What is Comparative Effectiveness Research and What Will It Mean for Patients, Physicians, and Payors?

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Authors:

Raj Sabharwal

Robert Giffin

Sneha Rangarao

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With the launch of the Patient-Centered Outcomes Research Institute (PCORI) in September 2010, the nation will embark on a new venture that has the potential to substantially reshape American health care. PCORI was included in the health care reform law enacted in March 2010, the Patient Protection and Affordable Care Act (PPACA)[1], with the goal of promoting and funding comparative effectiveness research (CER). But there are some important issues that must be addressed moving forward. How does CER differ from the way clinical and health services research are currently conducted? How does CER change the roles of the different stakeholders involved, e.g., patients, providers, researchers, payers, and product developers? How will it be decided what studies need to be done? And how will it be possible to develop the workforce and infrastructure with which to conduct all of this new research?

PCORI creates an enormous opportunity for the transformation of health care to a system that is based on the systematic creation and use of evidence in the delivery of care. However, there is great uncertainty about how PCORI will operate, what its priorities will be, and how it will lead this transformation. To shed light on these issues, this paper will provide an overview of CER and PCORI, review historical CER efforts, highlight some of the important questions and misconceptions that have been raised, and describe the challenges and strategic options that will be faced by the new institute.

Why So Little Evidence?

For many in the health care field, but often not those outside, it is increasingly understood that much of the practice of medicine is based on limited evidence of what actually works and what doesn't. Despite billions of dollars of clinical research funded largely by the National Institutes of Health (NIH) as well as the pharmaceutical and medical device industry, for many health conditions there is relatively little reliable evidence available for physicians and patients in selecting among multiple treatment options. As an example, physicians perform a wide array of therapeutic strategies to treat prostate cancer—from surgery to implantable radioactive seeds and external radiation regimens—with little knowledge of their comparative value or the impact on patient outcomes and quality of life.[2]

In addition, many of these new technologies, such as positron emission tomography (PET) imaging, stereotactic radiation, and next generation cancer drugs are much more expensive than existing treatments. For example, national expenditures on radionuclide imaging (RNI) increased from $6.6 billion to $13.7 billion between 2000 and 2005, despite a technical panel convened by the American College of Cardiology Foundation finding that there was insufficient evidence to enable agreement on the appropriate use of RNI.[3] The elimination of practices that offer little or no benefit to patients could provide significant cost savings.

The evidence required to guide clinical decision making about treatment choices is often very different from what most current clinical studies provide. Many studies are designed with other objectives and requirements in mind, such as obtaining Food and Drug Administration (FDA) approval or advancing the

knowledge of a drug's physiologic or metabolic effects. Many are poorly designed or executed—for example, having an insufficient number of patients, utilizing intermediate endpoints of limited value, or taking so long to complete that the results are irrelevant.

CER can be thought of as a set of methods that collectively generate research which is directly relevant to decision-making by patients and their doctors. First and foremost, studies must provide information that allows for clear and straightforward comparisons across a range of treatment options. The research must ask the appropriate questions and be conducted in a real-world clinical practice setting in order to shed light on these questions, suggesting a very different context and design than exists for most trials conducted today. Patients are central to the decision-making process in the design of CER clinical trials. Outcomes that are most important to patients may be different from those assumed to be important or most reliable by researchers and physicians. Finally, we must acknowledge that traditional randomized clinical trials—the gold standard in clinical research—may not always provide the information needed in the timeframe or context that would prove most useful to clinical decision-making. Implementing CER will require more flexible approaches, including pragmatic or adaptive clinical trial designs, observational research, and perhaps a combination of approaches that will best answer the critical questions.

Why PCORI Now?

PCORI was established to facilitate and fund the development of CER. The underlying premise of PCORI is that such research is not adequately being produced by the current research enterprise. Its goal is to rectify this by: (1) increasing the number of studies that are conducted to develop comparative evidence and (2) conducting clinical trials that differ in crucial ways from traditional trials. It also assumes that the current system has the capacity to conduct these studies on a large scale or at least that the capacity to do so can be developed. There are, however, important obstacles to generating studies that will better inform and influence current clinical practice. Intellectual and financial biases are built into the current clinical research enterprise. Comparative studies may threaten producers and users of expensive therapies that may offer no benefit over existing alternatives. Few researchers have experience in key aspects of CER such as engaging patients in trial design. And the academic-based research enterprise has limited access to and experience in undertaking research that emulates real-world, community practice.

The critical challenge for PCORI will be to determine exactly how to move the CER enterprise forward and overcome the obstacles identified above. In the long run, this will entail a significant transformation in the way we currently conduct research and deliver health care.

THE EVOLUTION OF FEDERAL CER POLICY

Historical Efforts

It is important to note that federal involvement in CER and health technology assessment is not new. Efforts reach back to the origins of Medicare and Medicaid and have included a congressional Office for Technology Assessment, which was abolished in 1995, as well as a National Center for Health Care Technology within the Department of Health and Human Services (HHS), which sunsetted in 1981.[4] A key

starting point for the recent dialogue regarding CER was the Medicare Modernization Act of 2003 (MMA), which authorized the Agency for Health Care Research and Quality (AHRQ) to conduct and support research with a focus on comparing the outcomes and effectiveness of different treatments and clinical approaches, as well as communicate its findings widely to a variety of audiences.[5] This coincided with the inclusion of a prescription drug benefit in Medicare and the expansion of other federal health initiatives, leading to specific priority areas of research for AHRQ.

While MMA provided an important first step for expanding federally supported CER efforts, many stakeholders noted the limitations of AHRQ in supporting only systematic reviews and syntheses of existing literature, as well as the relatively limited amount of funding provided to the agency (approximately $30 million annually).[6] This led to increased consideration among policymakers for the establishment of a national entity devoted to CER. Suggestions for the structure of such an entity varied from its placement within AHRQ, as a new agency within HHS, as a quasi-governmental institute, or within the private sector. [7]

Following a series of legislative proposals throughout the late 2000s that called for the creation of some type of CER entity, in 2009, the Obama administration dramatically advanced federally supported CER efforts by including $1.1 Billion in funding for CER as part of the American Recovery and Reinvestment Act (ARRA), more commonly known as the economic stimulus package. [8] This one-time funding was primarily distributed among AHRQ, NIH, and HHS Secretary, and included the establishment of a Federal Coordinating Council for CER (FCCCER) and funding for a new Institute of Medicine (IOM) effort to develop a prioritized listing of CER research topics through an open and broad stakeholder driven process. The efforts of the FCCCER also led to a concise and widely accepted definition for CER that is likely to be applied by PCORI in future work.

> CER is the conduct and synthesis of research comparing the benefits and harms of different interventions and strategies to prevent, diagnose, treat and monitor health conditions in "real world" settings. The purpose of this research is to improve health outcomes by developing and disseminating evidence-based information to patients, clinicians, and other decision-makers, responding to their expressed needs, about which interventions are most effective for which patients under specific circumstances.[9]

CER and the Patient Protection and Affordable Care Act (PPACA)

In their final health reform bills, both the Senate and House included the establishment of a CER entity, with the key difference being that the House version called for establishing such an entity within AHRQ while the Senate bill supported the formation of a non-profit institute. The final legislation largely followed the language from the Senate bill in founding the non-profit PCORI and its multi-stakeholder board.

This new public/private non-profit entity will be governed by an independent, 19-member board that will consist of federal and state agency representatives, including the directors of the National Institutes of Health (NIH) and Agency for Healthcare Research and Quality (AHRQ), as well as stakeholders representing patients and health care consumers, physicians and providers, private payers, product manufacturers and developers, and quality improvement or health services researchers.[10] While the members of the board are currently being determined, it is clear that a number of important questions remain unanswered regarding the activities of the Institute and future federally supported CER.

In addition, PPACA clearly states that the Institute and its research activities will be financed through the creation of a Patient Centered Outcomes Research Trust Fund. Initially, the trust will be funded through general appropriations of $10 million in 2010, $50 million in 2011, and $150 million in 2012. Beginning in 2013, in addition to the $150 million in appropriations, the trust will be supplemented by fees imposed on health insurance and self-insured health plans. Interestingly, PPACA clearly terminates funding for the Institute from the trust fund after fiscal year 2019. This time limitation creates doubts on the source of future funding and existence of the Institute past that date.

The Institute is also tasked with identifying national research priorities for CER as well as establishing and carrying out a research project agenda. This includes the ability to enter into contracts to manage the funding and conduct of research, with a preference for such contracts given to AHRQ and NIH. In addition, PCORI will be responsible for establishing a standing research methodology committee to develop standards for clinical comparative effectiveness. The Institute is also directed to appoint advisory panels who are experts in carrying out randomized clinical trials under the PCORI's research project agenda to advise the Institute on research designs or protocols, including important patient subgroups. In addition, specifically for research on rare diseases, the Institute is directed to appoint an expert panel to assist in research study design and review the relative value and feasibility of conducting the research.

To ensure transparency, credibility and access, the Institute is mandated to provide a public comment period prior to the adoption of its national priorities, research project agenda and methodological standards developed and updated by the methodology committee. This comment period also applies to findings from the Institute's peer-review process and draft findings from reviews of existing research and evidence. Further, within 90 days after the conduct or receipt of research findings, the Institute must make the results of the study or assessment available to clinicians, patients, and the general public. Such findings must be conveyed in a manner that is useful to these groups in making health care decisions including the limitations of the research, and when appropriate discuss what further research may be needed.

Notably, the research findings may not include practice guidelines, coverage recommendations, or payment or policy recommendations. In addition, while Medicare, Medicaid and other federal agencies are not prohibited from using the findings to inform payment, coverage and treatment decisions, the findings alone may not be used to deny coverage.[11]

Finally, the Institute is required to provide an annual public report to Congress and the President. This report is to include a description of the research projects, priorities and methodological standards

developed in the preceding year, the research project agenda and budget of the Institute for the upcoming year, the names of individuals involved in any peer-review processes, and other relevant information.

WHAT CER WILL LOOK LIKE IN PCORI

The definition of CER developed by the FCCCER explicitly states that comparisons should apply to "real-world settings", further differentiating CER from traditional forms of clinical research. This allows the information generated by CER to inform decision-making among physicians and patients in determining treatment choices. To meet this requirement, CER must include direct comparisons of available interventions and be disseminated in a manner which is understandable to varying types of decision-makers.

CER includes a variety of different approaches, such as reviews of existing studies to synthesize the available evidence, observational data analyses, and randomized clinical trials. It may also include combinations of these approaches. The proportion of each in the portfolio of studies funded by PCORI is unknown and will depend on its strategic assessment of how to achieve its goals. The characteristics of each approach, as well as some of the pros and cons, are discussed below.

Randomized trials

Randomized clinical trials are considered the "gold standard" in terms of developing definitive clinical evidence. If a clinical trial is well designed and executed—e.g., it includes a sufficiently large sample size, measures clinically useful outcomes, compares relevant treatment options, yields reliable data, and meets other criteria—then it may provide valuable comparative evidence. But clinical trials do not automatically provide useful results; that depends on how well they are designed and executed for the purpose of providing evidence for decision making.

Clinical trials have some inherent drawbacks for evaluating comparative effectiveness. They are often short in duration and may fail to evaluate longer-term outcomes that are important to patients and clinicians. In addition, they generally have limited study samples and may fail to detect some rare adverse events. Recruiting sufficient numbers of patients for a study of a rare disease can be very difficult. There are even certain conditions for which randomization is unethical. Finally, randomized clinical trials are very costly, may require large study populations, and can take many years to complete. For example, the well-known Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack (ALLHAT) study of hypertensives and lipid-lowering medications included over 42,000 patients at a cost of over $120 million, and results were published nearly eight years after the first patient was enrolled in the trial.[12]

Clinical trials for the purposes of CER, also known as practical or pragmatic clinical trials, can be even more difficult, more expensive, and take longer to complete than traditional clinical trials. There are a range of possible reasons for this. Such trials are likely to include more comparators in order to provide a realistic assessment of treatment options and they are likely to include longer term outcomes that are important

in treatment decisions. The need to assess real-world clinical practice will necessitate relaxed inclusion and exclusion criteria, meaning that there will be a wider range of severity and co-morbidities among the patients and therefore more statistical noise in the data.[13] These studies will also require additional time to engage and train community practitioners to participate in studies and to engage patients in the study design process. Some of the limitations of clinical trials can be mitigated through statistical techniques, such as cluster randomization and Bayesian methods which enable researchers to utilize prior knowledge of treatment effects to reduce the size of study sample required.[14]

Observational Studies

Observational studies can provide important insights into the comparative effectiveness of alternative treatments. These studies typically follow patients over a specified period of time to determine possible associations between a patient's exposure to an intervention and his or her health outcomes. Although observational studies can also be prospective, they often utilize patient information which resides in a database, such as Medicare claims data.[15]

Observational studies have several key advantages. Because they often utilize data from an existing database, they can be cost-effective to conduct. The can be conducted using large scale databases that may follow patients for long periods of time, which increases their ability to detect rare adverse events and long-term outcomes.

The development of a national information infrastructure that includes widespread use of electronic health records, the ability to share information across networks, the integration of clinical research functionality into these systems, and the sophistication of analytical methods increases the opportunities for richer and more useful observational studies. Many important efforts are currently underway to develop new methods and learn how to better capture existing data for comparative analysis from such approaches.

AHRQ's Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) network, for example, conducts CER through a network of 13 centers. The network focuses primarily on observational studies that utilize innovative methods for mining existing databases and developing registries and other sources of information for CER. DeCIDE studies have used Medicare Part D data screening to evaluate adverse drug events; studied the use of β-blockers in heart failure using electronic clinical and administrative data; examined the diffusion, effectiveness and safety of a new diabetes treatment in its first year using a large administrative database; and studied the management of chronic obstructive pulmonary disease patients using a combination of regional pharmacy data. The FDA Sentinel Initiative is the most ambitious of these electronic approaches, with a goal of accessing clinical records for 100 million patients in order to identify drug safety issues.

Observational studies also have inherent limitations, including their susceptibility to selection bias and the difficulties of adequately accounting for confounding factors in the absence of randomization. New methods are useful in addressing these problems, for example, propensity score adjustments and instrumental variable analysis. But the most important limitations are not analytical, but practical--the ability to link data from multiple sources, privacy issues, and the frequently poor quality of the data that is

extracted from these databases. As a result, observational studies are still limited in their ability to generate definitive comparative effectiveness results, and there are cases in which compelling evidence from an observational study is reversed upon the completion of a methodologically rigorous randomized controlled trial. For example, while observational studies showed benefit from hormone therapy, subsequent clinical trial results demonstrated both a lack of effectiveness and significant adverse effects.[16] And while observational studies are cost-effective compared to clinical trials, they can also be large and complex. For example, among the CER studies identified by AcademyHealth, typical registry studies ranged from $800,000 to $6 million and other large observational studies were in the $2 to $4 million range.[17]

Observational studies can be especially important as a supplement to prospective trials. Because of their large sample sizes, they can identify important signals missed by clinical trials, and can be particularly helpful in identifying potential subgroup differences in responses to therapies. However, it is unlikely they will substantially reduce the need for prospective randomized trials in the near term.

Systematic Reviews

Systematic reviews use a defined process to synthesize and evaluate the findings of existing research on a particular intervention. Such reviews typically address explicit research questions, include specific criteria for the inclusion or exclusion of a research study within the review, and provide a detailed narrative summary of the research findings. Reviews that include quantitative analysis of the studies are known as meta-analyses. Many of the studies included in a systematic review are traditional RCTs. Systematic reviews represent a less expensive alternative form of CER—typically costing $200,000 to $350,000.[18] Still, systematic reviews are only as good as the studies that are available for their review; generally speaking, these are the studies which have failed to provide the evidence necessary for clinical decision making across the great majority of conditions.

One example of these limitations comes from a recent Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) meeting. Preliminary results from a review of radiation therapies for the treatment of localized prostate cancer suggested that “definitive benefits of radiation treatments compared to no treatment or no initial treatment for localized prostate cancer could not be determined because available data were insufficient”. [19]

This is not to say that systematic reviews cannot be useful for decision making. These studies frequently clarify the evidence and can lead to genuine change in practice. Even when the results are indeterminate, these studies define research gaps that can direct scarce resources to the most important gaps in knowledge.

CHALLENGES FOR PCORI

The challenges facing the new board and staff of PCORI cannot be overstated, as expectations are high, resources are limited, and external pressures abound. The priorities and research findings of PCORI will have enormous ramifications for physicians, hospitals, drug and medical device companies, as well as both

public and private payors and purchasers of health care. Patient advocacy and rare diseases organizations also have high hopes that PCORI will target their needs. The research community has similar expectations that PCORI will support those areas of interest to researchers. Finally, the work of the Institute will take shape in a highly charged political atmosphere in which there are suspicions within Congress and the public about its real purpose.

Organizational Issues

Before PCORI begins to tackle its core mission--determining research priorities, developing methodologies, setting standards, and funding research—the non-profit organization must be incorporated, adopt bylaws, and determine its internal structure, staffing, operational approaches, decision making processes, and initial priorities.

A key decision must be made with respect to the relationship between the board and the methodology committee. The law requires that the Comptroller General, rather than the PCORI Board, appoints the Methodology Committee and clearly specifies several deliverables--the development of methodological standards, a translation table, and periodic report with recommendations. However, the actual independence of the committee is unclear. Many in the research community believe that a strong and independent methodology committee will ensure the integrity and independence of the scientific process for conducting CER. On the other hand, the methodology committee will be composed primarily of research scientists and may lack the diverse stakeholder composition of the board. Should it function independently, its lack of patient, practitioner, and other perspectives may lead to concerns about researcher bias. Ultimately, board decisions about priorities and methodology committee decisions regarding methods are interdependent, and will require close collaboration. The challenge for the Government Accountability Office (GAO) is to appoint leaders of each body who are capable of close and constructive collaboration.

Policy decisions

Once a functioning organization is established, there are a range of decisions the Institute must consider in order to fulfill its mission. The law specifies certain objectives and mandates several broad areas of activity and deliverables for PCORI, such as priority setting, the development of research standards, and the creation of training programs. Still, beyond these specifics, the law gives PCORI a great deal of discretion in defining the strategies it may pursue to achieve its objectives. Several key strategic considerations to be addressed by the board are discussed below.

Mix of systematic reviews, observational research, and randomized trials. Definitive head-to-head comparative studies will generally require new clinical trials. However, there are many questions, such as those on long term outcomes and rare events, which may only be properly answered through observational studies. As noted previously, systematic reviews, observational studies, and other CER methodologies can be used to refine clinical trials by identifying appropriate hypotheses and focusing the study design (future research paradigms may utilize all of these in combination to achieve the most efficient and effective research). Given short-term limitations in funding and the known difference in costs

between the types of CER methods, PCORI will need to consider the most useful mix of studies that should be pursued.

Infrastructure development. Some have argued that the current capacity to undertake large scale investments in CER is insufficient and that PCORI should take steps to enhance this capacity, even though this is not explicitly part of its Congressional charge. This might include creating support mechanisms to engage more physicians in clinical research and addressing aspects of the broad clinical research enterprise that make clinical research expensive, slow, and difficult to conduct. Examples include the complexity and slowness of the human subjects review process, complex and legalistic informed consent procedures, the limited numbers of patients willing to engage in clinical studies, and the related difficulties experienced by clinical trialists in recruiting patients. In order to address the "real world" practice requirements of CER and to expand patient recruitment, it will be necessary to find new ways to engage and support community practitioners in conducting research. While the law specifically charges AHRQ with training researchers, PCORI may supplement such training, and in particular, focus on training the new cadres of community-based practitioners.

Scaling up CER nationally. While the methodology committee will define recommended approaches and create standards for conducting CER, there are important questions about the health care system's ability to act on those recommendations. Note that there is a great deal of emphasis on engaging patients in CER—the name of PCORI itself, as an example. But patient engagement has been substantially absent from the vast majority of clinical research to date, and few clinical researchers have expertise in engaging patients. Given this lack of expertise, there is a risk that clinical trials will pay lip service to patient engagement without substantively addressing the key issues. A similar concern is the need to conduct CER under real-world practice conditions. Given that so little research is currently performed in this type of setting and that the capacity to accomplish it is unknown, there is a risk that this aspect of CER will be frequently overlooked.

Prioritization of clinical conditions and treatments to study. The IOM priorities report[20] provides a useful, preliminary assessment of priorities, but its methodology is not well-suited to PCORI. The Institute will need to develop a rigorous and transparent process for prioritizing research based on clearly defined and publicly vetted criteria, such as the number of people that are affected, the severity and quality of life implications of the condition, the degree of uncertainty about alternative treatments, the rate of technological development within the field, the potential difficulty and cost of obtaining definitive comparative evidence, and the costs of alternative treatment options. In addition, the Institute will need to balance these objectives against the expectations of the public and other stakeholders and the needs of patients with rare diseases. PCORI must also consider the overall portfolio of projects it undertakes and determine the need for early successes with longer term, foundational outcomes.

Leveraging PCORI's research dollars. Even with an estimated $650 million[21] in sustained annual funding in future years, the amount of research that PCORI can directly fund will be limited. Definitive, head-to-head comparative trials are likely to require large trials, perhaps in combination with prospective observational trials. When viewed next to NIH funding—the National Cancer Institute and National Institute of Allergy and Infectious Diseases had budgets of $4.8 billion and $5.1 billion, respectively[22]—and

considering the magnitude of the task, PCORI funding is not large. There are several strategies PCORI could utilize to leverage its direct research dollars. It could for example, collaborate with NIH, AHRQ and private sector research sponsors in sharing the costs of the trial itself by providing limited funding for study design and coordination. PCORI could also use part of its funding to support proof-of-concept studies that are meant to demonstrate approaches to conducting CER that could be sponsored by other private and public sponsors. Another strategy that has been discussed includes efforts to harmonize FDA registration trials and CER studies in order to reduce the frequent overlap in parallel sets of pre- and post-marketing studies.

Balancing independence versus collaboration with other federal entities. PCORI is statutorily obligated to give preference in funding research activities to AHRQ and NIH. However, funding studies through these agencies without broader collaboration would appear to be a lost opportunity. At the same time, these agencies have set research priorities, agendas, decision-making approaches, and dedicated funding streams. CER currently represents a very small fraction of NIH funding, and it is unclear how clinical trials that embody the elements of CER will be received by NIH study sections. At minimum, CER could affect longstanding approaches to prioritizing, funding and conducting clinical research. PCORI may present an opportunity to influence the research culture within NIH in ways that result in better alignment between traditional and CER clinical studies, but depending on how PCORI and NIH finalize their working relationship the emergence of two parallel research tracks within NIH is a possibility.

Asserting a coordinating role. An even more fundamental question has to do with current approaches to the research culture. For many clinical conditions, there may be dozens to hundreds of clinical studies, yet little useful comparative evidence to guide clinical practice. One reason for this is what is often described as the "cottage industry approach" to clinical research in the US; the vast majority of clinical trials are initiated by academic investigators or industry sponsors in order to answer a narrow question with little regard for how it will contribute to the broader understanding of the available treatment options. This uncoordinated approach can lead to duplication of efforts and wasted resources while failing to provide needed evidence. PCORI represents an opportunity to impose some order on the studies being conducted by defining the needed studies in advance and encouraging researchers to collaborate. This will be challenging, as it requires breaking down entrenched silos, cultures, and longstanding funding conventions.

CER and personalized medicine. There are concerns that the goals of identifying optimal therapies through CER will focus on the "average" patient and thus obscure important subpopulation differences. While these concerns can be addressed methodologically, adequately detecting and addressing subpopulation differences may increase the size and cost of studies. Additionally, usage of information from CER studies may attempt to apply results to all populations inappropriately, which would be beyond the control of PCORI. The Institute will need to consider explicit strategies for communicating results to minimize inappropriate use of study results.

IMPLICATIONS FOR PATIENTS, PHYSICIANS, AND PAYORS

The immediate impact of PCORI will be limited by the lead time required to establish the organization and determine research priorities, as well the length of time to fund and execute studies. On the other hand, some expect PCORI to attempt to achieve early successes by funding evidence reviews or fast track observational studies in high priority conditions or treatments. If useful new evidence comes from these early attempts, we are likely to see an immediate impact on clinical practice within those clinical areas and increased public trust for CER.

In the long-term, the impact of PCORI may profoundly impact the clinical practice of medicine and the health care delivery system. PCORI has the potential to not only improve evidence within the specific areas it funds; it could, for example, generate an entirely new paradigm for the development of clinical evidence that reaches across all of health care delivery, into the government-university-industry research establishment, the regulatory arena, and clinical practice. This could ultimately help to shape a new "learning health care system" in which health care outcomes are systematically measured through practice and the knowledge gained is rapidly translated back into practice. There has been gradual movement in this direction, but PCORI's leadership and models could provide the impetus for accelerating these changes. It must be noted, however, that until such approaches are embedded in the health care reimbursement structure, movement in this direction will be severely constrained.

PCORI and CER will potentially impact all Americans and present opportunities and challenges to many diverse stakeholders in the health care research and delivery systems. We focus attention here on three key groups that will have key roles in the outcomes of CER and PCORI—patients, physicians, and payors. Some key implications and considerations for each of these groups are discussed below.

Patients. Patients stand to benefit from CER and PCORI in several ways. Most importantly, the generation of new evidence and translation of that evidence into clinical practice will enable patients and their physicians to make more informed decisions about treatment options. In addition, increased clinical research resulting from PCORI will enable more patients to participate in studies and provide early access to potentially beneficial treatments. If the activities of PCORI raise the bar on the quality and relevance of studies that are conducted, fewer patients will be subjected to research that provides limited information on the value of medical treatments. As researcher Robert Califf has pointed out, conducting massive amounts of studies on human subjects of no apparent scientific value is a resource issue, an ethical issue, and depending on the risks involved, potentially a matter of human rights.

It is difficult to envision downsides for patients if the research that is conducted meets the goals set forth in PCORI legislation. Many have raised concerns that CER may be at odds with personalized medicine, as the search for comparisons of treatments may too often focus on the responses of the "average" patient, and obscure the heterogeneity of response to treatments widely experienced in practice. While this is a legitimate concern, and one that the Board should be vigilant about addressing, there is nothing in the law or within the research community that would suggest that it wouldn't be fully addressed. The potential for inappropriate application of CER information once released to the public does exist, and should be

addressed proactively through the communications strategies employed by AHRQ for the dissemination of PCORI findings.

Physicians. Like patients, physicians and other providers will benefit from the generation of new evidence that will enable them to make more informed decisions with their patients about treatment options. Systematic reviews of existing evidence may also make it far easier for physicians to assess and explain therapeutic options to patients and gain the confidence of patients with regard to those choices. The dissemination of definitive treatment information from PCORI may also speed the adoption of evidence into clinical practice.

Because CER is to be conducted in real-world practice settings, community physicians are likely to become far more involved in research, although it is unclear exactly how this will take place. Medical centers may reach out to community physicians to involve them in research. Specialty organizations may utilize and expand practice based networks as a platform for clinical research. However the process evolves, it holds the potential to reduce the divide between clinical practice and research.

Payors. Payors share with patients and physicians the need for evidence to inform clinical decision making within their insured populations, and they face the same inadequate evidence. In addition, payors utilize comparative evidence in making coverage decisions in an effort to deliver high value health care. While a number of large private payors develop their own research to supplement existing evidence, better evidence that is more transparent and widely accepted will enable payors to make better coverage decisions.

Payors also have unique opportunities to participate in the CER enterprise by bridging research and practice. Many payors have enhanced access to patients and providers, information systems that enable them to track medical care and outcomes over time, and the ability to communicate directly with patients. These characteristics present excellent opportunities for conducting observational studies, both retrospective and prospective, and to efficiently conduct clinical trials. Payors are also uniquely positioned to utilize the evidence they generate through clinical management, preventive care programs, and reimbursement incentives. Interest among payors is evidenced by the HMO Research Network's participation in the AHRQ's DEcIDE network to conduct studies focused on the development of CER within managed care systems.

Public payors such as the Centers for Medicare and Medicaid Services (CMS) and the Department of Veterans Affairs (VA) share the motivations of the private payors, as well as some of the advantages in participating in CER. While CMS has limited statutory authorities for using comparative evidence for coverage decisions, this may evolve as the strength of comparative evidence improves over time. CMS's existing data sources are already widely used to conduct observational studies. The VA uses comparative evidence to determine appropriate care for its patients and shares certain advantages in conducting CER with private payers--a closed provider network, and defined population, and well developed informatics for tracking and studying patient treatments over time.

Public and private payors will clearly be important users of the information generated by CER, and over time the research opportunities that they possess will likely lead to additional involvement in the performance of CER studies.

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