

The Lewin Group Center for Comparative Effectiveness Research Symposium 2010

“Responding to the National CER Agenda: Evolving Data Sources and Analytics”

Symposium Date: June 15, 2010

SUMMARY AND KEY FINDINGS

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1. Executive Summary

On June 15, 2010, coinciding with the 40th anniversary of The Lewin Group, its Center for Comparative Effectiveness Research convened noted experts to discuss comparative effectiveness research (CER) methods, how best to improve them, and important considerations in applying these methods. Carolyn Clancy, MD, Director of the Agency for Healthcare Research and Quality (AHRQ) and David Blumenthal, MD, Chairman of the Office of the National Coordinator for Health Information Technology, provided the keynotes at the event, attended by senior government officials, policy and thought leaders, and academics focused on CER.

Entitled “Responding to the National CER Agenda: Evolving Data Sources and Analytics,” the symposium focused on ways to improve and adapt diverse health care data sources and analytical methods to address the current and anticipated demand posed by CER. The discussion went beyond an identification of inherent challenges in meeting this demand to delving into practical solutions for overcoming these challenges.

Speakers and panels covered:

- the limitations of current data, as well as the uses of new data sources in CER and ways to link claims data to outcomes;
- the limits of randomized clinical trials in CER and methods of accounting for these limitations in their application, including in-depth discussion of propensity scoring, selection bias, and decomposition analysis; and
- Health Insurance Portability and Accountability Act (HIPAA) constraints, related to issues of privacy and confidentiality, and how to advance CER while maintaining these protections.

This white paper provides a summary of the rich discussion that took place at the event and the insights that it produced. In particular, the following themes emerged:

- 1) **The time is ripe for CER.** The nation is focused on reducing health care costs, while improving patient outcomes. Funding for CER from the American Recovery and Reinvestment Act of 2009 (ARRA), as well as incentives for the adoption of health information technology (HIT), represent an unprecedented investment and a critical opportunity to translate research into better patient care. We must seize this opportunity.
- 2) **CER holds great potential, but getting the research methods and analytical tools right is essential for achieving this potential.** Although we have access to vast quantities of data, we have to be able to adapt and improve these methods and tools to derive valid findings from the data and improve patient outcomes. Beyond simply acknowledging the challenges, we must develop innovative, yet practical solutions for meeting national CER priorities.

- 3) **Current methods, including randomized clinical trials (RCTs) and other clinical trials, have limitations, and new trial designs may be needed.** Although important for certain purposes (e.g., market clearance of products regulated by FDA), RCTs are less useful for other essential purposes in health care. Answering the questions presented by our changing system of care requires a variety of research methods, including new trial designs that more closely mimic real world settings.
- 4) **Analytical tools can help mitigate these limitations.** Analytical tools such as propensity scoring can improve the utility of other study designs such as observational studies for generating credible findings about the impact of interventions on health outcomes.
- 5) **Currently available data have limitations for CER.** Data in insurance claims, patient registries, and other sources that were not necessarily designed to assess the impact of health care interventions on outcomes have well-recognized limitations for CER. Still, their potential for serving the needs of CER can be improved by developing ways to link multiple sources and follow patients longitudinally, including as they move from one type of coverage to another (e.g., from commercial health plan to Medicare).
- 6) **Privacy concerns must be appropriately balanced with achieving research objectives.** Privacy concerns must be adequately addressed, including via de-identification and innovative database designs to achieve the full benefits of CER. Improved methods are needed to generate CER findings in diverse populations and health care settings without jeopardizing privacy.
- 7) **Collaboration is essential.** Fulfilling the purposes of CER will require collaboration among all interested parties: clinicians, patients, researchers, payers, policymakers, and others.

The following summarizes the symposium presentations and discussions that led to these insights.

2. Introduction

What is Comparative Effectiveness Research (CER)?

The Institute of Medicine defined CER as “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, clinicians, purchasers and policy makers to make informed decisions that will improve health care at both the individual and population levels.”¹

Essentially, CER involves the direct comparison of two or more health care interventions to determine which works best for which patients under *real-world* – not ideal – circumstances. We have many more treatment options and other health care technologies or interventions at our disposal than ever before. However, they do not all work for all indicated patients.

Although common use of the term is fairly new, CER itself is not. The Agency for Healthcare Research and Quality (AHRQ) has been formally involved in what we now recognize as CER at least since implementation of the Medicare Modernization Act of 2003, and the National Institutes of Health (NIH) has been conducting certain large clinical trials that meet current definitions of CER at least since the 1990s. Kaiser Permanente and some other health care systems have been conducting some form of CER as well. Though not new, the concept has gained popularity lately for its potential to improve health care quality, patient outcomes, and resource allocation.

President Obama and the Congress have committed significant resources to CER. The American Recovery and Reinvestment Act (ARRA) provided \$1.1 billion for CER, including \$400 million to the Office of the Secretary at the U.S. Department of Health and Human Services (HHS), \$400 million to NIH and \$300 million to AHRQ. ARRA also established the Federal Coordinating Council for Comparative Effectiveness Research (FCCER) to facilitate coordination of CER conducted or supported by the Federal government.

Further, the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, contains provisions supporting the development of CER, including the establishment of the Patient-Centered Outcomes Research Institute (PCORI), and closes down the FCCER. The purpose of PCORI is to “assist patients, clinicians, purchasers, and policymakers in making informed health decisions” through conducting CER and disseminating research findings.

¹IOM Consensus Report, “Initial National Priorities for Comparative Effectiveness Research,” released June 30, 2009.

Public Sector Commitment to CER

3. Carolyn M. Clancy, MD, Director, Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services



Dr. Carolyn Clancy provided the first keynote of the symposium, addressing the commitment to CER by AHRQ and the Federal government more broadly. As Cliff Goodman of Lewin's Center for Comparative Effectiveness Research noted in his introduction of Dr. Clancy, AHRQ has been involved with what we now recognize as CER since well before the passage of ARRA (2009) and even before its more formal involvement pursuant to provisions of the Medicare Modernization Act of 2003.

During this time, AHRQ has been involved not only in conducting and funding CER, but in developing the methods and other aspects of the state of the art of CER. AHRQ is strengthening the science and infrastructure of CER, guided in part by the recommendations of the Federal Coordinating Council for CER and the IOM. ARRA funding for CER represents an unprecedented investment and a critical opportunity to transform research into better patient care.

Dr. Clancy noted that there was a time not too long ago when there were few large sources of data for conducting CER, but now such data are increasingly plentiful. The challenge is to determine how to derive scientifically valid and clinically practical meaning out of such data. That is why developing improved methods is so important.

As Dr. Clancy indicated, we are increasingly seeing opportunities to inform policy with science, which is at once daunting and exciting.

Dr. Clancy described AHRQ's priorities, including a strong focus on patient safety; evaluating applications of health IT to ensure they improve quality and safety; and trying to determine how to draw on electronic health records (EHRs), including linking them to claims data and other sources, for CER. The funds allocated to the agency have been heavily invested in data analytics and methods, and ARRA funds have enabled AHRQ to make a very significant investment in evidence generation.

Dr. Clancy noted that AHRQ's priority is getting evidence-based, patient-centered information to the front lines of care. Indeed, she noted that the front lines of health care need to be incorporated into the research enterprise, given the wealth of information that can be drawn from every health care encounter. Higher quality patient information, with the ability to track patient experience over time, will enable better understanding of how patients are being treated in practice, what works, and what doesn't.

Dr. Clancy noted AHRQ's emphasis on building the necessary infrastructure for CER. Reports from both the FCCER and the IOM, which were both informed by broad stakeholder input, focused very strongly on infrastructure.

AHRQ has also focused on ensuring that the research addresses the needs of priority populations who might not normally be well represented in clinical and other studies. Dr. Clancy noted that, besides changing enrollment criteria for clinical trials and other studies, we need to build data resources, including EHRs, where these people get care.

She emphasized that the methods and scientific underpinnings of CER are relevant across the various agencies within HHS – from FDA's work on post-market surveillance to the Office of Minority Health and the Centers for Medicare and Medicaid Services (CMS), HHS is committed to coordinating efforts towards the goals of CER.

Dr. Clancy also commented on the importance of PCORI and its role in advancing the methods, analytics, and other aspects of CER.

In sum, Dr. Clancy noted that improving CER is mostly about improving the quality of health care in the U.S., and doing so will require being able to follow people over time and across health care settings. While incentives for implementing health IT, including EHR systems, will help make this possible, there is much work to do.

Dr. Clancy quoted Dr. Donald Berwick (the newly appointed CMS Administrator) as saying that "Only those who provide care can improve that care." And so Dr. Clancy reiterated that we have a critical opportunity and obligation to make incorporation of CER findings easy on the front lines of health care.

4. David Blumenthal, MD, MPP, Chairman, Office of the National Coordinator for Health Information Technology, U.S. Department of Health and Human Services



Dr. David Blumenthal served as the second keynote speaker at the event. The Office of the National Coordinator for Health Information Technology (ONC) is the principal federal entity charged with coordinating nationwide efforts to implement and use the most advanced health IT and the electronic exchange of health information to improve patient care.

As did Dr. Clancy, Dr. Blumenthal emphasized the transformational nature of current opportunities. With incentives and funding available from ARRA and the health care reform law, he believes we are well-positioned to overcome the challenges we face as we seek to implement the rapid adoption of health IT, which will be essential for enabling CER to improve health outcomes.

Dr. Blumenthal described information as the lifeblood of medicine, and health IT as the circulatory system that gets that information where it is needed. However, challenges remain for achieving widespread adoption of EHRs and other aspects of health IT.

In contrast to the gradual evolution of the health care system in the U.S., the Office of the National Coordinator was tasked in 2009 with implementing certain revolutionary changes in health IT in only a few short years. Beyond important legislative and regulatory actions, e.g., meaningful use criteria, many challenges remain for managing this change.

Dr. Blumenthal referred to meaningful use as “the cornerstone for the information so vital to our circulatory system.” He noted that, while the definition of meaningful use may change, the goal remains the same: for EHRs to capture health data and enable it to travel readily for use in patient care when and where it is needed.

Dr. Blumenthal referenced the five domains of objectives, criteria, and measures – identified by the Health IT Policy Committee (an ARRA-authorized federal advisory committee) – that should undergird the meaningful use concept:

- 1) Improving quality, safety, and efficiency of health care;
- 2) Engaging patients and families;
- 3) Coordinating care;
- 4) Improving population and public health; and
- 5) Ensuring privacy and security.

These domains have direct relevance to CER.

As described by Dr. Blumenthal, to reach the full potential of CER, we must first get data into an electronic format, primarily through creation of EHRs. Then we have to determine how to enable efficient exchange of that information. Aside from technical challenges involving hardware and software, the bigger challenge entails achieving the necessary collaboration of stakeholders with diverse health care ideologies, incentives and socioeconomic characteristics. Indeed, no country has achieved what we're trying to do. Meaningful use is an essential element of the economic rationale for exchange. Further, implementation standards and a common language are needed so that systems can talk to each other, that is, exchange data and information. In addition, we need to specify directions through the rule-making process about how to implement this exchange.

A related issue concerns authorized providers, that is, those who are authorized to receive private health information. Also, given the variety of payers in the U.S. and transition of patients among these payers, such as patients moving in and out of Medicaid programs with changes in eligibility and patients moving from commercial health plans into Medicare, the lack of standardization of electronic and non-electronic information held by payers and difficulty of tracking patients across time pose especially difficult challenges.

Further, although ONC and others are engaged in developing standards, protocols and policies for transmitting data over the Internet, patients and the public at large must trust that this transmission is secure to ensure widespread adoption and use of these systems. Dr. Blumenthal acknowledged that one of the most important societal questions we face is how to balance privacy concerns against the promise that CER and other aspects of health reform offer for improving patient care.

The ONC recognizes the importance of states in transforming health IT and has asked them to play a major role in this enterprise. States license physicians and nurses, and so they are well-prepared to designate authorized users. They also have at their disposal a vast repository of data in their Medicaid systems, they receive immunization records, and they regulate aspects of the health care industry. So the ONC is engaging and empowering the states in, for example, a series of demonstration projects called "beacon communities." These sites were selected because they have already demonstrated some measure of success in terms of solving health IT challenges, but they are also tasked with showing further demonstrable results within 36 months.

Dr. Blumenthal used the analogy of an escalator to illustrate how we are adopting health IT, with getting providers to enter personal health information into electronic form as the first step. CER is the goal at the top of the escalator.

Dr. Blumenthal acknowledged the critical need for consensus from clinicians and hospitals during this adoption period. He noted that we need to change the perceptions among clinical physicians that electronic health records are simply receptacles of information; instead they must be seen as vehicles to further ends. He added that clinical decision support – broadly speaking, the systems, applications or processes that help health care professionals make clinical decisions to enhance patient care – is the next big enabler of health IT.

The ONC recognizes the considerable economic and social barriers to the national health IT transformation. Certainly, provider organizations and payers in competitive environments may not be naturally inclined to share data. However, Dr. Blumenthal expressed confidence that these barriers can be overcome, in particular through partnerships the ONC is developing with professional medical societies and other major stakeholder groups.

Dr. Blumenthal further expressed confidence that, in particular as new generations of medical students enter the field, consensus will emerge that EHRs, and health IT more broadly, are integral to the practice of medicine.

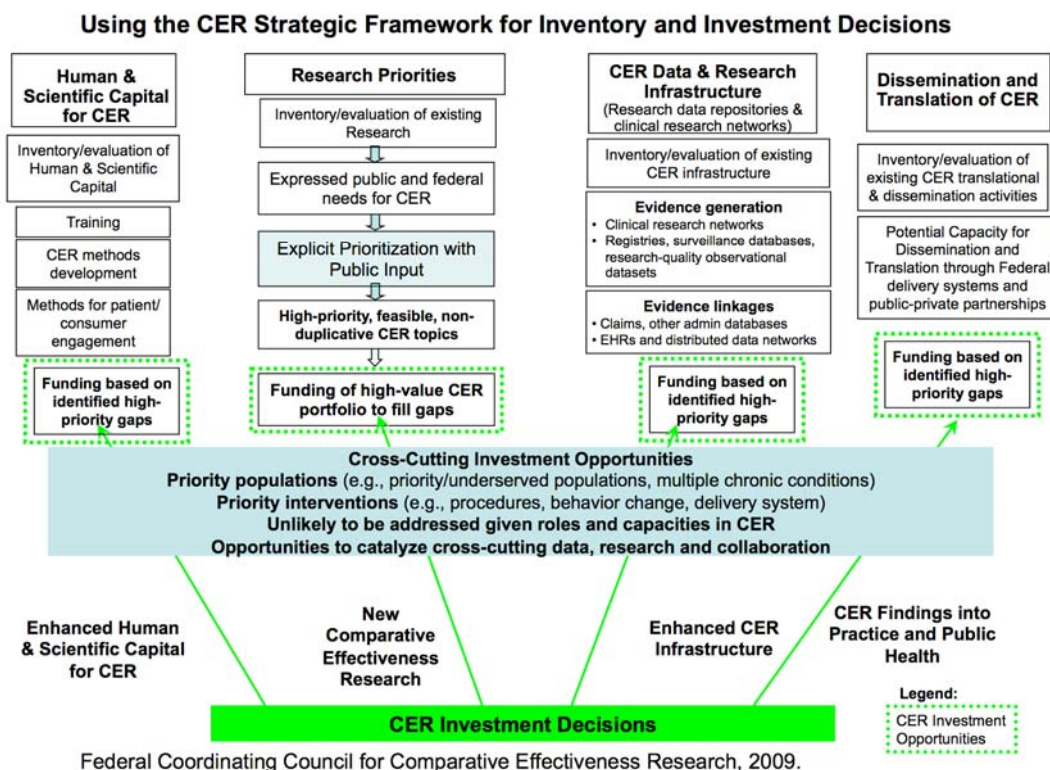
Expert Input on CER From The Front Lines: Researchers, Economists, Clinicians, Policy Experts

5. What Are The Limits of RCTs and Other Clinical Trials for CER? Then What?

The first panel of the symposium focused on the limitations of RCTs and related trial designs for CER and on ways to mitigate these limitations, for example through new trial designs that reflect real world settings and through the establishment of appropriate infrastructure and standards. Panelists noted that, while they remain central to market approval for certain products regulated by the FDA, the methods that have long been considered the gold standards of biomedical research can fall short with respect to needs of CER. Rather than any single research method, CER necessarily entails an evolving toolkit of methods.

- **Clifford Goodman, PhD, Vice President and Acting Director, The Lewin Group Center for CER**

Dr. Clifford Goodman introduced this panel by addressing the limits of traditional RCTs and other clinical trials for CER, and suggested how these shortcomings can be addressed through CER. While noting that comparing the impact of alternative interventions on patient outcomes to guide treatment and coverage decisions is not new, there is far greater demand currently for conducting this type of research in a systematic and scientifically valid way. Doing so on a large scale requires extending beyond traditional clinical trial approaches to designs that better account for diverse patient populations and health care settings, with methods that draw on and link alternative data sources.



To the extent that traditional RCTs are conducted under highly controlled protocols in which research participants are selected and treatments are administered in ways that do not reflect real-world circumstances, their findings may be of limited relevance to practice. Data used in CER should reflect more realistic scenarios – including varied patient characteristics and circumstances of care that could affect patient outcomes. CER methods should account for how interventions work under routine, community circumstances. Toward improved CER data sources and methods, and consistent with the CER infrastructure described in the 2009 FCCER report, significant portions of ARRA funding are being devoted to human & scientific capital (i.e., training and methods development) and to data infrastructure (e.g., wider use of claims data and registries and linking these with other sources such as EHRs to conduct CER). Also emphasized in the 2009 FCCER and IOM reports on CER priorities, CER must emphasize subgroup analyses and priority populations that have not been included extensively in past research to enable the evidence base needed to support care decisions for individual patients, including to fulfill the goals of “personalized medicine.”

In addition to generative valid CER findings, it is necessary for this new evidence to be converted into user-friendly information and made available in media and formats that inform care decisions and policies. As such, a significant portion of ARRA funds for CER are being devoted to translation and dissemination of CER.

- **Sheldon Greenfield, MD, Executive Director, Health Policy Research Institute, University of California, Irvine**

Dr. Sheldon Greenfield detailed certain limitations of current clinical trial designs. Among these, large treatment groups that are characterized as being largely homogeneous actually comprise subgroups that may respond differently to interventions. Further, in the context of RCTs, patients assigned to “usual care” groups receive care that is far better than patients in real practice receive. Together, these factors can dilute or mask detection of real treatment effects in some treated patients. In effect, large numbers of relatively well people participate in trials, leaving out those with additional conditions, the elderly and others. Citing diabetes research, Dr. Greenfield noted that RCTs that are not designed to study effects in subgroups can miss important harms and benefits that cannot be detected in larger, homogeneous treatment groups. Intervention effects may not be evident in the larger group, but may have noteworthy effects in subgroups. Toward meeting narrowly defined protocols for studying treatment effects in particular types of patients and avoiding confounding effects, which often means excluding patients with comorbidities, many RCTs enroll patients who are disproportionately in better health than others with the index condition, excluding those with additional conditions, the elderly and others.

Dr. Greenfield described the role of adaptive clinical trials in mitigating some of these challenges. To address these limitations, Dr. Greenfield maintained that adaptive trials hold great promise, as was documented in the June 2010 issue of *Medical Care Journal*. Further, rather than being locked into a strict protocol once a trial starts, adaptive trials can improve trial efficiency by assigning newly accruing patients to particular treatment groups after the trial starts to respond to early observed differences in patient responses to interventions.

Dr. Greenfield noted that it is most important to build the infrastructure and establish widely adopted standards to address the barriers inherent to CER. In addition to the requirements for head-to-head comparisons in realistic health care settings, subgroups must be adequately characterized so that patients fit into them easily, and the use of “usual care” as a basis of comparison must be clearly defined and truly reflect the care that patients receive in practice.

- **Michael Lauer, MD, Director, Division of Cardiovascular Sciences, National Heart, Lung and Blood Institute, National Institutes of Health**

Dr. Michael Lauer concurred regarding the shortcomings of RCTs for CER, although he underlined their central role for other purposes, including market approval or clearance of products regulated by the FDA. He added that some RCTs, particularly those conducted on technologies that are already in practice, are obsolete by the time they are conducted and reported.

In order to be “brilliant experimenters,” Lauer said we must go to the next level: CER. This will involve using new trial designs that reflect real world settings, randomize not just patients but health care units (e.g. hospitals) in a trial, and use the Internet routinely to recruit and enroll trial participants. This will enable CER to make a major contribution to diminishing the adoption and use of technologies that are ineffective or even harmful.

- **Eleanor Perfetto, PhD, Senior Director, Reimbursement & Regulatory Affairs, Pfizer, Inc.**

What is the perspective on CER of the innovative pharmaceutical industry? Dr. Eleanor Perfetto emphasized that success will require collaboration between different methods and experts, the development of standards and infrastructure and the continuous advancement and adoption of CER findings.

CER enables us to ask different and more complicated questions and, with greater public and private sector investment, more of them. This requires a variety of research methods in a variety of settings, as no single study design can answer the range of evidence questions that will arise. The potential of CER stems from its broad research methods portfolio. This broader methods portfolio should enable generating relevant evidence closer to real-time, in contrast to the often much longer timelines involved in conducting and reporting on traditional clinical trials that often yield findings that are outdated by the time they reach clinical practice.

The contrast between the real-time nature of CER and the traditional route of conducting RCTs and other trials within regulatory frameworks also poses barriers for industry. That is, in addition to generating certain types of evidence to satisfy multiple regulatory agencies around the world (e.g., the FDA and the European Medicines Agency), the growing reliance of major third-party payers on CER and related forms of inquiry such as health technology assessment makes conditions for reimbursement highly variable. After being oriented to meeting certain regulatory requirements, companies will be challenged by having to alter their research methods to meet shifting evidence requirements, and systems need to be put in place to guide and encourage assimilation of these approaches.

Dr. Perfetto expressed the need to give greater consideration to personalized medicine and how it will be incorporated into systems of care. More than determining how well a treatment works, we need far better information about *when* it works for particular types of patients and *how* to bring this information into practice. While EHRs hold great potential for facilitating personalized medicine, including for data collection as well as guiding personalized use of particular treatments, much work needs to be done to ensure that they capture enough current and longitudinal data, are linked to other sources, and are adopted widely enough to reach that potential.

Industry is responding to these problems, she said, citing collaboration among such large companies as Pfizer, Eli Lilly and Merck. This type of collaboration arises as such companies recognize that the necessary changes must be system-wide.

Dr. Perfetto concluded that for CER to be effective, it must be understood more holistically as a multi-stakeholder effort to establish standards of methodology, translation and interpretation that can enable evidence to improve whole communities of care. She stressed that CER is not a one-time fix, but is instead an evolutionary advancement of health care science.

6. Propensity Scoring, Selection Bias, and Decomposition Analysis

With the greater interest in alternatives to clinical trials for meeting certain CER needs, the symposium's second panel focused on some of the statistical methodologies for the analysis of observational data, including such methods as propensity scoring, selection bias, and decomposition analysis. While the speakers noted that identifying and addressing confounding variables through methods such as propensity scoring are not appropriate for all types of evidence questions, these methods can offer valid ways to derive findings from observational studies that augment what is known about real-world effectiveness.

- ***William H. Crown, PhD, President, i3 Innovus***

Dr. Crown began his remarks by highlighting a point made in the prior panel that CER is driving increased emphasis on analysis of observational data because of the focus on real-world patient outcomes. He noted the recent significant progress in the development of statistical methodologies for the analysis of observational data, particularly in health economics, labor economics, and epidemiology.

Observational research, like clinical trial research, has its limitations, but Dr. Crown asserted that the very good methods we have, coupled with appropriate study design, can help to overcome some of the challenges of drawing reliable statistical inferences from observational data.

Dr. Crown addressed some misperceptions about the relationships between study design and data quality. He noted that when people think of observational data, they often think of the types of data pulled only from administrative systems, without recognizing that we can, for example, collect the same level of clinical detail in a registry, which is also an observational study, as we can from a clinical trial. Although it is certainly true that randomized trials are generally the strongest study designs for establishing the internal validity of a cause-and-effect relationship, it is possible to conduct observational studies with comparable levels of data quality and clinical detail. The issue then becomes one of selecting appropriate study designs and statistical methods for the analysis of observational data.

Regarding the hierarchy of evidence, Dr. Crown noted that quasi-experimental designs with pre/post-comparisons for treatment and control groups can approach the validity of a traditional controlled clinical trial. Lower down on the hierarchy are weaker analyses of observational data with no controls, which characterizes most of the evidence drawn from observational data. Dr. Crown noted that there are many challenges associated with drawing reliable inferences from data of this type.

Dr. Crown also reviewed certain challenges associated with clinical trials, including that these types of trials measure efficacy rather than real-world effectiveness, and that they are typically designed to measure *average* treatment effects. As such, there is the potential that these trials may overlook heterogeneity of treatment response within different arms (assigned patient groups) of these trials. He noted that these limitations can be addressed, at least in part, with observational data, in ways that were discussed by subsequent speakers.

Dr. Crown discussed three common models for measuring treatment effect. The usual model for measuring treatment effects in outcomes research is to include a simple indicator variable that reflects the treatment received by the patient. Such variables are commonly known as dummy variables. The most commonly used analytic approaches for measuring treatment effects with dummy variables do not account for the potential interaction of treatment with other factors such as patient characteristics in influencing patient outcomes. A better approach involves accounting for the interaction of treatment with all other explanatory variables. This allows all of the variables to affect patient outcomes differently for each treatment. Although theoretically attractive, this approach is often difficult to implement. A third approach is to estimate separate use outcome models for each treatment cohort. This is very similar to the interaction approach but avoids some of the statistical problems often encountered with models that include interaction terms.

With the stand-alone dummy variable approach, we are measuring the gap in expected outcome (i.e., measure of disease relapse or measure of hospitalization) after controlling for everything else. However, this model produces an extremely limited estimate of treatment effect because it assumes that all other characteristics of the patient are related to outcomes in the same way, irrespective of which treatment the patient received.

An alternative is to consider interactions of treatment with all other explanatory variables, thereby capturing the difference in expected outcomes for the patients but also measuring how their characteristics differ in terms of how they are related to their outcomes. As Dr. Crown noted, the problem here is that, when we try this approach, these interactive terms tend to be very highly correlated with the things with which they are interacted, making it difficult to yield a statistically significant result.

A third approach is to split up the model and estimate separate equations for each of these groups, in this way creating a fully interacted model. The challenge is trying to pull a treatment effect out of these separate equations. The advantage here, Dr. Crown noted, is that we learn a lot more about the heterogeneity of treatment response. We can see how all the patient characteristics are related to outcomes within each one of the groups, making it easier to test whether the responses are different. As such, this third approach does provide a means to assess heterogeneity of treatment response. Dr. Crown pointed out that this approach has been used in various types of inquiry, including studies of wage discrimination and racial disparities in health services research.

Dr. Crown commented that we have good statistical methods for observational data, but cautioned that we need to be very thoughtful about study design and the selection of appropriate methods to answer specific research questions—such as developing an improved understanding of the heterogeneity of treatment response.

In summary, Dr. Crown emphasized that data quality matters. ARRA's financial incentives and penalties pertaining to failure to adopt health IT are expected to speed the widespread adoption of EHRs. Enabling the linkage between EHR data and claims data will help to overcome the limited amount of clinical content historically available in claims data. Although the quality of data is critical, the ability to select appropriate statistical methods for the analysis of specific CER questions is also crucial to drawing reliable conclusions from observational data.

• ***John D. Seeger, PharmD, DrPH, Chief Scientist, i3 Drug Safety***

Of paramount importance to CER is the ability to address selection bias and confounding variables, which often characterize traditional research methods, according to Dr. Seeger. Often, flaws in studies are incorrectly attributed to matters of study design, where the flaws actually may arise from poor quality data.

Dr. Seeger explained this distinction using the example of research in statin drugs for managing high blood lipids in which several different large-scale RCTs unexpectedly produced fairly heterogeneous results. When researchers compiled characteristics of the intervention and control groups of these trials, it became evident that selective prescribing occurred; that is, patients with coronary disease and risk factors were more likely to be prescribed statins than those patients without those diseases and risks. Dr. Seeger explained that this reassessment of the results showed that selection bias and patient characteristics, not the statin treatments, were at least partly responsible for the heterogeneous results across the trials that contributed to ambiguity about the appropriate use of statins.

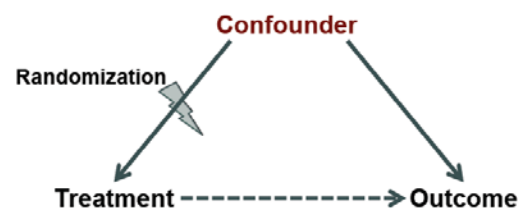
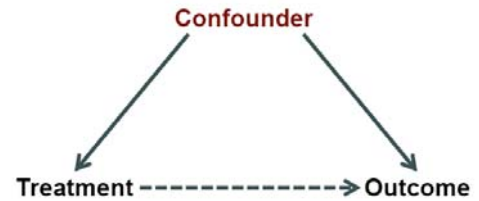
Dr. Seeger categorized confounding variables – patient factors associated with treatment choice and risk factors – into three groups: the “known knowns,” the “known unknowns” and the “unknown unknowns.” Dr. Seeger said that it is vital that researchers in CER have a firm grasp of all these potential confounding variables and think creatively about what could be causing an observed treatment effect, and then work to isolate those factors.

While addressing confounding variables isn't a “silver bullet” for CER, it enables improving the state of the art of observational research. Dr. Seeger noted that the complex aspects of treatment research reflect the high degree of complexity that physicians often face in practice. CER can benefit from probing both types of complexity to add to the evidence on how to improve outcomes in both the clinical and research settings.

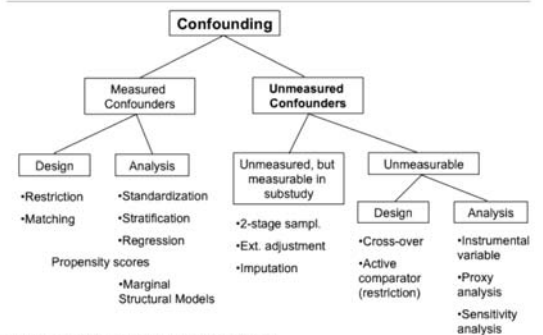
- **Joshua J. Gagne, PharmD, MS, Division of Pharmacoepidemiology, Department of Medicine, Brigham & Women's Hospital**

How should researchers account for confounding variables? Dr. Gagne offered for this purpose high-dimension propensity scoring, in which researchers collect extensive patient characteristic data before a treatment and then adjust for the variables that impact outcomes. He noted that researchers could get closer to understanding impacts on treatment effects if they relied more on EHRs to account for more variables, including administrative, demographic, pharmaceutical and lab data, among others. In the near future, we could begin thinking of incorporating thousands of proxies to identify which variables could bias an outcome, and then adjust for those in the study. However, propensity scores themselves must be identified through a good quality study design, further complicating the research process. Dr. Gagne concluded that propensity scoring helps observational analyses yield findings nearly as beneficial as those generated from RCTs.

While claims and supplemental data captured via CPT codes are currently the main way of identifying unknowns, Dr. Gagne emphasized that the widespread adoption of EHRs will very likely yield great improvements in generating useful data.



Confounding control in observational data

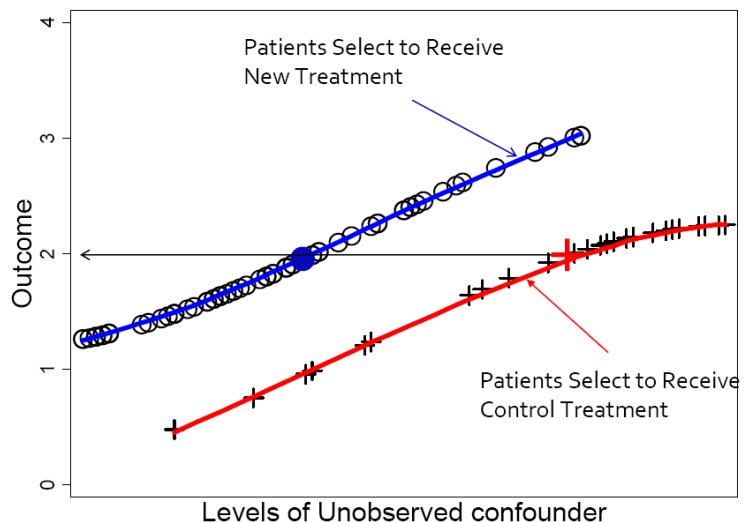
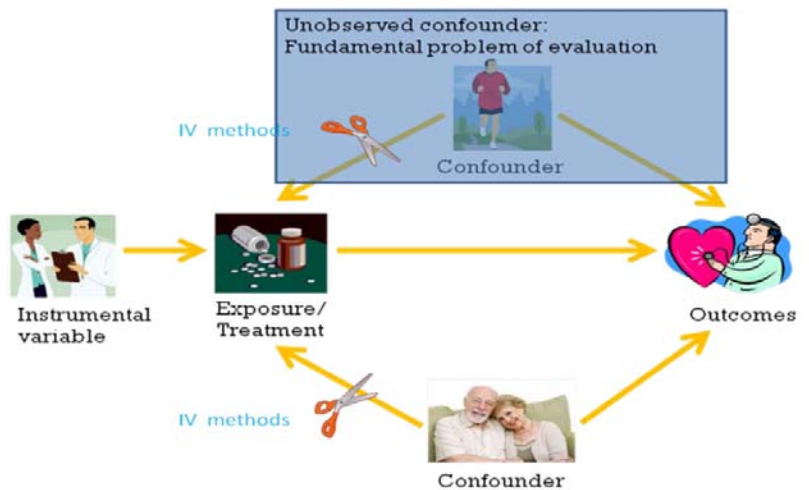


Source: Schneeweiss S. Pharmacoepidemiol Drug Saf. 2006;15:291-303.

• **Anirban Basu, PhD, Assistant Professor, Department of Medicine, University of Chicago**

Dr. Basu began by reminding all that, in the real world, patients have considerable say in selecting their treatment, and that researchers and physicians must support better treatment choices with research that reflects real-world circumstances.

As such, Dr. Basu advocated that instrumental variable analyses, which accounts for observed and unobserved confounders, be used to inform health care policy. In these analyses, the focus is on identifying the appropriate instrument for measuring outcomes rather than on interpreting those results. However, given broader awareness of the role of heterogeneous treatment effects, he emphasized that we must begin to focus more on studying the interpretation of results through observational studies, recognizing the unique opportunity we have to exploit provider- and system-level variations that influence treatment selection but are not linked to outcomes.



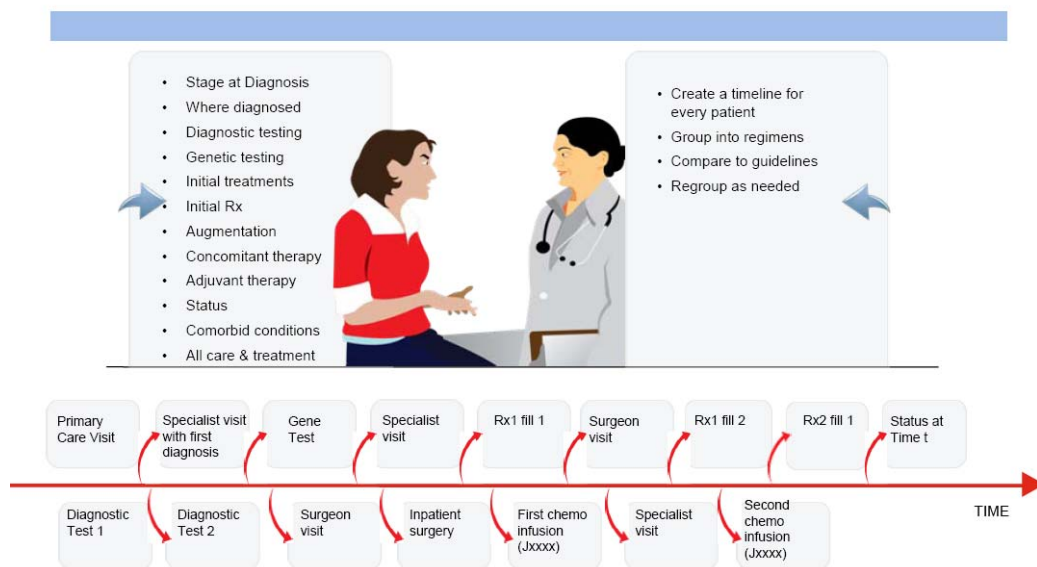
7. What are the New Data Sources? Linking Claims Data to Outcomes

The symposium’s third panel focused on new data sources for CER, including such matters as data accuracy for patient status, services, outcomes, and costs; tracking patient experience over time and through transitions from one health plan or payment status to another; maintaining patient privacy; and the emerging benefits of data collection from integrated health networks. The speakers examined the challenges and benefits in these data sets and linkages, noting the importance of accurate patient identification and privacy subject to HIPPA regulations and newer policies arising from health reform legislation.

• **Taylor Dennen, PhD, Managing Director, The Lewin Group for Comparative Effectiveness Research**

Taylor Dennen, Managing Director for Lewin’s Center for Comparative Effectiveness Research, spoke on the value of large administrative data sets for CER and the opportunities to yield findings through linkages across these sources. He emphasized the benefits of claims and other observational data for capturing the breadth of health care across settings, the depth or detail of patient data (e.g., including pharmacy, laboratory, and socioeconomic data), and patient experience over time.

Among their important uses, large data sets enable specifying a population with a particular disease or set of risk factors, by including identification of new cases, utilization of related services over time, and associated costs. Claims data and EHR data are being increasingly linked, for example, in such areas as oncology care provided in integrated health networks. These types of analyses can help to discern patterns of diagnosis and treatment in those populations and their respective subsequent health events and certain outcomes in real practice. Further, that information can provide insights regarding more or less successful interventions and related patient management.



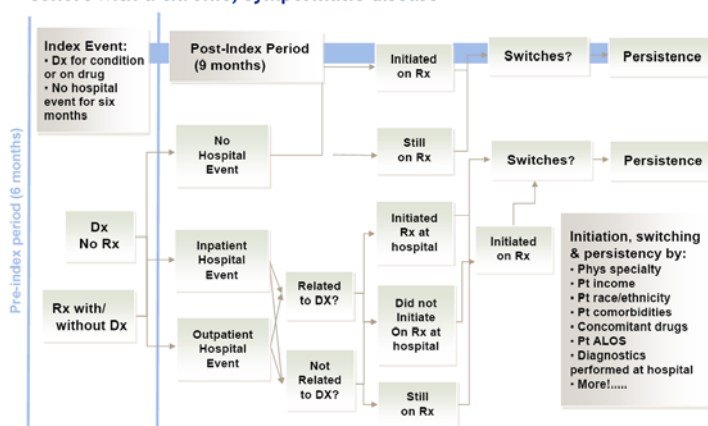
An important research application of claims data is to analyze the feasibility of conducting clinical trials, for example, by determining the availability and geographical location of particular types of physician investigators and patients that would meet the specifications of a clinical trial and related needs for recruiting physician investigators and enrolling patient subjects. Subject to appropriate IRB or privacy board approval, claims and other observational data from individual members of a family can be linked to form family units, which can provide highly useful information that could not be discerned from the individuals alone. An example of a public health application of such linkages would be to determine the immunization or other health-seeking behavior of parents for siblings born after a child who was diagnosed with autism. Of course, there are limitations in applying claims and EHR data. For example, while these sources can show that a physician has prescribed medications for a patient, they may not reveal whether that patient actually fills the prescription or adheres to a regimen. Another type of shortcoming that can diminish the utility of these sources is lack of standardization in data fields and completeness.

Essential to linking data sources for CER is appropriately maintaining protected health information (PHI) and personally identifiable information (PII). Using PHI and PII, such as combinations of name, social security number, exact date of birth, or other items can achieve high reliability of identifying or matching patients across data sets. However, a variety of permissions and reviews are typically required to allow using PHI/PII for linking purposes. Another protective approach is encryption of data fields, a methodology taken by many health care providers. Probabilistic matching is another approach for patient identification that involves inferring that patient A who received certain services is the same as patient B who received certain services because they share the same name and attended a particular doctor's office on the same day. However, the large magnitude of many data sources and the frequency of incomplete or flawed data can diminish the accuracy of patient identification using probabilistic matching.

Dr. Dennen noted that the considerable variations in how physicians and other providers deliver health care, whether in managing diabetes or schizophrenia or other conditions, greatly complicate understanding of what factors have affected health care outcomes. While recognizing the benefits and limitations in claims, EHRs, and other observational data sources, much can be learned by

linking these to provide a better picture of patient flow over time across sites and providers, use of interventions and related delivery patterns, and health outcomes. This real-world patient experience can be used to improve health care pathways and outcomes.

Case Study: Impact of a hospital event on therapy use by a patient cohort with a chronic, symptomatic disease



• ***Mary L. Durham, PhD, Senior Investigator, Director, The Center for Health Research and Vice President/Research, Kaiser Permanente***

Dr. Durham described the longstanding experience of Kaiser Permanente in using data sources in an integrated health care system and its more than \$6 billion investment in its clinical information system. Kaiser Permanente's HealthConnect clinical data system has been implemented for more than 9 million people across the Kaiser Permanente's consortium of health plans in eight regions in the U.S. Among other distinguishing attributes of this system are its longitudinal coverage of the large population of enrollees who have been Kaiser Permanente members for a lifetime and its models of integrated health care and payment. This provides a large and unique health data environment for conducting health services research.

Currently, Kaiser has funded and will continue to fund a variety of CER and other forms of clinical and health services research funded by NIH and other sources, including some 3,500 studies and 1,200 clinical trials.

In recent years, and as part of the HMO Research Network, Kaiser Permanente has been developing an integrated data warehouse that can be used across the various member plans. Although pulling together these regional data assets has been challenging, it is yielding an increasingly valuable research resource.

Areas of research that have produced notable findings include those in atrial fibrillation, warfarin and blood clot prevention, Chlamydia screening to reduce pelvic inflammatory disease, Cesarean-sections, and myocardial infarction.

Dr. Durham emphasized the ongoing success arising from the collaborations with NIH and the HMO Research Network, as well as the importance of continued focus on privacy protections. Citing its members as its greatest assets, Durham emphasized the importance of maintaining the integrity and reputation of Kaiser Permanente and the benefits to be realized by addressing national CER priorities.

8. HIPAA Constraints, Privacy and Confidentiality in Today's Research Environment

The final panel of the symposium focused on a topic that was referenced by most previous speakers: how to maintain privacy and confidentiality while advancing the use of observational data in CER. As noted above, Dr. Blumenthal identified this as one of the most important societal concerns pertaining to health care research. Speakers concurred that building public trust through rigorous data management practices is essential for success in CER, as is ongoing pursuit of high-quality data and valid research findings. This panel focused on solutions to this challenge, in particular on appropriate and effective means of de-identification and the use of innovative data management technologies for data sharing and applications to improve the yield of CER.

- ***Marcy Wilder, JD, Partner, Hogan Lovells***

Ms. Wilder, a nationally recognized data protection lawyer who specializes in health information law, opened the panel with an overview of the federal laws governing health policy. She noted that the Health Information Technology for Economic and Clinical Health Act (HITECH) is the biggest change to the health care privacy and security environment since enactment of the HIPAA privacy rule in 1996.

Ms. Wilder referred to HIPAA as the health privacy baseline, with HITECH strengthening, rather than changing, privacy protections for health information through enhanced enforcement mechanisms, including new requirements and penalties. For example, whereas penalties for civil violations were previously capped at \$25,000 annually per provision violated, HITECH increased this cap to \$1.5 million annually per provision violated, with mandatory fines for violations resulting from "willful neglect."

Ms. Wilder noted that penalties have always applied to covered entities, including providers, health plans and clearinghouses. Under HITECH, HIPAA rules now extend directly to business associates such as service providers.

HITECH also includes mandatory periodic audits by HHS and stringent federal data breach notification rules. Under HIPAA, covered entities must notify individuals, HHS and the media, as well as attorneys general in some states. Under HITECH, notice must be provided within 60 days of discovery, and HHS posts on its web site all breaches that affect 500 or more individuals.

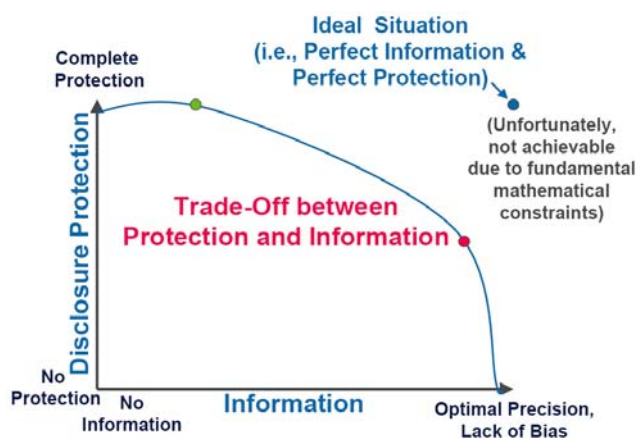
HITECH also requires HHS to issue new guidance on de-identification of data.

• **Daniel C. Barth-Jones, PhD, MPH, Assistant Professor of Clinical Epidemiology, Columbia University Mailman School of Public Health**

Dr. Barth-Jones focused his remarks on de-identified data sets, and in particular on statistical de-identification. He noted that de-identification has very important advantages for CER using observational data. While these data have been collected for other purposes, they have great utility for research and their use can avoid some of the selection and information biases that might otherwise apply. Dr. Barth-Jones emphasized that rich de-identified data from EHRs provide great promise for the future of CER.

Although not the main focus of his remarks, Dr. Barth-Jones addressed HHS guidance on “safe harbor” provisions pertaining to breach of health data, what needs to be removed to be classified as de-identified under this provision, and the reasons that safe harbor data are, in many circumstances, less suitable for CER.

Consistent with previous speakers, Dr. Barth-Jones noted the challenges of linking de-identified data, including the expansion of complexity arising from efforts to link continual streams of data for analyzing the longitudinal experience of patients. Further, this may raise the risk of re-identification attacks. Dr. Barth-Jones provided specific examples of such attacks.



Key regulatory provisions on re-identification state that the risk must be very small that the information could be used in combination with other reasonably available information by the anticipated recipient to re-identify the individual. He observed that there is a fairly constant expansion of what can be considered “reasonably available information.”

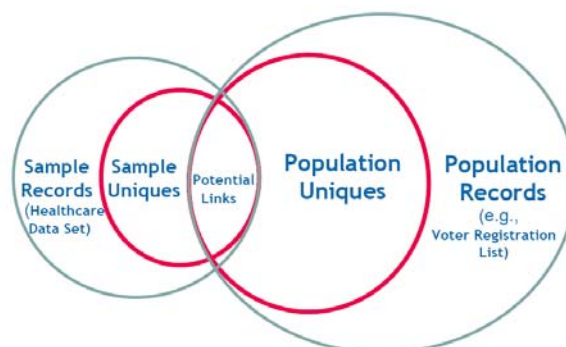
Dr. Barth-Jones identified three common misconceptions about HIPAA de-identified data. One is that “it doesn’t work,” i.e., that it fails to provide important privacy protections. He offered that, while de-identification is not perfect, it is 400-1,000 times more protective of privacy than permitting direct access to personal health information.

A second misconception about de-identification is that “it works,” i.e., that it frees data from all subsequent privacy concerns and that data remain de-identified regardless of how it is used subsequently.

A third misconception is that perfect de-identification is either possible or desirable. That is, there are tradeoffs between pursuing perfect de-identification and costs. Dr. Barth-Jones also discussed the impracticality of the developing a perfect population register.

Dr. Barth-Jones emphasized the ongoing need to reduce re-identification risks, and that “success” means appropriately balancing disclosure risks and statistical accuracy. He noted that HHS recommendations for de-identification are forthcoming, and said that these recommendations should continue to support a very low risk threshold, given the great societal good that can be derived with de-identified data.

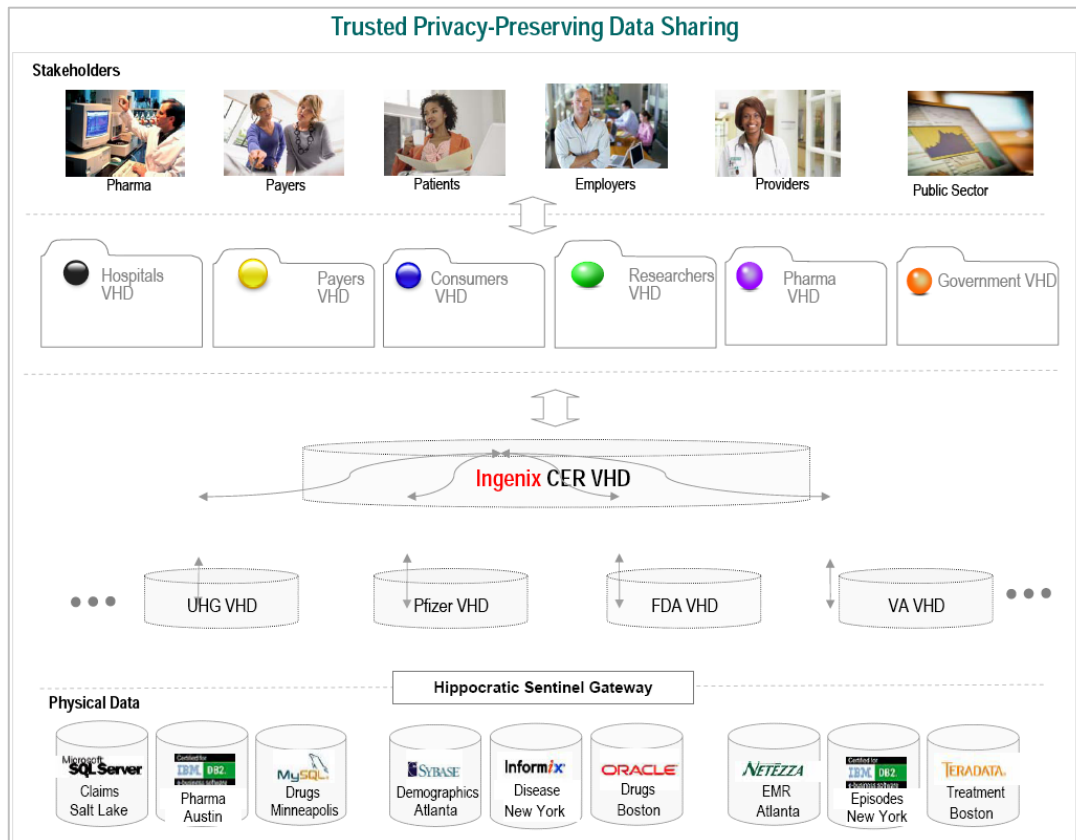
Measuring Disclosure Risks



- **Adindu Uzoma, MS, Senior Fellow, Ingenix; Chief Visionary, UHG Enterprise Technology**

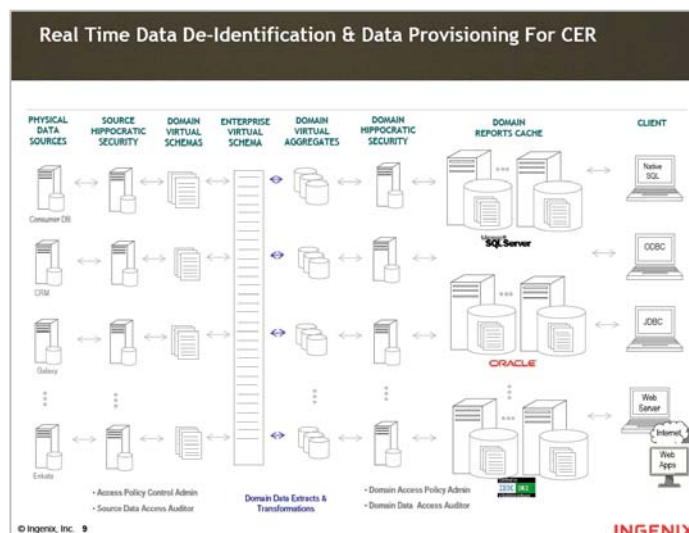
Adindu Uzoma described a new framework for trusted data-sharing among heterogeneous sources, such as different health plans or medical record systems, known as a virtual Hippocratic database (VHD).

As described by Mr. Uzoma, the VHD model holds major advantages over traditional approaches to data sharing. He noted that traditional, centralized approaches to data linkage may not adequately protect privacy, and modern federated approaches are at best inefficient. The VHD provides strong privacy protections, as well as efficient research operation.



Mr. Uzoma described numerous benefits of VHD for CER, including that it:

- Implements multi-stage, purpose-specific, real-time virtual data extraction, de-identification, transformation and aggregation from a federation of heterogeneous data sources;
- Eliminates the need to bring actual data extracts into a physical environment (e.g., warehouse);
- Increases the variety of data views that can be created quickly from many heterogeneous data sources based on purpose and needs;
- Provides data anonymization and watermarking;
- Provides “on-the-fly” policy-driven data masking and Hippocratic security and access control;
- Provides fine-grained access audit; and
- Increases the speed with which research and other questions can be answered.



In summary, Mr. Uzoma emphasized that the manner in which VHD removes privacy concerns and facilitates trusted data sharing in a federated data environment for optimal research results.

• **Deven McGraw, JD, LL.M., MPH, Director, Center for Democracy and Technology**

Deven McGraw described the role of The Center for Democracy and Technology as a non-profit public interest organization working to enhance free expression and privacy in communications technologies. She stated that people want the benefits and ease that come from the adoption of health IT, but they also want strong privacy protections. In the absence of such protections, she suggested that people will engage naturally in “privacy-protective behaviors.”

Rather than viewing privacy and security protections as obstacles to adoption of health IT, Ms. McGraw said they should be considered enablers. That is, a comprehensive privacy and security framework will help facilitate the trust, acceptance, and adoption of health IT.

Ms. McGraw described this comprehensive framework as incorporating the baseline protections of HIPAA and HITECH, and that additional layers are needed, including strengthened standards for de-identification. These strong data practices and appropriate accountability and oversight for privacy and security of health data will help to build public trust in CER.

Conclusion

Comparative effectiveness research (CER) holds great promise for improving the quality of health care and patient outcomes. By comparing the real-world effectiveness of alternative interventions, CER can provide physicians and patients with better information to support clinical decisions for particular patients. CER can also strengthen the evidence base for informing decisions and policies of health professional organizations, health plans and other payers, health care institution managers, patient groups, and others. In doing so, CER can improve the efficiency of health care spending.

The CER symposium hosted by The Lewin Group's Center for Comparative Effectiveness Research on June 15, 2010, extended beyond a discussion of the challenges associated with CER implementation, engaging experts in a dialogue about real solutions to these challenges, in particular with regard to data sources and analytical methods and tools. Experts from a variety of fields probed pertinent clinical, methodological and social issues and shared progress and new ideas for continuing to advance the resources for and state of the art of CER. The Lewin Center for CER will continue to be directly engaged in these collaborative, interdisciplinary efforts to advance the field.

About The Center

The Lewin Group Center for Comparative Effectiveness Research draws on expertise from The Lewin Group, i3, and Ingenix to provide independent, data-driven, evidence-based policy recommendations regarding approaches for implementing CER and evaluating its impact. The Lewin Group, established in 1970, brings more than 40 years experience to assist government, private sector, and academic institutions to establish CER programs, design and facilitate appropriately conducted research, provide access to data sets required for sound CER programs, and interpret and communicate CER findings. This research can inform the decisions that help achieve the most effective patient outcomes, health care policies, and deployment of health care resources. For more information, visit www.lewin.com/CER.



Center for Comparative Effectiveness Research

3130 Fairview Park Drive, Suite 800 • Falls Church, VA • 22042 • From North America, call toll free: 1-877-227-5042 • engage@lewin.com
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