Improving Quality and Efficiency in Health Care through Comparative Effectiveness Analyses: An International Perspective

by Gerry Fairbrother, Ph.D.; Ellen O'Brien, Ph.D.; Rosina Pradhananga, M.P.H.; Kalipso Chalkidou, M.D., Ph.D.

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Executive Summary

The combination of rising health care costs, efforts to achieve universal or near-universal coverage globally, and growing drive for better outcomes brings an urgent demand to spend health care funds efficiently and in accordance with each country's priorities. A response to such demand requires, first, an understanding of what technologies and interventions (drugs, devices, procedures, diagnostics, and health care services) increase the quality and value of health care and, second, knowledge of the policy levers that encourage health care systems to adopt appropriate technologies. Comparative Effectiveness Research (CER) and Health Technology Assessment (HTA) are important tools used in different ways by countries to achieve these goals.

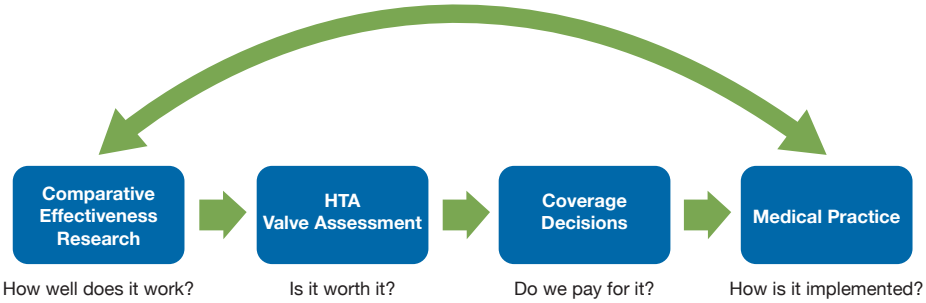
CER is primary research that compares the effectiveness of alternative interventions, with the intent of determining whether one technology or service works better than another for a given population or group of patients. In the United States, CER studies have been publicly funded for a number of years;[1] however, public investment significantly expanded beginning in 2009. In contrast, the publicly financed comparative effectiveness entities in most other high income countries are focused on HTA, which typically involves coupling the synthesis of existing evidence on clinical comparative effectiveness with an assessment of the cost-effectiveness.

This paper provides an overview of HTA activities in Europe, Canada, and Australia and examines the new public investments in CER in the United States. It also seeks to place the new United States federal investments in evidence generation in the context of the rather different investments that are predominantly focused on HTA in other industrialized countries.

Overview of CER and HTA Activities in the United States and Other Countries

Figure 1 illustrates a simplified pathway from CER to medical practice to demonstrate the relationship between

Figure 1: Comparative Effectiveness Decision Framework: From CER to Coverage and Practice



Source: Based on Docteur and Berenson. How Will Comparative Effectiveness Research Affect the Quality of Health Care? 2010.[2]

CER and HTA activities. CER can provide evidence to inform patients' medical decisions and clinicians' recommendations to their patients, but CER also may feed into HTA and then into health plan coverage decisions, which shape care delivery and clinical decisions.

In high-income countries other than the United States, most comparative effectiveness analysis activities focus on HTA, the second step in Figure 1 and are conducted by government agencies. In essence, HTA programs in Europe, Canada, and Australia, among others, assess the comparative clinical effectiveness of technologies while asking if a particular technology is worth its cost to that country's national health system. Clinical practice guidelines for incorporating the results of these analyses are often developed concurrently with HTA. Policy decisions about what technology or service is to be covered by insurance then follow.

Medical practice in most countries is affected in a direct way by policy decisions on coverage by (often national) insurance and other payment policies, which flow from HTA. The result might be expanded access to new technologies at no charge or restricted access to new technologies either through refusal of coverage or placement of limits on use to a subset of the population.[3] In contrast to other nations examined in this report, payment and coverage decisions in the United States are made by a complex mix of decisions by private health plans, state Medicaid programs, and occasional national coverage decisions in the Medicare program in a decentralized insurance system; each develops its own appraisal of a technology's value and, as a consequence, decisions may vary widely across plans and payers.

HTA in Europe, Canada, and Australia

The topics and scope of HTA activities vary significantly across countries. For example, some HTA entities focus exclusively on the relative value of drugs (Australia), while others concentrate on drugs as well as medical devices and other health care interventions for diagnosis and treatment. Some also develop or deal with clinical practice guidelines (the United Kingdom and Germany). The United Kingdom's HTA body, the National Institute for Health and Care Excellence (NICE), also conducts assessments of public health interventions and programs and, more recently, has begun developing guidance on social care. In France, the HTA organization has a wide-ranging remit: from reviewing the value of pharmaceutical products to hospital accreditation and clinician certification.

Analyses of cost-effectiveness are an important feature of HTA. Cost-effectiveness analysis using the Quality Adjusted Life Year (QALY) as the main outcome measure is the norm in Canada, Australia, the United Kingdom, and Sweden, with France recently also considering this

metric. Many countries then set a threshold amount that they are willing to pay for a QALY; the threshold can vary considerably across countries. For example, in the United Kingdom the cost-effectiveness threshold range is about $34,000 to $51,000 per QALY, while in Sweden the range is about $77,000 to $85,000 per QALY (both in 2014).[4,5] Thus, in these countries, if the cost of new technology is under the threshold, it would be incorporated in the insurance coverage. Since overall health budgets do not increase with the adoption of a technology with a cost per QALY value above the threshold, inclusion of such technology would need to be at the expense of other health care expenditures. Although QALY is broadly accepted as a measure of health benefit, debate continues about its exclusive use, particularly because it does not capture the social value of interventions nor quality of life.[6,7]

CER and PCOR in the United States

The expansion of publicly financed HTA activities in most other industrialized countries stands in contrast to the United States experience. In Europe, Canada, and Australia, an authoritative body—publicly financed, transparent, and at arm's length from payers—synthesizes and assesses existing research, offers an appraisal of alternative health care interventions, and makes recommendations for coverage. In the United States, HTA has been fragmented, decentralized, and uneven. Although many federal health care agencies produce or use CER, there had historically been no government agency (or other publicly financed entity) to coordinate research.

However, significant new public investments in CER were made in 2009 through The American Recovery and Reinvestment Act (ARRA) ($1.1 billion)[8] and in 2010 through The Affordable Care Act (ACA) with the establishment of the Patient-Centered Outcomes Research Institute (PCORI) as an independent nonprofit corporation (with an estimated $3.5 billion available over 10 years).[9] These new federal investments focus on improving the quality and relevance of primary research available mainly to patients and their care providers but also to health plan decision-makers and policy makers.

The new investments are designed to reorient research to make it more relevant, especially for patients. In fact, the organizing vision for PCORI is "research done differently."[10]

The new CER effort is designed to address patients' questions, to assess the outcomes of interventions in real patients and real-world settings, and to learn about what forms of health care are most effective in improving health. Furthermore, it focuses not only on generating new evidence, but also on uptake of that evidence into decision-making. The term patient-centered outcomes research (PCOR) was meant to emphasize that the CER they fund focuses on topics and outcomes that are highly relevant to patients, draws on patient data, and engages patients in the research and decision-making processes by answering questions such as:

- "Given my personal characteristics, conditions, and preferences, what should I expect will happen to me?"
- "What are my options and what are the potential benefits and harms of those options?"
- "What can I do to improve the outcomes that are most important to me?"
- "How can clinicians and the care delivery systems they work in help me make the best decisions about my health and health care?"[11]

PCORI's emphasis is on generating new evidence, which requires funding prospective trials or observational studies of patient outcomes from data available in insurance claims systems, electronic medical records, or clinical registries. Methodological rigor is a central part of PCORI's work.

Given how recently PCORI was established and PCOR defined, the field is evolving and maturing. Examining HTA processes in other countries reveals several similar dimensions to their processes which can yield some interesting observations for the United States as we continue to evolve our approach to evidence generation and use. Specifically, this paper examines approaches to priority setting, patient and other stakeholder engagement, and dissemination of results to users.

Discussion and Concluding Thoughts

Differences in health care systems in the United States and other countries lead to variations in scope, organization, and financing of CER or HTA activities and mechanisms for moving research findings into practice and policy. Some of the HTA entities in Europe, Australia, and Canada have the authority to determine or recommend coverage decisions as well as to develop clinical guidelines for how the technology is to be implemented. These direct mechanisms for bringing into practice results of effectiveness analyses for technologies are far more complex in the United States. The PCORI strategy encourages adoption through widespread and strategic dissemination of findings as well as strategic involvement of the stakeholders who would adopt the technologies at every step of the research lifecycle.[12]

An issue for the United States, going forward, is whether the indirect approach will sufficiently induce broad system-level adoption of more effective drugs, devices, and interventions. Given the many differences between the countries included in this review, much remains to be learned of the relative strengths, weaknesses, and impact of alternative approaches to CER and HTA. The enhanced CER and HTA activities in the United States, European nations, and other countries underscore the need for overall assessments of the effects of CER and HTA on health care systems and their cost, quality, and access. Countries increasingly want to know if CER and HTA efforts are improving clinical practice, patient care, and health outcomes. Do we see appropriate use of health care technologies and delivery of evidence-based, high-value care? Have these comparative effectiveness analyses helped improve quality and efficiency in health care? There have been calls for overall evaluations in Europe. The Government Accountability Office (GAO) is conducting such an evaluation for PCORI efforts in the United States which will be released in early 2015. Evaluation of the effects of CER and HTA on the health care system is important and could inform the future direction of CER and HTA efforts internationally.

Introduction

In all health care systems, there is increasing pressure to improve health system performance—to do more to ensure that health care plans and programs pay for interventions that work—with the goals of improving health and moderating cost growth. Budget austerity, aging populations, and increased emphasis on value in health care have served to both emphasize the importance and increase the use of comparative effectiveness analyses—both evidence generation and evidence synthesis—to shed light on what works in health care and for whom.

Comparative effectiveness research (CER) is the generation and synthesis of evidence that compares the benefits and harms of alternative methods—to prevent, diagnose, treat, and monitor a clinical condition or improve the delivery of care.[13] [See Box 1 for complete Institute of Medicine's (IOM) definition.] In essence, CER compares the effectiveness of alternative treatment options, with the intent of determining whether a new technology, for example, works better than the one currently in use. In the United States, major public investments are centered on CER. In contrast, the publicly financed entities in most industrialized countries are focused on health technology assessment (HTA), which typically involves the synthesis of existing research evidence to arrive at an assessment of clinical comparative effectiveness as well as an assessment of the cost effectiveness, or value, of drugs, devices, or other interventions.

Given the recent expansion of CER investments in the United States, examining HTA processes in other countries can yield some interesting observations for the United States of similar processes as we continue to evolve our approach to evidence generation and use. Specifically, this paper examines approaches to priority setting, patient and other stakeholder engagement, and dissemination of results to users.

Box 1. Definitions

Comparative Effectiveness Research (CER)

The definition of comparative effectiveness research published by the Institute of Medicine committee (IOM) charged (in 2009 federal legislation) with identifying priorities for such research follows:

- Comparative effectiveness research is the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care. The purpose of CER is to assist consumers, purchasers, and policy makers to make informed decisions that will improve health care at both the individual and population levels.[13]

Patient-Centered Outcomes Research (PCOR)

In the United States, the Patient-Centered Outcomes Research Institute (PCORI) refers to its CER activities as "patient-centered outcomes research" in order to emphasize its strong patient focus.[14,15] PCOR involves CER focused on topics that are highly relevant to patients or that engage patients in various research-related decision-making processes.

Health Technology Assessment (HTA)

The definition used by the European Network for Health Technology Assessment (EUnetHTA), the umbrella group of HTA entities in Europe, follows:

- Health technology is the application of scientific knowledge in health care and prevention.[16]
- Health technology assessment is a multidisciplinary process that summarizes information about the medical, social, economic, and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, robust manner. Its aim is to inform the formulation of safe, effective, health policies that are patient-focused and seek to achieve best value. Despite its policy goals, HTA must always be rooted in research and the scientific method.[16]

Overview of CER and HTA Activities in the United States and Other Countries

In recent years, HTA has advanced rapidly in other high income countries—in the United Kingdom, Germany, Sweden, France, Canada, and Australia, for example. In the United States, there has been substantial expansion in public investment in CER with the establishment of the Patient-Centered Outcomes Research Institute (PCORI). The driving forces behind the creation of this new institute were: beliefs that clinical studies had, in fact, not been sufficiently comparative, nor had they mainly evaluated effectiveness in general populations (as opposed to selected groups) or addressed heterogeneity well. Further, the research objectives and approaches themselves had not been selected with consideration of patient needs and preferences (in the United States or elsewhere), let alone their engagement in the research process itself. The overriding rationale for the creation of PCORI was that more targeted, comparative, and patient-centered outcomes research (PCOR) was necessary for better decision-making at all levels.

The purpose, scope, and function of CER and HTA activities in the United States and other countries vary widely, with the differences rooted in the structure of respective health care systems. However, the ultimate goal of all of these national HTA and CER activities is the same: to improve the health of individual patients and of populations and to increase the efficiency and effectiveness of health care.

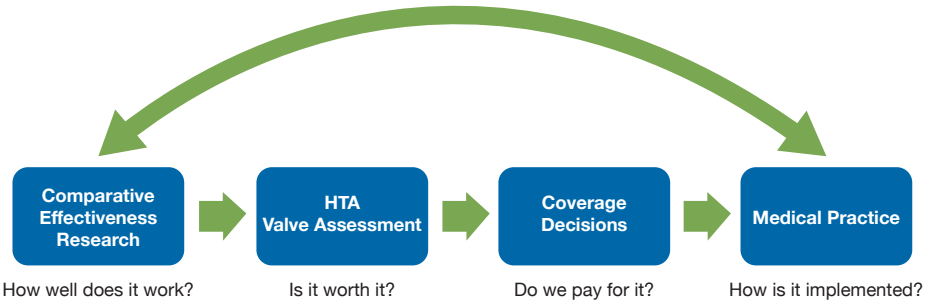
The difference between the United States and other countries in their approach to CER or HTA activities reflects, at least in part, different approaches to health care financing. In the United States, health insurance is a complex mix of public and private payers, with payment and coverage decisions made by the individual payers—including Medicare, Medicaid, as well as private insurance companies. Health insurance plans in both the public and private sectors conduct HTA, but there is little transparency in how those decisions are made and how evidence is incorporated and judged. There has been less publicly financed HTA in the United States. In Europe, Canada, and Australia, on the other hand, broadly speaking, health care is organized and financed centrally, and there is a fixed budget within which allocations

must be made. A single body or set of bodies makes decisions about the adoption of new drugs, devices, procedures, or interventions. A HTA body—with a federal mandate and federal funding—evaluates evidence and makes decisions (or recommendations) about coverage and payment decisions. Thus, the United States' approach emphasizes improving the evidence base in part to inform the HTA processes of a diverse set of payers and decision-makers. Indeed, the need for better evidence for these coverage decisions is implicit in the funding strategy for PCORI: the majority of the budget comes from a fee levied on health plans based on the number of covered lives. Our peer nations with robust HTA capabilities tend to conduct effectiveness analyses from mostly non-comparative efficacy studies, using modeling and other analytic techniques on secondary data to estimate comparative effectiveness and value.

Figure 1 illustrates a simplified pathway from CER to medical practice to illustrate the relationship between CER and HTA activities. CER can directly inform patients' medical decisions and clinicians' recommendations to their patients, but CER also may feed into HTA and then into health plan coverage decisions, which shape care delivery and clinical decisions.

In high-income countries other than the United States, most comparative effectiveness analysis activities focus on HTA, the second step in Figure 1 and are conducted by government agencies. That is, HTA programs in Europe, Canada, and Australia, among others, assess the comparative clinical effectiveness of technologies while asking if a particular technology is worth its cost to that country's national health system. Clinical practice guidelines for incorporating the results of these analyses are often developed concurrently with HTA. Policy decisions about what technology is to be covered by insurance then follow and is sometimes carried out by the same body that conducts HTA and sometimes by another council or body. Payment decisions may also take place at this stage, such as decisions regarding payment for specified health outcomes.

Figure 1: Comparative Effectiveness Decision Framework: From CER to Coverage and Practice



Source: Based on Docteur and Berenson. How Will Comparative Effectiveness Research Affect the Quality of Health Care? 2010.[2]

Medical practice in most countries is affected in a direct way by policy decisions on what is covered by (often national) insurance and other payment policies which flow from HTA. The result might be expanded access to new technologies at no charge or restricted access to new technologies either through refusal of coverage or placement of limits on use to a subset of the population.[3] In contrast to other nations examined in this report, payment and coverage decisions in the United States are made by a complex mix of decisions by private health plans, state Medicaid programs, and occasional national coverage decisions in the Medicare program in a decentralized insurance system. Some plans have sophisticated HTA methodologies, while others base coverage decisions on cost alone. In any case, each develops its own appraisal of a technology's value and, as a consequence, decisions may vary widely across plans and payers.

Given the level of recent activity both in the United States and abroad, it is reasonable to take stock of evolving practice internationally and to examine what can be learned in a mutually beneficial manner from global experiences, especially from new directions in CER and HTA activities. It is useful, as well, to put the new United States federal investments in evidence generation in the context of the rather different investments in HTA in other high income countries. This paper provides an overview of HTA activities in Europe, Canada, and Australia and examines the new public investments in CER in the United States, which are now primarily led by PCORI. We conclude with some brief comments about common concerns and areas for collaboration across countries.

HTA in Europe, Canada, and Australia

Adoption of HTA has advanced steadily in the last several decades in Europe, Canada, and Australia as countries have established agencies and programs dedicated to HTA. The number of HTA bodies and the breadth of their activities have expanded, with one or more entities assuming a key regulatory or advisory role in policymaking, typically with regard to coverage and reimbursement and, sometimes, pricing decisions. There are historical, structural, and cultural factors affecting the way in which HTA bodies have evolved and the way and extent to which their recommendations are linked to decisions about standards, coverage, and payment within each system. While there are many differences in the form and function of the organizations, there is one common theme that binds them all: their role is to turn evidence into policy with the ultimate objective of sustaining their countries' universal access to care. As such, they all consider, in different ways, economics—value for money is central when it comes to defending the principle of universal access.

Box 2. HTA Entities in Europe, Canada, and Australia

Country	HTA Entity	Scope of HTA
United Kingdom	National Institute for Health and Care Excellence (NICE)	Drugs, devices, diagnostics, interventional procedures, clinical and public health interventions, service delivery, social care, pay-for-performance schemes, human resources and staffing norms
Australia	Pharmaceutical Benefits Advisory Commission (PBAC)	Drugs and vaccines
Germany	German Institute for Quality and Efficiency in Healthcare (IQWiG)	Drugs, devices, surgical procedures, quality control interventions, diagnostic tests, clinical practice guidelines of disease management programs, lay information for patients
Canada	Canadian Agency for Drugs and Technologies in Health (CADTH)	Health care technologies
France	French High Health Authority (HAS)	Drugs, devices, surgical procedures, and diagnostic tests; clinical guidelines for disease management; public health guidance on disease prevention and health care system organization, accreditation, and QA of providers
Sweden	Swedish Council on Technology Assessment in Health Care (SBU)	Health care technologies

Sources: Chalkidou and Anderson. Comparative Effectiveness Research: International Experiences and Implications for the U.S., 2009; [23] Sorenson and Chalkidou. Reflections on the Evolution of Health Technology Assessment in Europe, 2012; [7]

What is Health Technology Assessment (HTA)?

Health technology assessment (HTA) is a method of evidence synthesis that considers evidence regarding clinical effectiveness, safety, cost-effectiveness, and, when broadly applied, includes social, ethical, and legal aspects of the use of health technologies. The precise balance of these inputs depends on the purpose of each HTA. A major use of HTA is in informing reimbursement and coverage decisions, in which case HTA should include benefit-harm assessment and economic evaluation.[17] Set up in 1987, Sweden's Council on Technology Assessment in Health Care (SBU) is one of the oldest HTA agencies. Australia's Pharmaceutical Benefits Advisory Commission (PBAC) is another pioneer in applying HTA to pharmaceutical policy, with cost-effectiveness analysis becoming a mandatory requirement for listing of pharmaceutical products in 1993.[18,19] Canada's Agency for Drugs and Technologies in Health (CADTH) was set up in 1990 and the United Kingdom's National Institute for Health and Care Excellence (NICE) followed in 1999.[20] The French High Health Authority (HAS) and German Institute for Quality and Efficiency in Healthcare (IQWiG) were established shortly thereafter.[21,22]

The topics and scope of HTA activities vary across countries. [Box 2] For example, some HTA entities focus exclusively on the relative value of drugs (Australia), while others focus on drugs as well as medical devices and other health care interventions that focus on areas such as diagnosis and treatment. Some also develop guidelines (Germany and the United Kingdom). The French HAS has a wide ranging remit, from reviewing the value of pharmaceutical products to hospital accreditation and clinician certification. The United Kingdom's NICE also conducts assessments of public health interventions and programs and, more recently, has developed guidance on social care. Since NICE is well-established, and is one of the HTA entities better-known globally, and because one of the authors of this paper is with NICE, we draw many of our examples from NICE and use its experiences to make overall points.

While some have proposed that HTA entities should also assess alternative service delivery models, most countries' HTA programs have not expanded their activities to service delivery or quality and safety, at least not yet.[23] In the United Kingdom, however, NICE is increasingly receiving requests by the National Health Service (NHS) executive for health services guidance and has recently developed guidance on safe staffing levels for secondary and tertiary care providers. This difference may be due to the history of the different entities. From the beginning, NICE brought together the conventional HTA functions on drugs with the clinician-led guidelines program. Over the years, the two converged methodologically, with economics now a core component of clinical guidelines and HTA applied from whole pathways of care to deriving quality standards and audit measures.[20] Conversely, in Australia, the PBAC has a specific drug focus with other committees concentrating on devices and guidelines.

HTA and cost effectiveness analysis

Most countries undertaking HTA in a public-sector agency include an assessment of cost-effectiveness when comparing alternative treatment approaches. Methods and approaches to evaluating cost-effectiveness vary. Cost-effectiveness analysis using the Quality Adjusted Life Year (QALY) as the main outcome measure is the norm in Canada, Australia, the United Kingdom, and Sweden, with France recently also considering this metric. Germany, on

Box 3. What is a QALY? Measuring the Value of Interventions

HTA answers the question: does treatment result in improved health outcomes (outcomes that matter for patients) by extending life, reducing disability, increasing function, or reducing pain? To determine the value of a wide range of treatments, standard measures of value are essential for assessing and comparing various treatments across various diseases. A convenient metric is the Quality Adjusted Life Year (QALY).

QALY represents a person's health over time as a series of "preference-weighted" health states, where the quality weights reflect the desirability of living in a given health state—typically from perfect health (weighted 1.0) to death (weighted 0.0). Once the weights are obtained for each state, they are multiplied by the time spent in each state; the products are summed to obtain the QALY. A QALY resulting from an intervention may be derived from an improvement in a patient's survival, an improvement in quality, or both.

QALYs may be used in cost-effectiveness analysis to guide decisions about resource allocation. The cost-to-QALY ratio may be compared across interventions to determine the most cost-effective way to deliver health benefits.[27]

the other hand, has developed a different system for assessing the cost/benefit equation of new pharmaceutical products, the efficiency frontier.

Broadly speaking, a QALY—the metric most commonly used—is a year in full health.[7] [Box 3] Many, but not all (e.g. France and Germany), countries then set a threshold amount that they are willing to pay for a QALY [Box 4] which serves as a decision rule to guide judgments about cost-effectiveness.[4] The threshold could be set based on political, ethical, and societal considerations though it reflects actual spending levels and the productivity of the health care system and can be derived using empirical evidence as has recently been done in the United Kingdom. The level at which the threshold is set can vary considerably. For example, in the United Kingdom the cost-effectiveness threshold range is £20,000 to £30,000 per QALY (or about $34,000 to $51,000 in 2014), while in Sweden the range is £45,000 to £50,000 per QALY (or about $77,000 to $85,000 in 2014).[4,25,26]

In theory, adoption of technologies with incremental cost-effectiveness ratios (ICERs) in these ranges would not displace other more cost-effective health care services. Since overall health budgets do not increase with the adoption of a technology with a cost per QALY value above the threshold, inclusion of such technology would need to be at the expense of other health care expenditures and, as such, it carries what is known as an opportunity cost.

Although QALY is broadly accepted as a measure of health benefit, debate continues about its exclusive use, particularly because it does not capture the social value of interventions nor quality of life.[6,7] Social value considerations are especially relevant for decisions about the cost and value of technology for very expensive treatments, such as those at end-of-life care or for seriously ill individuals.

HTA agencies are working on how to include value judgments in the decision-making process alongside economic evaluations. France, for example, is developing a social benefit measure that not only evaluates the therapeutic benefits of interventions but also accounts for economic endpoints and important ethical, social, and legal considerations.[7] Similarly, "Value Based Assessments" aim to incorporate societies' values on end-of-life care and other related topics, bringing together two characteristics not necessarily captured by the QALY: disease severity (Burden of Illness—proportional QALY shortfall) and the impact of a disease on productivity (Wider Societal Benefits—absolute QALY shortfall). Usually, such additional weights would only be used if the group that would receive the technology was small. The application of such weights within an existing national health care budget would mean that the new more expensive technology is displacing some other form of care. All of these issues reflect societies' values and need to be balanced in the framework of the HTA.[28]

How are priorities set?

HTA is driven by the needs of decision-makers in national health programs. Different agencies have established different models for topic selection. They range from considering every new drug or indication, as in Australia's case, where listing by PBAC is a prerequisite for use in the country's public system, to a more selective approach where topic referrals are triggered by payers, as in Germany's case. IQWIG receives topics from G-BA, the Federal Joint Committee that comprises representatives of physicians, dentists, hospitals, and health insurance funds and is responsible for the benefit catalogue of the statutory health insurance funds across Germany. In between the two models, there are selective processes such as NICE's, which considers all cancer drugs and effectively every new drug or technology that is likely to lead to a significant investment by the NHS. The health service through its executive, NHS England, and the British government refer non-technology specific topics to NICE, such as the development of cost-effective metrics to populate the NHS's pay-for-performance schemes for primary care providers or the newly launched financial incentives scheme for regional payers, the Clinical Commissioning Groups. Some of NICE's programs, targeting potentially cost saving innovations, rely on topic referrals by manufacturers while others, focusing on safety of new surgical and diagnostic procedures, run on referrals from the country's surgical or clinical community.

Topic selection mechanisms vary across countries and reflect the structure and role of the HTA agency in the broader health care landscape. For example, the United Kingdom's NICE has more independence as it issues its recommendations directly to the NHS, including payers and providers, whereas the French HAS needs to work through the insurers of the country's social security system as does the German IQWIG. Overall, however, there are core

Box 4. Thresholds

The threshold is a decision rule which, combined with an incremental cost-effectiveness ratio (ICER) coming out of a cost-effectiveness evaluation, will guide the decision as to whether a technology is good value for money and ought to be paid for. Thresholds are therefore linked to budgets and to the demand on those budgets by the various technologies (new and existing) and the health care needs of the population. While there have been several studies on willingness to pay thresholds, in real life, and unless population wishes can be translated directly into health care budgets, thresholds reflect the productivity of the health care system at the margin, given the budget, and, therefore, can be empirically derived if adequate data on inputs and outputs are available.[29,30]

similarities across systems. They include a focus on reviewing technologies and services where there currently is, or there is potential for, significant variation, where there is evidence of effectiveness, and where there is potential for significant health gains and/or budgetary impact in case of country-wide adoption.

What is the role of patients and other stakeholders?

Across entities, opportunities for stakeholder involvement vary, but most have focused on the need to engage stakeholders—industry representatives, health professionals, and patients and patient groups. Stakeholders generally have opportunities to submit topics for consideration and manufacturers have opportunities to submit data and analysis for consideration.

For example, the United Kingdom's NICE has encouraged extensive stakeholder involvement in all areas of its work. In the case of technology appraisals, stakeholders are involved in defining the key questions and the clinical alternatives to be examined. Manufacturers have the opportunity to submit data and analyses for the assessment group to consider. All stakeholders, including manufacturers, professional groups, and patient organizations, and the NHS have the opportunity to comment on the assessment and appraisal and the final appraisal determination. Stakeholders can also appeal the final appraisal.[31]

Stakeholders have different roles in the analysis stage. For example, in the case of the United Kingdom's NICE, depending on the program, evidence syntheses and economic models can be produced in house, outsourced to universities and consultancies, or submitted by the manufacturers. Australia's PBAC relies fully on industry submissions critiqued by the academic groups it subcontracts with, while Sweden's SBU does not call for industry submissions.

Patients and the public have been the least involved in the HTA processes, but a number of countries have sought to provide opportunities for more substantive patient engagement in recent years. The United Kingdom's NICE established a Citizens' Council in 2002 to gather information on social and ethical issues, including the application of QALY thresholds. The French HAS and German IQWiG have established similar opportunities.[7] NICE is also rather unique in having a dedicated team of experts to help identify, train, and support patients in articulating their views as well as offering training to senior clinicians who head up many of its committees, to support them in empowering patients in the context of committee meetings. NICE also has lay people (patients and care-givers) chair its specialist committees.

What are the methods for synthesizing evidence?

Study designs and methodological techniques flow from the overarching purposes of the HTA entities. Information on clinical effectiveness and cost are the building blocks of HTA, which comes from a synthesis of available evidence from CER studies. The United Kingdom's NICE, for example, commissions joint teams of systematic reviewers and modelers or health economists to carry out its HTA.[32] The systematic reviewers need to work closely with the modelers or economists and with the decision-makers (clinicians, insurers, and patients) to ensure that the research question is the right one and data sources other than conventional ones are consulted, including expert opinion and grey literature. Further, in order to be relevant to the real-world, the synthesis needs to incorporate both observational and experimental data, including patient testimonies, unit cost, patient preference data, and, increasingly, individual patient-level data as seen by the regulators.

HTA entities across most countries stress methodological rigor and the need to adhere to high standards. However, across countries, there are differences in interpretation of methodological rigor and in how much weight to place on evidence from randomized trials—the "gold standard" for evidence. The United Kingdom's NICE, which has long been "recognized for its methodological rigor, and in particular, its assessment guidelines, which set standards for consistency and compatibility of the studies submitted,"[7] has increasingly been divesting itself of evidence hierarchies. Its German counterpart tends to follow a more traditional evidence-based medicine or Cochrane model with randomized controlled trials at the top of their evidence rankings—though this more traditional approach of the latter is also gradually being relaxed.[33]

The role in setting standards has recently been enhanced for NICE. At the request of the Gates Foundation, NICE has recently embarked on an effort to set standards for carrying out cost-effectiveness analysis to inform investments in global health. This is a unique opportunity to standardize the methods of economic evaluations, which in turn drive billions of dollars of spending in aid globally.[34]

How does HTA affect policy and practice?

Ultimately, the goal of HTA is to affect medical practice and to provide high value for the health care system. This happens through linking the results of HTA to decisions on coverage, reimbursement, and sometimes pricing. There are some

important differences in the role these organizations play, in particular, their roles in decision-making related to coverage. In the United Kingdom, the HTA entity is akin to a regulatory body vested with decision-making authority and is involved in both assessment and appraisal processes, especially on pharmaceutical products going through the technology appraisal process. As a result, the United Kingdom's NICE is closely linked to and therefore influential in the policy process. For example, NICE's positive recommendations for pharmaceutical products are mandatory and are issued directly to budget holders and providers across the NHS. NICE's health services delivery and clinical practice recommendations are advisory but are increasingly included in payment systems. In the NHS, insurance programs have to cover drugs approved by NICE. Similarly, in Australia approval by PBAC is required (though it is not enough as the Minister can still say "no") to list a given drug on the national formulary.

In contrast, the German and French HTA bodies assume advisory roles that align with the structure of their social insurance-based health care systems. In these countries, HTA agencies conduct the assessments and make recommendations on coverage, which also inform reimbursement. In Germany, the HTA body transmits its recommendations to a group of insurers and providers to make coverage decisions (G-BA). In France, the HTA entity also advises other individual insurance plans about the appropriateness of coverage of health services.

Recognizing that data may not be sufficient at the point that the HTA is conducted, most countries provide an option for coverage subject to a requirement for additional data acquisition (or "coverage with evidence development"[35,36]). A HTA's or CER's initial time frame may not have allowed for the manifestation of all benefits and harms or the statistical power may not have been sufficient to detect rare adverse effects. Post-marketing studies that follow real-world use of a technology can address these limitations and can be linked to payment subject to data collection.

HTA entities in the United Kingdom, Sweden, Germany, and France are experimenting with new approaches to generate better pre- and post-marketing data. For example, many of these countries have developed some form of coverage that involves evidence development, risk-sharing arrangements, or patient access schemes, whereby coverage of a technology is conditional upon arrangements for additional post-marketing evidence collection or the achievement of certain health or financial targets.[7] However, perhaps because of the burden of evidence collection and analysis, the emphasis—at least in the United Kingdom—increasingly addresses price deals in the beginning as opposed to coverage conditional on HTA arrangements post-approval. Such trends in Europe may be driven to some extent by the role of the European Medicines Agency (EMA), the European regulator, which is increasingly getting into effectiveness evidence and is keen to help accelerate market access post approval. European Commission initiatives such as the European network for Health Technology Assessment (EUnetHTA) has also played a positive role in encouraging some standardization across HTA agencies and more experimentation with risk-sharing, again working closely with the EMA in the context of joint early EMA-HTA scientific advice to product manufacturers.[37]

Coverage decisions may not always have the intended effect of changing clinical practice. In the United Kingdom, for example, even though positive NICE guidance on technologies is mandatory, continuing evidence of variation in medical practice has drawn attention to the need to both monitor changes in clinical practice and develop additional tools that bring practice into line with evidence-based guidelines. In addition, NICE's "implementation directorate" is responsible for collecting and sharing case studies of best practice in the implementation of NICE guidance.[23] Increasingly, provider payment (pay-for-performance in primary care; Healthcare Resource Groups in secondary care), contractual arrangements, and quality regulation are linked to compliance with NICE guidance.[38,39] A common theme across countries is an increased emphasis on measuring compliance and then trying to hold payers and providers accountable through payment schemes, contractual arrangements, peer pressure, media and patient information campaigns, and other relevant levers.

CER and PCOR in the United States

The expansion of publicly financed HTA activities in most other countries stands in contrast to the United States experience. In Europe, Canada, and Australia, an authoritative body—publicly financed, transparent, and at arm's length from payers—synthesizes and assesses existing research, offers an appraisal of alternative health care interventions, and makes recommendations for coverage. In the United States, HTA has been decentralized leading to substantial variation in the degree to which evidence is used to inform assessments and coverage decisions. In particular, the assessment and appraisal of new health care interventions are often made without adequate evidence about comparative effectiveness and sometimes even without adequate information about safety and efficacy. Although many federal health care agencies produce or use CER,[1] there has been no single government agency (or other publicly financed entity) to coordinate research on comparative effectiveness. However, significant new public investments in CER were made in 2009 and 2010. These new federal investments focus on improving the quality and relevance of the primary research available mainly to patients and their care providers, but also to health plan decision-makers and policy makers.

The implementation of these public investments is new and evolving as processes are implemented, evaluated, and improved. Here, we highlight key features of this new CER program, which is led by PCORI. This section describes the goals and expectations for CER and, more specifically, patient-centered outcomes research (PCOR), a brief summary of PCORI's funding announcements to date, and the principles and strategies that PCORI has developed or augmented to guide the effort. We also summarize those processes which we described in other countries' HTA efforts, namely priority setting, engagement of patients and other stakeholders, methodological approaches, and dissemination.

What is Comparative Effectiveness Research (CER)?

Clinical research is often focused on determining the efficacy and safety of medical care treatments. Randomized, placebo-controlled trials are considered the gold standard for regulators and the basis for determining which treatments are efficacious and in which patients. In contrast, CER asks about the relative risks and benefits of alternative approaches to diagnosis, treatment, and prevention. CER generally requires the comparison of two or more treatments. CER focuses on questions such as "does the treatment work better than alternatives?" and "does it have some additional benefit in all patients or in a subset of patients?" CER addresses these questions directly, through primary research, and CER also includes evidence synthesis.

Why do we need more CER?

In the United States, there historically has been relatively little CER. Part of the reason for the lack of true comparative effectiveness studies has to do with methodological and data related challenges and the cost of conducting large clinical trials, which have been the primary research method for CER studies. However, lack of public funding has been the more significant challenge. Publicly financed efforts designed to evaluate the relative value of health care technologies have met resistance from some sectors and ultimately have been de-funded or eliminated.[40,41]

The significant new federal investment in CER is designed to fill this gap and avoid some of the challenges encountered in past efforts. The new investments are being implemented by PCORI to reorient the research to what patients care about and to make it more relevant to patients. It is designed to address patients' questions, to assess the outcomes of interventions in real patients and real-world settings, and to learn about what forms of health care are most effective in order to improve health. "The goal is to learn what forms of health care work best, so that we can abandon those that are ineffective and adopt those diagnostic tests, treatments, and approaches to prevention that do the most to improve health."[42] Hence, patient engagement is viewed as critical to the overall success of the CER investments, in helping to shape the research questions and define the outcomes. As such, it is being implemented to be "research done differently."[10]

The new CER effort focuses both on generation of new evidence and uptake of that evidence into practical decision-making. Stakeholder engagement, which brings stakeholders—patients, as well as others—into the research process from the beginning, is also important for maximizing the likelihood that findings from the research will be incorporated into practice. There have been CER studies in the past that have not made a major impact on clinical and policy decisions for a number of reasons. It is difficult to change clinical practice, the findings do not always help patients and clinicians make decisions, and often the findings are not disseminated effectively or there is no infrastructure for building them into clinical practice and the policy decision-making process. Involving stakeholders in the research process is part of PCORI's strategy to promote implementation.

Building a sustained CER effort is a very large undertaking. PCORI is establishing research priorities and at the same time building a research program that is wide-ranging, ongoing, and responsive to changes in health care delivery. The goal is to move the United States' health care system toward a "learning system" that has an infrastructure for learning about what works and mechanisms for applying that knowledge effectively in health care decision-making.

What is Patient-Centered Outcomes Research (PCOR)?

The ACA calls for PCORI to "assist patients, clinicians, purchasers and policymakers in making informed health decisions by advancing the quality and relevance of evidence concerning the manner in which diseases, disorders and other health conditions can effectively and appropriately be prevented, diagnosed, treated, monitored, and managed through research and evidence synthesis that considers variations in patient subpopulations, and the dissemination of research findings with respect to the relative health outcomes,

Box 5. Recent Federal Investments in CER in the United States

The American Recovery and Reinvestment Act (ARRA) of 2009 invested $1.1 billion for comparative effectiveness research (CER), with funding for the National Institutes of Health (NIH), the Office of the Secretary in the Department of Health and Human Services (HHS), and the Agency for Healthcare Research and Quality (AHRQ).[8] A Federal Coordinating Committee (FCC) convened by HHS and the Institute of Medicine (IOM) both identified priorities for CER in statutorily mandated reports to the Congress that were issued on June 30, 2009. The IOM developed a working definition for CER, created a list of 100 priority topics for research to address, and provided 10 recommendations to implement the infrastructure for a sustained CER effort.[13]

In 2010, a substantially larger federal investment in CER was made, with a 10-year funding stream and authorization for a new publicly financed entity to coordinate and manage these investments. The Affordable Care Act (ACA) established the Patient-Centered Outcomes Research Institute (PCORI) as an independent nonprofit corporation and makes an estimated $3.5 billion available (over 10 years) for CER through the Patient-Centered Outcomes Research Trust Fund (PCORTF). PCORI is governed by a board of directors representing diverse stakeholder groups—patients, payers, providers, and drug and device manufacturers—as well as the heads of the NIH and AHRQ. This new program seeks to reshape the way health care research is done to meet the practical needs of patients and their health care providers.

clinical effectiveness, and appropriateness of medical treatments, items and services…."[43] The term "research" is defined as research evaluating and comparing health outcomes and the clinical effectiveness, risks and benefits for two or more medical treatments, services, and items.[43]

PCORI further defined PCOR through a process led by their (statutorily required) Methodology Committee and informed by diverse stakeholder input. The definition begins with the ultimate purpose of the research: "PCOR helps people and their caregivers communicate and make informed health care decisions, allowing their voices to be heard in assessing the value of health care options." It then goes on to offer examples of the types of patient questions answered by this type of research:

- "Given my personal characteristics, conditions, and preferences, what should I expect will happen to me?"
- "What are my options and what are the potential benefits and harms of those options?"
- "What can I do to improve the outcomes that are most important to me?"
- "How can clinicians and the care delivery systems they work in help me make the best decisions about my health and health care?"[44]

The emphasis is on research that answers real-world questions for patients and clinicians and acknowledges the need to modify existing approaches to health care research. To provide this information, CER must assess a comprehensive array of health-related outcomes for diverse patient populations. Interventions compared may include medications, procedures, medical and assistive devices and technologies, behavioral change strategies, and delivery system interventions.[44] The research must consider "variations in patient subpopulations," which means it needs to uncover clinical differences among patients that help predict which patients will benefit most from alternative interventions."[42] It must be tailored, much more than it has been in the past, to the clinical situation and to patient priorities.

How are PCOR priorities set?

There have been several efforts to identify research priorities in the United States—topics that will address the most pressing concerns of patients and clinicians. The IOM, with diverse stakeholder input, narrowed a list of suggested topics from more than 2,000 to just 100 initial priorities for research.[13] These topics include a wide range of interventions, populations, and approaches and include research on the dissemination of CER and on CER methods.

Rather than identify priorities or require PCORI to develop a research agenda based on the IOM priorities, the ACA identified criteria to help define PCOR. [Box 6] The ACA further called upon PCORI to prioritize studies based on their likely effects on health care decision-making and health, and to select studies with an eye toward their ability to improve health system performance, their likelihood of influencing decision-making, and their ability to be patient-centered.[45]

These criteria guide PCORI's assessment of research proposals and their funding decisions. PCORI focused on identifying research questions with the greatest probability of changing clinical decisions. The questions include: (1) What is the potential for new information to improve care and patient-centered outcomes? (2) What are the facilitators and barriers that would affect the implementation of new findings in practice? (3) How likely is it that new CER on the topic would provide better information to guide clinical decision-making? (4) How likely is it that the results of new research would be implemented "right away?" [46]

Rather than developing a list of research questions or adopting the IOM priority list, PCORI developed five overarching research priority areas to capture its goals for changing the way research is done and disseminated. The five priority areas are:

1. Assessment of Prevention, Diagnosis, and Treatment Options
2. Improving Healthcare Systems
3. Addressing Disparities
4. Communication and Dissemination Research
5. Accelerating PCOR and Methodological Research [47]

The scope of PCORI's research agenda is thus quite broad. PCOR includes traditional CER topics (the assessment of prevention, diagnosis, and treatment options), but PCOR also comprises studies of health care system interventions and research designed to assess interventions to reduce health disparities.

Box 6. Statutory Criteria for PCORI-Funded Research

1. Effect on individuals and populations
2. Probability of improvability through research
3. Inclusiveness of different populations
4. Current gaps in knowledge/variation in care
5. Effect on health care system performance
6. Potential to influence decision making
7. Patient-centeredness
8. Rigorous research methods
9. Efficient use of research resources

PCORI's funded projects

Four years into implementation, PCORI has made more than 350 awards, investing $519.2 million in CER, data infrastructure and methods, and dissemination and implementation research [Table 1]. To date, 65% of PCORI's research funding has focused on CER, 26% has been focused on data infrastructure building and methods research, and 9% on communication and dissemination research.

Table 1. PCORI Research Award Funding, by Priority Area

Priority Area	Funding	Percent of Total Funding
CER	**$ 338,087,798**	**65%**
Assessment of Prevention, Diagnosis, and Treatment Options	$129,716,941	25%
Improving Healthcare Systems	$120,748,218	23%
Addressing Disparities	$87,622,639	17%
Communication and Dissemination Research	**$48,761,292**	**9%**
Accelerating PCOR and Methodological Research	**$132,395,902**	**26%**
Total Awards (to date)	$519,244,992	100%

Source: Authors' calculation based on PCORI, "Complete List of Funding Awards," pfaawards.pcori.org, downloaded on September 12, 2014. Awards for Pilot Projects and Engagement Awards are not included.

PCORI has funded research that reflects a wide range of priority areas, diseases, treatments, delivery approaches, and populations. The funded projects include studies likely to produce results quickly, as well as longer-term initiatives. PCORI solicited proposals through relatively open funding announcements and selected for funding proposals by whether they answered high priority questions, met PCOR criteria, and had appropriate research designs. These projects are investigator-initiated, but more recently PCORI has released more targeted funding announcements for specific high-priority questions—related to asthma treatment in African American and Hispanic populations and approaches to preventing falls in the elderly, for example. [Box 7]

PCORI has funded a number of studies designed to develop and evaluate tools, structures, and incentives that can help make results available for "real-time" decision-making. For example, this implementation-focused research is designed to assess the potential role of communication tools and shared decision-making models in motivating patients and providers to make evidence-based choices when considering alternative approaches to diagnosis, treatment, and care management.[48]

What are the methods for generating evidence?

PCORI's emphasis is on generating new evidence. Its Methodology Committee is charged with developing methodological standards for PCOR. The four general areas identified by the committee in which standards have been or are being developed are: 1) prioritizing research questions; 2) using appropriate study designs and analyses; 3) incorporating patient perspectives throughout the research continuum; and 4) fostering efficient dissemination and implementation of results.[49] A Congressionally-mandated Methods Report describes the standards.[50] It is important to note that the methods developed in the context of PCOR are important and pertinent broadly and not just in the PCORI context.

The work of the Methodology Committee was intended to overcome some of the weaknesses of methods frequently used and to ensure that CER produces information that is meaningful, unbiased, timely, and actionable.[49] With respect to randomized controlled trials (RCTs), serious problems concern the time and cost it takes to complete them. Because participants in a clinical trial are enrolled prospectively, RCTs can require years to enroll patients and to observe the outcomes of alternative treatments. A second problem is that, in an attempt to make comparisons as "clean" as possible, studies often impose exclusion criteria that result in a homogeneous study population that is not representative of the "real world." For example, for any number of reasons, a study population might exclude individuals with comorbidities or exclude the elderly. Further, studies may not take place in settings where care is routinely delivered.

The Methodology Committee also set forth standards for using large databases in observational studies. There is a need for large-scale observational databases from claims, electronic health records, or registries. These are needed to provide a sufficiently large population to detect rare events and to provide a resource for rigorous observational studies that yield results more rapidly than randomized trials. However, while existing claims and clinical databases and registries offer a convenient resource, observational studies often do not control for important differences in groups, such as individuals who adhere to a drug regimen compared to those individuals who do not.

Some of the most important methodological advances set forth by the Methodological Committee that address these issues include pragmatic trials, adaptive designs, and assessment of causal inference. Table 2 describes the advantages and limitations of the research methods used for primary CER.[50-52]

PCORnet: The promise of "big data" networks for conducting patient-centered research

PCORI has also funded projects designed to improve the data and methods for primary CER studies. Projects are focused on the measurement of patient-centered outcomes, on methods for pragmatic trials and observational research, and on building a data infrastructure and research network for PCOR.

Box 7. Examples of PCORI Funding Awards, by Priority Area

Assessment of prevention, diagnosis and treatment options

- Comparative Effectiveness of Broad vs. Narrow Spectrum Antibiotics for Acute Respiratory Tract Infections in Children
- Benchmarking the Comparative Effectiveness of Diabetes Treatments Using Patient-Reported Outcomes and Socio-Demographic Factors
- Comparing Patient-Centered Outcomes after Treatment for Uterine Fibroids
- Generating Critical Patient-Centered Information for Decision-Making in Localized Prostate Cancer
- Shared Decision-Making in the Emergency Department: The Chest Pain Choice Trial
- Comparative Effectiveness of Rehabilitation Services for Survivors of an Acute Ischemic Stroke
- Comparative Effectiveness of Adolescent Lipid Screening and Treatment Strategies
- Promoting Informed Decisions about Lung Cancer Screening
- Smoking Cessation Versus Long-Term Nicotine Replacement among High-Risk Smokers
- Physical Therapy vs. Internet-Based Exercise Training for Patients with Knee Osteoarthritis
- Comparative Effectiveness of Behavioral Interventions to Prevent or Delay Dementia

Improving healthcare systems

- Randomized Trial of a Multifactorial Fall Injury Prevention Strategy: A joint initiative of PCORI and the National Institute on Aging of the National Institutes of Health*
- An Integrative Multilevel Study for Improving Patient-Centered Care Delivery among Patients with Chronic Obstructive Pulmonary Disease
- Changing the Healthcare Delivery Model: A Community Health Worker/Mobile Chronic Care Team Strategy
- Increasing Healthcare Choices and Improving Health Outcomes Among Persons with Serious Mental Illness
- Improving the Quality of Care for Pain and Depression in Persons with Multiple Sclerosis
- A Comparative Effectiveness Trial of Optimal Patient-Centered Care for US Trauma Care Systems
- Redesigning Ambulatory Care Delivery to Enhance Asthma Control in Children
- Improving Healthcare Systems for Access to Care and Efficiency by Underserved Patients
- Advance Planning for Home Services for Seniors

Addressing disparities

- Asthma Treatment Options for African Americans and Hispanics/Latinos (7 projects)
- A Helping Hand to Activate Patient-Centered Depression Care among Low-Income Patients (AHH)
- Impact of Patient Navigators on Health Education and Quality of Life in Formerly Incarcerated Patients
- Peer Health Navigation: Reducing Disparities in Health Outcomes for the Seriously Mentally Ill
- Improving Health Outcomes among Native Americans with Diabetes and Cardiovascular Disease
- Integrative Medicine Group Visits: A Patient-Centered Approach to Reducing Chronic Pain and Depression in a Disparate Urban Population
- Telehealth Self-Management Program in Older Adults Living with Heart Failure in Health Disparity Communities
- Nueva Vida Intervention: Improving QOL in Latina Breast Cancer Survivors and Their Caregivers
- Rural Options At Discharge Model of Active Planning (ROADMAP)
- A Patient-Centered Intervention to Increase Screening of Hepatitis B and C Among Asian-Americans

* The IOM identified research on falls in older adults in the top quartile of its final list of 100 priority topics: "Compare the effectiveness of primary prevention methods, such as exercise and balance training, versus clinical treatments in preventing falls in older adults at varying degrees of risk"

The National Patient-Centered Clinical Research Network (PCORnet) is one of the major and signature programs in the PCORI portfolio. It aims to build a national research network, linked by a common data platform and embedded in clinical care delivery systems. This network will enable studies, and in particular randomized trials, that have been impractical to conduct to date. PCORnet currently includes 11 Clinical Data Research Networks (CDRNs), 18 Patient-Powered Research Networks (PPRNs), and a coordinating center. The 11 CDRNs are large data networks from health plans, academic medical centers, outpatient and inpatient hospitals, and others, such as Kaiser Permanente, Oregon Community Health Information Network, and The Children's Hospital of Philadelphia.[53] Each CDRN is committed to building a large patient cohort with comprehensive, longitudinal electronic clinical data and building the capacity to participate successfully in multi-network randomized trials and observational studies.[53]

The PPRNs consist of 18 disease-specific data repositories, with 9 representing common conditions and 9 representing rare diseases.[54] Each PPRN consists of patients, caregivers, or families who are linked by the experience of a shared condition (e.g., inflammatory bowel disease, major depressive disorder/bipolar disorders, sleep apnea, primary immunodeficiencies).[53] Each CDRN and PPRN will be self-governed, and each network will securely maintain its own data. The hope is that these PPRNs will help empower patients and their families and caregivers to generate large amounts of data about their conditions. Further, by shifting research control from traditional researchers and funders to patients who own their data and can choose to share them, PPRNs have the potential to more systematically address the question of genuine importance to patients.[55]

Together the CDRN/PPRN repositories are geographically dispersed, with patients in 50 states.[53] They are organized as distributed data networks, each with its own governing

Box 8. Examples of PCORI Funding Awards: Dissemination and Methods Research

Communication and Dissemination Research

- Shared Decision-making and Renal Supportive Care
- Randomized Trial to Increase Adherence to Cervical Cancer Screening Guidelines for Young Women
- Comparing Traditional and Participatory Dissemination of a Shared Decision-making Intervention
- Improving Communication for Chemotherapy: Addressing Concerns of Older Cancer Patients and Caregivers
- Patient-Identified Personal Strengths (PIPS) vs. Deficit-Focused Models of Care
- Presenting Patient-Reported Outcomes Data to Improve Patient and Clinician Understanding and Use
- Shared Medical Decision-making in Pediatric Diabetes
- Relapsed Childhood Neuroblastoma as a Model for Parental End-of-Life Decision-Making
- Creating a Patient-Centered Tool to Help Medicare Beneficiaries Choose Prescription Drug Plans

Accelerating PCOR and Methodological Research

- Facilitating Patient Reported Outcome Measurement for Key Conditions
- Statistical Methods for Missing Data in Large Observational Studies
- Improving the Use of Patient Registries for Comparative Effectiveness
- Measuring Patient-Centered Communication for Colorectal Cancer Care and Research
- Developing Patient-Centered Outcomes for Dementia: Goal Setting and Attainment
- Understanding Treatment Effect Estimates When Treatment Effects Are Heterogeneous for More Than One Outcome
- Evaluating Methods to Engage Minority Patients and Caregivers as Stakeholders
- Improving Patient Engagement and Understanding Its Impact on Research through Community Review Boards
- The National Patient-Centered Clinical Research Network (PCORnet)

board but adhering to common data standards. They use a distributed query approach, which permits analyses to be conducted behind institutional firewalls.[53] For researchers, this network of electronic medical records will make observational and interventional trials easier to launch, more representative of diverse, real-world populations, and capable of providing much-needed answers to comparative effectiveness research questions with greater accuracy. Some examples of the types of questions that can be answered through PCORnet are:[56]

- What are the best strategies for managing localized prostate cancer?
- Which of the available primary care strategies for children with attention-deficit hyperactivity disorder are most effective?
- What are the best treatment strategies for low back pain?
- Which interventions are most effective for reducing disparities in hypertension outcomes?

PCORnet has recently set its first research target–a $10 million pilot clinical trial on the use of aspirin to prevent heart disease. Participants will take daily doses of aspirin that fall within the range typically prescribed for heart disease and will be monitored to determine whether one dosage works better than the others.[57] The aspirin trial, while important in its own right, is also a "proof of concept" for conducting research through PCORnet.

PCORnet is tackling many fundamental challenges to the conduct of multisite research. These include the technical challenges of collecting and harmonizing longitudinal data from multiple and fast-growing sources, as well as the ethical and regulatory challenges of conducting research in this new environment, including obtaining informed consent, use of central institutional review boards, and the protection of patient privacy.[53,56] Thus, PCORnet holds the promise to transform clinical research.

Evidence synthesis and appraisal: What is PCORI's role?

PCORI is authorized to conduct primary research—to generate additional and improved evidence about what works—and to engage in research synthesis. [Box 9] The PCORI investments have been focused on the primary evidence generation component of CER and not on the synthesis and appraisal activities. However, these evidence reviews are a central feature of HTA, and are conducted by other entities (e.g., AHRQ, Cochrane Review).

Historically, reviews of existing evidence have been conducted by the AHRQ under the Effective Healthcare Program which was established in 2003 by the Medicare Modernization Act.[58] However, support for this effort is in question with the advent of PCORI and elimination of funding for the Effective Healthcare Program separate from PCOR funds transfers. PCORI may yet extend its role to reviews of evidence.

A central feature of HTA is review and synthesis of evidence. HTA is conducted by (or on behalf of) a variety of private and public payers including the Veteran's Administration, Medicare, and Medicaid, and private health insurance issuers and large, self-insured employer-based plans. [Box 10] They may undertake their own assessments, relying on inputs from entities that have expertise in evidence synthesis and make appraisals for coverage, benefit design, and payment.

Table 2. Methods for Conducting Primary CER (Generating New Evidence)

Study Design	Features	Advantages	Limitations or Other Considerations
Randomized Controlled Trials (RCT)	Gold standard of comparative effectiveness research; randomize individuals or groups to different study arms, usually treatment and control.	With sufficiently large sample size, confounders are balanced across different study arms, enabling assessment of unbiased treatment effect(s).	RCTs usually require considerable time; imposition of exclusion criteria results in a homogeneous study population that is not representative of real-world population; study settings may not reflect places where routine care is delivered.
Pragmatic Randomized Controlled Trials	Pragmatic or practical trials involve: (1) comparison of clinically relevant alternative interventions, (2) diverse population of study participants, (3) participants from heterogeneous practice settings, and (4) data on broad range of health outcomes.[51,52]	Research in real-world setting with diverse populations.	Large number of participants and diversity of study sites; can use routinely occurring variation in health care systems.
Propensity Scores and Causal Inference Methods	Strategy to approximate randomized controlled trials; use of large electronic clinical and administrative databases; use of propensity scores to create a similar covariate distribution between groups.	Can be conducted more rapidly and with less cost compared to randomized trials; in large databases, researchers can "observe" the differences between those using and not using a treatment or intervention.	Individuals or groups that received the intervention or treatment may differ systematically from those that did not; cannot confer rigor of RCTs.
Adaptive and Bayesian Trial	Adaptive trials build on the approaches used in most randomized trials but allow for changes during the course of the study for parameters such as what proportion of participants is randomized to which group, sample size, eligibility criteria, and end points [50]	Reduces the rigidity of design specifications in rapidly changing world and minimizes time to completion.	Improper adaptations may give rise to bias.

Sources: The PCORI Methodology Report, 2013 [50]. Tunis et al. Comparative effectiveness research: Policy context, methods development and research infrastructure, 2010 [51]. Chalkidou et al. The role of pragmatic randomized controlled trials (pRCTs) in comparative effectiveness research, 2012 [52].

PCORI will not undertake the kind of appraisal activities that are common in the HTA agencies in other high-income countries. The ACA specifically excludes certain kinds of appraisal activities from PCORI's purview. For example, the ACA forbids the use of cost per QALY "as a threshold to establish what type of health care is cost effective or recommended."[43] The ACA also states that the research findings of PCORI funded research can "not be construed as mandates for practice guidelines, coverage recommendations, payment, or policy recommendations."[43] Nevertheless, there is an expectation that the new CER will make higher quality evidence available to plan decision-makers, enabling health plans to orient coverage and payment policies toward health care interventions and delivery system strategies that produce better outcomes at lower cost.

What strategies are needed to promote uptake of research findings?

In addition to more and better evidence, enhanced patient choices and outcomes, and faster uptake, we need more uniform uptake of evidence. The myriad reasons for poor uptake and use by decision-makers have been well-documented and include: the evidence may not be compelling to patients or clinicians; clinicians may have a hard time changing practice patterns; contextual factors such as current payment incentives hinder behavior change; or the findings may not be widely disseminated.[62,63] Patients, for example, may have the greatest incentive to use CER, but "relatively few are equipped to make use of the highly technical scientific evidence generated through CER and to understand how it applies in their particular situation."[2] Consequently, even when CER findings are relevant and informed by patient and stakeholder engagement, they must be packaged and disseminated in ways that ensure that they meet the needs of different target audiences, including patients, clinicians, and policy makers to encourage uptake.

To address these weaknesses, implementation considerations are a factor in each step of the PCORI process, from the prioritization of research questions, to the selection of a study design and choice of outcome measures, to the consideration of how the evidence is likely to be used in decision-making. A core component of the PCORI strategy for maximizing uptake is intensive, interactive patient and stakeholder engagement from priority setting, to inclusion in the research team itself, to deep involvement in merit review of applications. The organizing vision is that this deep involvement will enhance uptake by producing "dissemination ready" findings. To further maximize the likelihood of uptake from research findings, PCORI is also funding dissemination and implementation research studies and the PCORTF provides funding directly to AHRQ to undertake this type of research. While PCORI has no

Box 9. Evidence Synthesis: Definitions

Research synthesis, which is often included under the rubric of CER, is a process through which "researchers seek to summarize the information from multiple studies addressing similar research questions."[13]

"A comparative effectiveness systematic review summarizes available scientific evidence in which investigators collect, evaluate, and synthesize studies in accordance with an organized, structured, explicit and transparent methodology. They seek to provide decision-makers with accurate, independent, scientifically rigorous information for comparing the effectiveness and safety of alternative clinical options, and have become a foundation for decision-making in clinical practice and health policy including informing coverage decisions for therapeutics in health care." The methods for systematic review include: activities related to how the questions are framed, how the quality of the available evidence is assessed, and the standards that are applied to existing research. This evidence assessment or synthesis activity often feeds into an appraisal process in which questions about cost are addressed.[13]

Box 10. HTA in the United States

The Federal Agency for Healthcare Research and Quality (AHRQ) is the lead source of systematic reviews which are used for HTA.59 A mix of federal and nonfederal partners nominates topics, and researchers who participate in a network of AHRQ-funded Evidence-based Practice Centers (EPCs) produce the evidence synthesis reports. EPCs are housed in academic centers (at the Oregon Health Sciences University and at Johns Hopkins University, for example), but AHRQ also funds EPCs at the Blue Cross/Blue Shield Association Technology Evaluation Center, the Kaiser Permanente Research Center, and the Minneapolis VA. The AHRQ evidence based practice center reports are intended to provide information useful to patients and clinicians to improve care as well as to health plan decision-makers to inform coverage and payment decisions.

Many large private insurers and Pharmacy Benefits Management programs (PBMs) have sophisticated HTA programs staffed by clinical experts and financial analysts and supported by sophisticated data systems.[59] Smaller health plans have much more limited staffing and often depend on technology assessments produced by outside private or public agencies. Little information is available regarding the scope, internal processes and conduct of HTAs by private insurers and PBMs. WellPoint makes its HTA guidelines publically available, but while the output is available, the HTA process itself is typically a black box: there is often little transparency regarding the evidence and approaches used to arrive at coverage decisions.[59] Coverage decisions based on the HTA activities of private insurers can vary widely.

The nation's major public payers—Medicare, Medicaid, and the Veterans' Health Administration—also use CER to inform coverage decisions. The Medicare Coverage Division within CMS is responsible for undertaking or commissioning HTA reports to support considerations for a national coverage decision.[60] Most evidence-related coverage determination efforts rely on synthesizing existing clinical and often health services research literature by means of formal or informal systematic reviews.[40] Medicare can request a formal evidence report from AHRQ.[61] The ultimate coverage decisions, along with evidence dossiers and, other meeting materials, are placed on the CMS website for transparency, and issued through National Coverage Decision memoranda. Notably, the Coverage Division is explicitly prohibited by law from considering evidence related to the cost or cost-effectiveness of technologies when making coverage decisions.[61] Medicare Part D outpatient drug program operates separately from the Medicare Coverage Division, with all coverage decisions made by Part D contractors.

State Medicaid programs often purchase HTA's from private organizations that specialize in this area. In general, the operating budgets for state-level HTA activities are insufficient for the workload.[59] For HTA around drugs, 14 states use the comparative effectiveness reports on drugs produced by the Drug Effectiveness Review Process at the Oregon Health and Sciences University.[40]

direct oversight on how AHRQ uses these funds, there are ongoing efforts to, and expectation of, coordination of these linked responsibilities.

While PCORI can set the stage for uptake and maximize conditions that will encourage uptake, PCORI has limited policy levers at its disposal and partnerships with a broad range of stakeholders in the health care system will likely be needed. While PCORI has a mandate to disseminate PCOR findings (the ACA set out a 90-day timeframe for the dissemination of results from completion of the research), more than dissemination is needed to ensure good uptake. PCORI has set in motion a set of strategies and research to understand factors that influence dissemination and implementation. Understanding the processes through which research findings are implemented in general, and in particular the influence of stakeholder involvement in uptake, will be crucially important in the coming years.

Discussion and Concluding Thoughts

The combination of rising health care costs and the move toward universal or near-universal coverage globally brings an urgent demand to spend health care funds on effective technologies and interventions and to do so efficiently and in accordance with each country's priorities. A response to such demand requires an understanding of what technologies increase the quality and value of health care along with knowledge of the policy levers that encourage health care systems, patients, and clinicians to adopt appropriate technologies. These forces enhance the importance of CER and HTA activities and the mechanisms that promote the adoption of best practices.

Although the organization and financing of health care are different in the United States and Europe, Australia, and Canada, which lead to diverse mechanisms for both CER and HTA, there are common issues and opportunities for improvements in methods that can inform HTA and PCOR across countries. The opportunities for international collaboration are perhaps greatest in four areas: patient engagement, observational research methods, meta-analysis, and implementation research. [Box 11] International exchange and collaboration can be key for improving and establishing HTA.

One key area for future collaboration is approaches to implementation—that is, undertaking deliberate strategies to encourage the implementation of evidence-based clinical decision-making and evidence-based coverage and payment policy. In Europe, Canada, and Australia, there are direct mechanisms for bringing results of effectiveness analyses for technologies into practice that are not present in the United States. However,

Box 11. Areas within CER and HTA with Potential for Mutual Learning

Patient engagement: How do you include patient and family perspectives and benefit from them? How do you coach and train people to be good participants?

Observational research methods: How can observational data be used to make CER more practical, relevant, and timely? How will they be generated and analyzed?

Meta-analysis methods: Network meta-analysis and indirect comparisons can be looked into by all HTA bodies and PCORI

Approaches to implementation: How do you translate evidence and knowledge in a more decentralized practice system?

there is also a need for additional activities focused on local implementation. An issue for the United States, going forward, is whether the dissemination and implementation activities to be undertaken by PCORI will be sufficient to encourage widespread change in health care coverage and delivery.

Across countries, the question of the impact of CER and HTA is never far from view. This leads to questions like: how do we assess whether we have had an impact in clinical practice? How does the impact compare with desired outcomes? And equally important, if there is no impact, an investigation about barriers to impact would be necessary. Was the time frame too short? Were the incentives for adoption not strong enough or, worse, were perverse incentives in place? Of course, financial incentives—like payments for particular outcomes or actions—need to be aligned with the HTA decisions for these to have maximum impact on practice. Methods and strategies from the emerging field of Research Impact Assessment (RIA) may be useful here.

Another significant aspect of impact assessment is timing. When is the right time to evaluate the impact of CER or HTA? In the United States, a GAO evaluation of PCORI is due to Congress by March 2015. The primary objectives for the review are to examine: (1) whether PCORI established research priorities and funded research in accordance with its legislative requirements, and (2) the extent to which PCORI has established plans and undertaken efforts to evaluate the effectiveness of its work.[64] The time frame for this evaluation is appropriate for examining issues around use of funds (e.g., whether funded studies addressed the most pressing issues in the most effective ways), but it is too short to assess the quality and relevance of the findings from the research funded, what effect the CER has had on medical practice, and certainly too short to look at effect on health care outcomes. This question is particularly important for PCORI, since an impact assessment will be done by GAO in 2017, just before PCORI's authorization and funding expires in 2019.[43,65]

In sum, the enhanced CER and HTA activities in the United States, European nations, and other countries underscore the need for overall evaluations of the effects of CER and HTA on health care systems. Increasingly, countries want to know if CER and HTA efforts are improving or likely to improve clinical practice, patient care, and health outcomes while enhancing the performance of their health care systems. Do we see appropriate use of health care technologies and the delivery of evidence-based, high-value care? Have these comparative effectiveness analyses helped improve quality and efficiency in health care? There have been calls for overall evaluations in Europe.[7] GAO is conducting such an evaluation for PCORI's efforts in the United States. Evaluation of the effects of CER and HTA on the health care system is important and could inform the future direction of these efforts internationally. Further engagement by researchers and stakeholders in the United States, including PCORI's leadership, in international developments will promote mutual learning and could enhance the impact of PCOR investments in this country.

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