare purchaser, the federal government has made several significant investments in comparative effectiveness research. Notably, in 2009 the American Recovery and Reinvestment Act allocated \$1.1 billion for comparative effectiveness research, and in 2010 the Patient Protection and Affordable Care Act established a federal institute to organize the federal investment in comparative effectiveness research going forward. Over the past several years, comparative effectiveness research from the public and private sectors has begun to provide a foundation for innovation within the insurance and life sciences industries. Health plans and other payers are experimenting with nuanced coverage and reimbursement policies informed by comparative effectiveness evidence. Anticipating changes in payer, patient, and provider behaviors, drug manufacturers are refocusing their efforts on the development of novel and better-differentiated medications. As more comparative research becomes available in the future, continued innovation in payer and manufacturer strategies appears likely.

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As stakeholders continue to strive for greater value in the US healthcare system, many are calling for more research to inform treatment decisions, particularly for providers and patients choosing between available multiple interventions. This charge has helped to ignite interest in comparative effectiveness research (CER), which aims to provide evidence on the effectiveness, benefits, and harms of competing treatment options for a clinical condition. As a growing purchaser of healthcare and a provider of public goods, the federal government has expanded its role in recent years, making increasingly significant investments in CER.

With healthcare costs outpacing inflation year after year, the policy community has been more attuned to ways of controlling spending, and one popular target has been the elimination of “wasteful” or unnecessary care. At best, CER is seen as a potential way to identify this excess, while simultaneously providing better information for decision makers at the point of care. At worst, CER is seen as a way for the government and payers to rationalize cost-cutting, undermining the autonomy of providers, and limiting patient choice.

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CER may even hinder innovation by increasing the cost of drug development and failing to recognize the true value of incremental product improvements.

The research expansion will have important implications for the insurance and life sciences industries; in particular, CER has the potential to stimulate innovation in healthcare. In fact, we already see 2 significant changes in the commercial areas of the healthcare system. First, payers are using research findings on competing treatments to deploy innovative payment methods, such as tiering and bundling, across a wider range of therapeutic areas. Second, drug manufacturers are anticipating payment changes, shifting their commercialization strategies to create novel and better-differentiated medications. Although the gradual market adjustment to these new realities may bring some near-term difficulties across the healthcare system, and their robust application is not a foregone conclusion, an increase in CER may help to create a more efficient, innovative system in the future.

The State of Comparative Effectiveness Research

For much of the past 3 decades, US investment in CER has been driven by myriad organizations in the public and private arenas, all of which pursued independently derived research agendas. These organizations include the BlueCross BlueShield Technology Evalua-

tion Center, the Cochrane Collaboration, and the Drug Effectiveness Review Project, among others. Government organizations, such as the Agency for Healthcare Research and Quality (AHRQ) and the National Institutes of Health historically had dedicated a portion of their funding to CER, but did not influence the direction of the US investment overall. As part of the effort in 2003 to expand Medicare coverage for prescription drugs, the federal government made its first explicit investment in CER, allocating up to \$50 million to AHRQ's Effective Health Care Program for "the outcomes, comparative clinical effectiveness, and appropriateness of health care items and services (including prescription drugs); and strategies for improving the efficiency and effectiveness of such programs."¹

While CER was gaining momentum, some policymakers and thought leaders were seeing missed opportunities. The fragmented CER investment was reflecting the priorities of the entities asking the questions, and focused on a narrow set of topics; this left important areas of inquiry unaddressed. Existing incentives, however, provided little motivation for researchers to fill these research gaps. Furthermore, the model for determining research priorities lacked the necessary participant and stakeholder engagement to ensure that research focused on the most clinically relevant questions. Given these obstacles, many saw a role for the federal government in providing leadership and funding to optimize CER in the United States.

Over the past 2 years, the federal government has taken significant strides to fill this role. In 2009, the American Recovery and Reinvestment Act (ARRA) allocated \$1.1 billion for 2 years of research.² In 2010, the Patient Protection and Affordable Care Act established a permanent US CER entity called the Patient-Centered Outcomes Research Institute (PCORI) to guide the federal CER enterprise. The law appropriates \$1.26 billion to this public-private, stakeholder-governed institute from 2010 to 2019,³ with a mandatory fee on health plans and Medicare beneficiaries augmenting the budget beginning in 2013. Given that PCORI's central function is to organize and coordinate the federal CER investment, the model for determining research priorities is at the cusp of a transformation. PCORI has already appointed a methodology committee to establish research standards, and it plans to release CER priorities later in 2011.

Federal Investment as a Marker of CER Demand

To understand the potential impact of recent federal CER efforts, it is important to examine how the federal investment has been deployed. The largest part of the ARRA CER awards—46%—supports projects to devel-

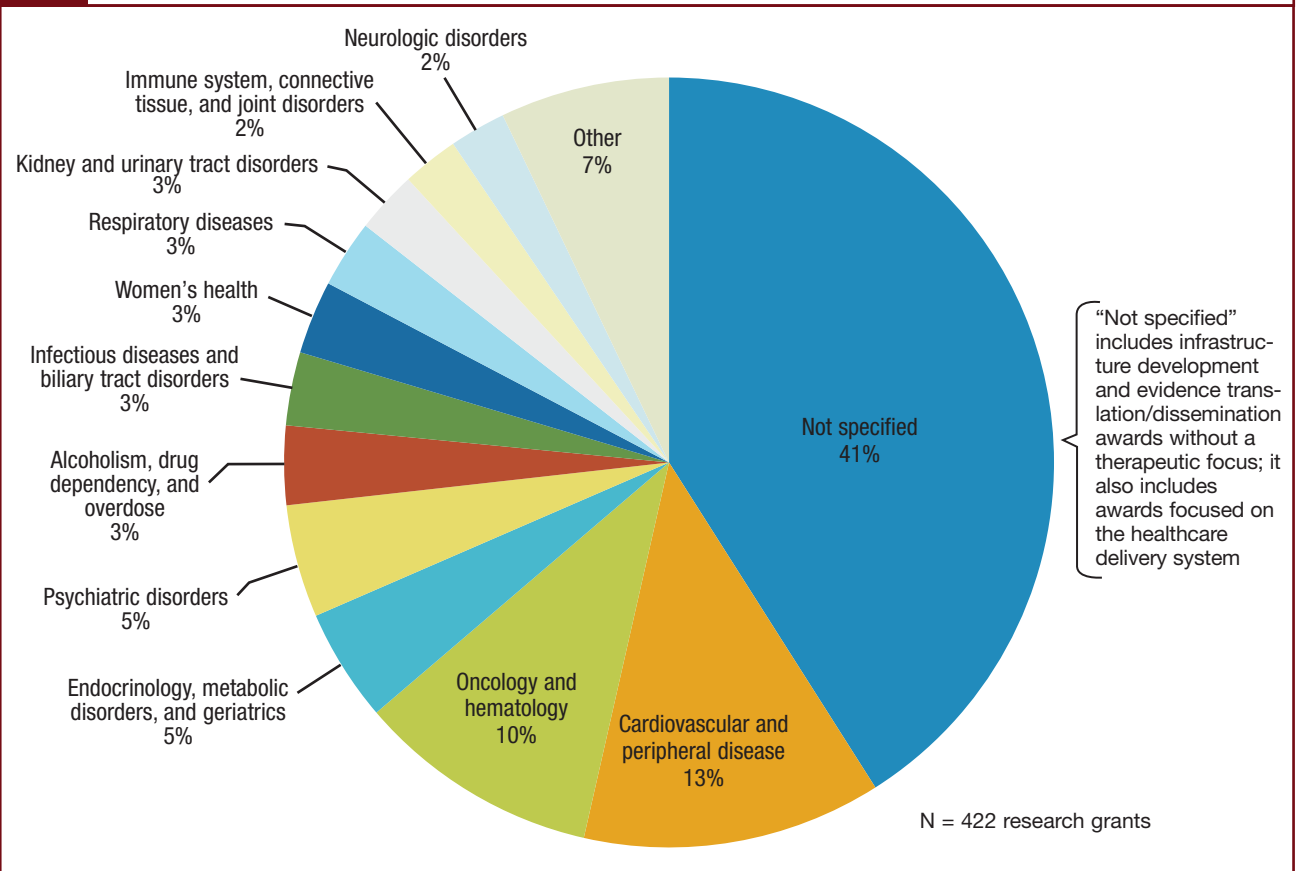
KEY POINTS

- The intensifying focus on value in healthcare has helped to fuel public and private sector interest in comparative effectiveness research (CER), which provides evidence on the effectiveness, benefits, and harms of competing treatment options for a clinical condition.
- In 2009, the American Recovery and Reinvestment Act allocated \$1.1 billion for 2 years of CER, and in 2010, the Patient Protection and Affordable Care Act established a permanent entity, the Patient-Centered Outcomes Research Institute, to organize federally funded CER going forward.
- Concurrent with the increase in federal funding for CER, health plans and other payers are becoming more sophisticated, data-driven organizations.
- Recognizing changes in their customer base, drug manufacturers are beginning to reexamine their product development strategies. Increasingly stringent payer standards for value are likely to encourage the development of more innovative medications.

op more sophisticated research infrastructures and methodologies.⁴ Infrastructure building includes activities such as linking patient registries and adapting existing data sources so that they can be used for CER. Although in the past there has been an imperative to demonstrate the immediate value of CER to policymakers and taxpayers, ARRA's investment in infrastructure shows the intention to construct a more sustained research program.

The next largest ARRA commitment to CER—38% of awards—supports new evidence development, primarily through observational trials and evidence synthesis.⁴ Approximately 27% of these awards (or 10% of ARRA awards overall) focus on generating new evidence on pharmaceuticals. The remaining 16% of the overall ARRA CER investment supports the dissemination and translation of evidence.⁴ This type of award includes the creation of multilingual reports for subpopulations at elevated risk for specific diseases, among other projects.

The **Figure** displays the 422 research grants and contracts funded through ARRA, by therapeutic area. A large proportion of awards—41%—did not have a disease focus; this includes a number of infrastructure development awards, as well as studies on healthcare delivery system interventions, such as accountable care organizations and the medical home.⁴ Not surprisingly, among awards with a therapeutic focus, many concern high-cost or high-incidence diseases. Cardiovascular and oncology

Figure ARRA CER Investment by Therapeutic Area (Avalere EBM Navigator)

ARRA indicates American Recovery and Reinvestment Act; CER, comparative effectiveness research; EBM, evidence-based medicine.
Courtesy of Avalere.

research received the highest number of awards, which totaled \$121 million and \$124 million, respectively.⁴

Although it is not yet clear whether the ARRA investment will lead to the creation of meaningful tools and resources for CER, the considerable focus on infrastructure is cause for optimism. The material question now is how well PCORI can build on the progress made under ARRA as it identifies, funds, and pursues its own CER priorities.

Health Plans' Business Models Build on CER Demand

The federal government is one marker of the state of CER in the United States, but it is not the only one. Health plans and other payers are important stakeholders and contributors in the US CER marketplace. Today we see 2 main manifestations of this. First, recognizing the possible applications of CER, the commercial sector is growing its data and analytic expertise. Second, plans are making a concerted effort to creatively leverage find-

ings (internally or externally generated) to inform their decisions. Taken together, these changes demonstrate the transformation of health plans and pharmacy benefit managers (PBMs) from risk intermediaries to more sophisticated, data-driven organizations.

Positioning Research Expertise as a Commercial Asset

Early signals of this movement date back a decade or more, with UnitedHealth's founding of Ingenix in 1996⁵ and WellPoint's acquisition of HealthCore in 2003.⁶ Both deals marked a first step toward a more research-oriented business model. More recently, in fall 2010, the PBM Medco acquired United BioSource Corporation (UBC), a global scientific and medical affairs organization, to enhance and expand its own research capabilities. Not surprisingly, when discussing this with the investor community, Medco CEO David B. Snow, Jr., positioned CER as a healthcare reform opportunity and

the acquisition of UBC as a component of the corporate growth strategy.⁷

Another marker of an evolving business model is the increased partnership between health plans and the federal government. For instance, the US Food and Drug Administration's (FDA's) Sentinel Initiative, launched after the passage of the FDA Amendments Act in 2007, is an active drug surveillance system and includes participation from a wide range of organizations, such as America's Health Insurance Plans, Humana, HealthCore, and Kaiser Permanente Center for Effectiveness and Safety Research.⁸ An additional example is the contract that the Department of Health and Human Services awarded to Ingenix Public Sector Solutions in 2010 to build a multipayer claims database for CER.⁹

Expanding the Use of CER in Decision-Making

The second part of the equation is how health plans and payers are translating the demand for CER into meaningful healthcare purchasing decisions. A few recent examples illustrate potential uses:

- ***Creation of clearer standards for evidence use.*** In May 2010, WellPoint became the first health benefits company to release CER guidelines, making more transparent its evaluation process for coverage and reimbursement decisions.¹⁰ This effort to explicitly standardize the data that informs decisions signals WellPoint's plan to use more diverse evidence in future decisions.
- ***Innovative payment methods to incentivize efficiency.*** Last fall, UnitedHealth Group announced a new cancer payment model aimed at improving the quality of care for patients with breast, colon, and lung cancers.¹¹ Under the pilot, an oncologist will be paid a flat fee based on the wholesale price of a predetermined drug regimen for a patient, plus a case management fee. Although other services will continue to be reimbursed on a fee-for-service basis, this payment change will encourage physicians to select appropriate products and apply them as efficiently as possible. The pilot represents a much different way to pay for care. By considering all services, including medical and pharmacy, as part of a single bundle, payers and clinicians are compelled to more explicitly assess the value of each available component of care.
- ***CER-infused Medicare coverage policy.*** In January 2011, Medicare carrier Palmetto GBA announced its intent to drop coverage of bevacizumab (Avastin) for metastatic breast cancer.¹² Palmetto GBA's statement followed an FDA recommendation in December 2010 to remove this indication from bevacizumab's label. The FDA had granted accelerated approval for Avastin for metastatic breast cancer in 2008, after

promising but uncertain early results; however, in 2 subsequent randomized controlled trials comparing treatment regimens with and without bevacizumab (which the FDA required of the manufacturer), the FDA found that the drug did not perform well.¹³ This led the agency to modify its earlier position on bevacizumab's net benefit in patients with metastatic breast cancer. Although Palmetto GBA has rescinded the policy change while the FDA's recommendation is under appeal (by the manufacturer), their initial actions, as well as the assurance that they "will continue to review relevant clinical trials results and literature addressing the effectiveness of Avastin in the treatment of breast cancer,"¹⁴ illustrate payer interest in leveraging CER findings for coverage decisions.

Innovation in the Life Sciences Industry

In response to the wider availability and broader payer use of effectiveness data, manufacturers are also beginning to shift gears, modifying their approach to commercialization. Although this is an evolving process, so far we have seen the following 3 clear ways that drug manufacturers are adapting.

Reassessing Drug Development and Commercialization Strategy

Externally generated CER may expose drugs to head-to-head comparisons and class reviews; commercial success in a crowded or partially generic class has become harder to achieve than it was 10 or 20 years ago. In this way, CER encourages 2 modifications in the traditional processes for development and commercialization.

The first involves the compounds and assets developed. With increasing challenges to commercial success in certain drug classes and therapeutic areas, manufacturers are recognizing the need to invest in more targeted medications focused on subpopulations (be they demographic, genetic, or otherwise defined).

The second shift, which is structural and operational, is that drug manufacturers are seeking product differentiation earlier in the development pipeline. This is not surprising, because many industry leaders have acknowledged for some time the need to adjust course. Comments dating as far back as 2006 reflect clear understanding that the pharmaceutical business model is at a crossroad.

Reimagining Their Customer Base

Another change we are seeing is in the way manufacturers are engaging their customers. As payers become savvier, drug manufacturers are turning more of their energy toward satisfying evidentiary requirements, and focusing less on their traditional customer base—physi-

cians and patients. A recent article on drug development summarized this change, suggesting that “physicians have been demoted from key decision-maker to stakeholder, while payers have gone from stakeholder to key decision-maker.”¹⁵

In line with this shift, AstraZeneca recently announced a collaboration with WellPoint to conduct real-world CER studies using a range of electronic health data.¹⁶ With a focus on chronic conditions, their goal is to maximize value by identifying and encouraging the most efficient use of medications. Although it presents a meaningful risk to AstraZeneca brands (because they may not always fare well in the research), this unique partnership acknowledges the need for drug manufacturers to work with payers to meet their increasingly stringent effectiveness standards.

Transform and Redeploy Clinical Research Expertise

For some companies, there are more seismic changes afoot, which may lead to a very different pharmaceutical sector. For example, Pfizer recently announced its plans to close its research facility in Kent, England. This move was part of an effort to refocus its research and development program, shifting away from urology and internal medicine to maintain or expand focus in immunology, oncology, neuroscience, and inflammation.¹⁷ Pfizer CEO Ian Read explained, “We continue to closely evaluate our global research and development function and will accelerate our current strategies to improve innovation and overall productivity.”¹⁸ In other words, industry leaders are responding to the greater demand for different kinds of scientific evidence with significant structural and organizational changes.

Conclusion

The rise in CER is encouraging interesting and important changes across the healthcare sector. The federal CER investment is but one indicator of the demand for more comparative evidence. The private sector has also begun to focus more on CER-generation, suggesting that regardless of the direction of government funding, the marketplace is actively seeking inventive ways to create and apply this evidence. With more data available, payers are experimenting with coverage and reimbursement policies that promote the use of high-value products. In turn, manufacturers have begun to rethink ways of developing products that meet payers’ high standards for value.

The cumulative effect of this increase in CER may not be fully understood for some time. However, the

business environment is already changing as various participants find their role and support their value proposition. For interested parties, there is a great deal of opportunity to help shape the way scientific evidence is used in healthcare decision-making in the future. ■

Author Disclosure Statement

Mr Ali, Ms Hanger, and Dr Carino have reported no conflicts of interest.

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