Exhibit 1: What is RWE?

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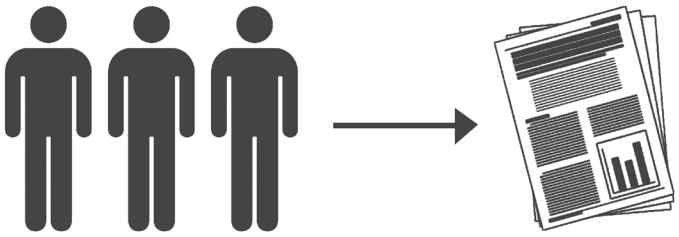
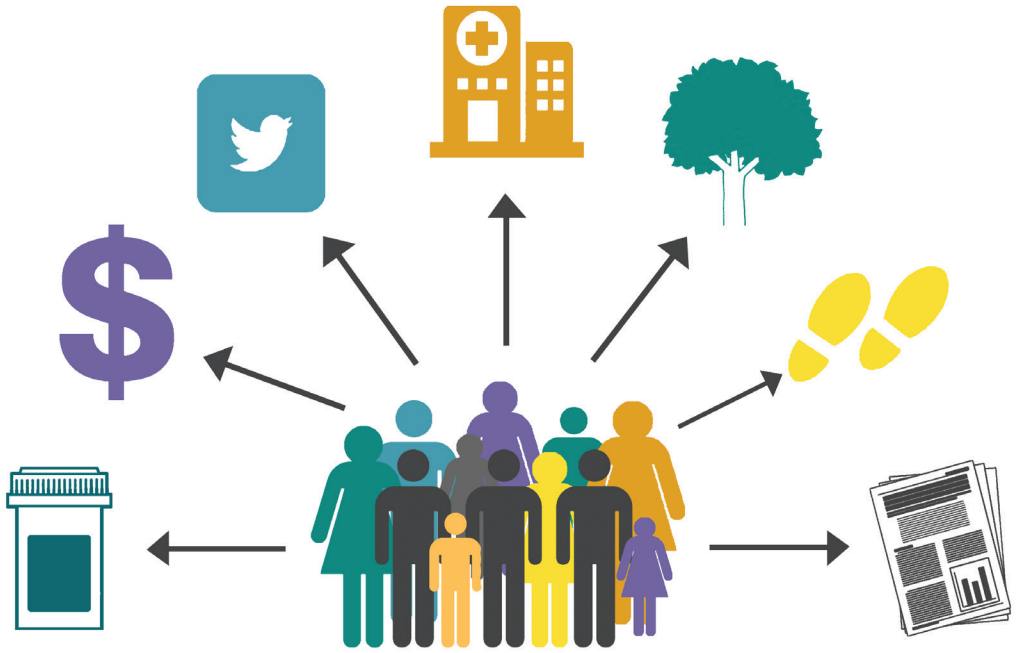


Evidence has traditionally been derived from the “gold standard” of randomized clinical trials, where patients recruited are typically highly homogenous and data collected is closely controlled and monitored.

REAL WORLD EVIDENCE



RWE is derived from data associated with outcomes from the care of heterogenous patients as experienced in real world practice settings Data relevant to RWE comes in multiple types and forms. For Example:

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- **Patient-powered Data** derived directly from the patient experience.

Exhibit 2: Types and Sources of RWE Data

Real World Evidence is now generated from multiple types of data, collected from multiple sources, aggregated, shared and often reaggregated in multiple sectors of the health care system.

	claims	clinical trials	clinical setting	pharmacy	patient powered
Types of Data	Medical Claims	Clinical Trial Data	EHR Data	Point of Sale Data	Patient Reported Outcomes
			Genomic Data		
			Lab Tests		Social Media
	Prescription Drug Claims			Prescription Fill Data	
			Specimen/ Tissue Pathology Data		Patient Centered Outcomes
Primary Aggregators/Users	State Medicaid	NIH	Providers	Pharmacies	Patients
	Insurance Companies	FDA	Clinical Labs	Prescription Benefit Managers	Patient Communities/ Social Networks
	CMS	Pharma & Device Companies	Private Genetic Test Companies		
Secondary Aggregators/Users	Insurance Company Analytics Subsidiaries	Third Party Analysts	Genomic Databases		Patient Advocacy Orgs
	FDA Sentinel	Patient Advocacy Orgs	Professional Society Clinical Registries		Patient Powered Networks
	All Payer Claims Databases		PCORnet		

Issue Brief

THE NETWORK FOR EXCELLENCE IN HEALTH INNOVATION

September 2015

Real World Evidence:
A New Era for Health Care Innovation

Executive Summary

Real World Evidence (RWE), a potentially transformative force in U.S. health care

A new era of health care innovation could be unleashed by merging multiple sources of patient data to generate Real World Evidence.

Evidence from "real world" practice and utilization – outside of clinical trials – is seen as a way to tailor health care decision making more closely to the characteristics of individual patients, and thus as a step towards making health care more personalized and effective. Robust RWE will not only tap increasing volumes of data, but weave together different sources of data, such as clinical data, genomic data and socioeconomic data, to yield a better picture of individual patient characteristics and improve medicine's ability to treat individual patient needs.

RWE is not just "Big Data" –
it's the integration of multiple sources of data

RWE promises to transform patient outcomes, but it also threatens to upend long-established norms in the generation and use of health care evidence. RWE challenges the traditional paradigm in which the only authoritative medical evidence is generated through prospective randomized clinical trials (RCTs), validated through peer reviewed publication in reputable journals and incorporated into broadly applied clinical practice guidelines.

Few experts believe that RWE will supplant the prospective RCT; yet, appropriate adoption of RWE by sponsors of new drugs and devices and regulators could streamline or supplement data from RCTs. RWE is already generating new forms of evidence that many decision makers want to consider alongside traditional RCT evidence. Indeed, prospective trials that analyze Real World Data (RWD) alongside classic RCT data are emerging as an important complement to RCTs. While manufacturers will likely remain the dominant sponsors of RCTs for new medicines and devices, the proliferation of new data sources and new methods is enabling many more stakeholders to generate evidence and assert their own recommendations on the adoption, coverage, reimbursement and use of products. Though likely subject to legal provisions to protect patient data confidentiality, nearly all of these stakeholders are unregulated as to their conduct in assembling, analyzing and disseminating data. Many stakeholders do subscribe to codes of conduct that outline ethical standards and best practices relating to the use of data, but standards and methods for collection of RWD and generation of Real World Evidence have not yet reached a level of authority such that standards for grant-making, peer-reviewed publication, clinical practice guideline development and regulatory guidance are following suit.

To truly meet patients' goals and needs stakeholder groups must reach consensus on a long list of issues we detail below.

Key Findings

RWE definition

While the definition of Real World Evidence is still evolving, most proponents associate RWE with data that is derived from medical practice among heterogeneous sets of patients in real life practice settings, such as insurance claims data and clinical data from electronic health records.

Application of RWE

RWE has the potential to support all phases of the innovation process in U.S. health care.

- ***Clinical research***: Analysis of RWD can help expedite generation of research hypotheses that sharpen the focus of clinical research, including the design of RCTs. Use of RWD sources may also expedite the recruitment of patients for clinical trials.
- ***Pre-regulatory approval***: RWE analysis may augment conventional RCT data with data from patients whose diversity reflects real world practice, resulting in better insight on safe and effective use of innovations.
- ***Post-approval***: Analysis of patient outcomes from the use of innovations in real world settings generates further insight on safety and efficacy. RWE generated from long-term observation of patient outcomes will identify factors in safety, clinical effectiveness and the personalization of care that are difficult to identify among short-term RCTs conducted among highly homogenous groups of patients.

Barriers to Use

Numerous barriers impede the full realization of benefit from RWE.

- ***Data quality***: Most sources of RWD are not collected for research purposes. Many researchers become "data janitors," forced to "clean" gaps and inconsistencies in data through methods that may not yet have wide acceptance for statistical validity.
- ***Cost***: While the cost of collecting and maintaining data may be an established cost of doing business for manufacturers (clinical trial and outcomes data) and payers (claims data), financial models for data maintained by other stakeholders (patient groups, professional societies, providers) are much less certain, particularly to the extent they rely on government funding.
- ***Patient protection***: Repeated data breaches in the health care industry undermine patient confidence in data privacy, and thus the political will to support investments that support RWE development and use among all stakeholders. Meanwhile, there is little settled law or regulation on when and how often patients must give consent for use of their data.
- ***Disparate rules on stakeholders***: FDA-regulated entities, like pharmaceutical and medical device firms, are generally prohibited from making claims or commenting on uses of their products that are not part of FDA-approved labeling and not supported by evidence from RCTs. Other stakeholders with access to "Big Data," like insurers and providers, do not face similar restrictions. RWE from disparate sources needs to be developed and evaluated in an open transparent manner by all stakeholders.
- ***A challenge to traditional peer review and publication:*** As RWD sources proliferate, so does the ability of stakeholders to generate "do it yourself" RWE. The pace at which RWE is generated may surpass the pace at which conventional studies are typically released. This represents a huge force for valuable innovation, but it also challenges the traditional paradigm in which consensus on valid medical evidence is developed through peer reviewed publications.

The Biopharma and Medtech Industries Face Regulatory Barriers to Use of RWE

Manufacturers face both special opportunities and special restrictions in the use of RWE. Manufacturers remain subject to FDA regulations that create substantial risk for manufacturers who seek to initiate communication and share data about any use of their products beyond uses that are indicated on their FDA-approved labeling. FDA rules on communication (and the lack of such rules relative to communication of economic evidence) thus limit manufacturers' ability to proactively offer research that may be relevant to clinical and cost goals that are becoming increasingly important as both public and private payers shift health care payment into value-based models, including issues of off-label use, evidence on sub-population outcomes, and evidence on health care utilization and total costs of patient care. Pharmaceutical manufacturers can and do respond to unsolicited requests for information from payers and providers, but whether unsolicited requests for RWE on patient outcomes, experience and utilization fully meet the needs of payers and providers remains unclear.[1]

Drivers of RWE Policy and Practice

Despite regulatory restrictions, the interest of manufacturers in communicating RWE now appears to be converging with the interest of many payers in using RWE to make coverage and reimbursement decisions. Meanwhile many influential stakeholder groups, including patient advocates, clinical leaders, the NIH and CMS are vigorously promoting a movement towards open data and open science, including policy that will facilitate the replication of all forms of medical evidence, be it in classic RCT form or some form of Real World Evidence.

Several specific trends could drive development of consensus on practices that will expedite transparent, scientifically robust and replicable RWE in the years ahead:

- Federal open data initiatives (e.g. OpenFDA, new CMS policy that opens CMS data to external researchers, including commercial researchers);
- Continued expansion of clinical trial data access (e.g. Yale's YODA project, PhRMA-EFPIA Principles for Responsible Clinical Trial Data Sharing);
- Maturation of state All Payer Claims Databases;
- Evolution of the FDA Sentinel Program;
- Potential FDA regulatory changes to allow expanded product labeling based on RWE;
- Potential update of FDA regulations regarding manufacturers' ability to communicate product information;
- Full development of the PCORnet networks, including Patient Powered Research Networks;
- Federal Meaningful Use policy shaping collection of EHR data; and
- Improvements in the federal Blue Button initiative for patient acquisition of their own data.

NEHI 2014 Round Table

This summary of issues in RWE is informed by a group of stakeholder experts convened at NEHI's December 2014 roundtable, "Real World Evidence: Ready for Prime Time?".

These experts included:

- ***Ann Bonham, PhD***, Chief Scientific Officer, Association of American Medical Colleges (AAMC)
- ***Cliff Goodman, PhD***, Senior Vice President and Director, Center for Comparative Effectiveness Research, The Lewin Group
- ***Marcia Kean,*** Chairman, Strategic Initiatives, Feinstein Kean Healthcare; Partner, iConquerMS Patient Powered Research Network
- ***Theodore Lystig, PhD***, Distinguished Statistician, Strategic Scientific Operations, Medtronic, Inc.
- ***Kenneth Park, MD***, Vice President, Payer and Provider Solutions, HealthCore
- ***Richard Platt, MD***, Professor and Chair of the Department of Population Medicine, Harvard Pilgrim Health Care Institute
- ***Matthew Rousculp, PhD***, Senior Director, Comparative Effectiveness Research & Health Policy Research, GlaxoSmithKline
- ***Joe V. Selby, MD***, Executive Director, Patient-Centered Outcomes Research Institute (PCORI)

RWE Defined

The research community has called for the use of patient outcomes data in medical evidence for many years but the concept of Real World Evidence is a more recent phenomenon.[2] While there is no formal definition of Real World Evidence, most proponents associate RWE with data that is derived from medical practice among heterogeneous sets of patients in real life practice settings, such as insurance claims data and clinical data from electronic health records. The term is also stretched to encompass data that might not qualify strictly as outcomes data, such as genomic data, patient socioeconomic data and environmental data.

An important dynamic element in the emergence of Real World Evidence is the fact that the organizations or individuals who are the sources of data are also and increasingly analysts of data as well. For example, patient communities that pool their data for research can also act as researchers and analysts. Multiple types of data are now aggregated, analyzed, shared, re-aggregated, analyzed and re-shared in hybrid combinations, facilitated by data networks and even networks-of-networks (e.g. PCORnet). The methods used to analyze data and way in which studies are released differ depending on which organization or which sector of the health care system performs the analysis. Exhibit 2 suggests the multiplicity of data sources and data holders

Case Study 1

Use of Beta Blockers in Heart Attack Patients: An Early Application of Real World Evidence

Well before the term "Real World Evidence" gained currency, findings from observational data lent crucial support to the case for use of beta blockers in patients who suffer heart attacks. In the 1990s, Medicare sponsored the Cooperative Cardiovascular Project, which examined medical records of over 200,000 heart attack (myocardial infarction) patients. The project found substantial reductions in mortality among patients receiving beta blockers, including patients for whom use of beta blockers had previously been counter-indicated.[3] The Cooperative Cardiovascular Project bolstered previous evidence from randomized clinical trials and helped accelerate use of beta blockers in heart attack patients as a standard practice. In 2007, the National Committee for Quality Assurance (NCQA) ceased reporting use of beta blockers in heart attack patients as a quality measure after finding use of the therapy had become widespread.[4]

For all practical purposes, the working definition of RWE is evidence derived from any and all sources of data that may contribute to more effective health care, including health care best tailored to the needs of individual patients. The premise behind generation and use of RWE is that richer data will yield better health care decisions and better care.

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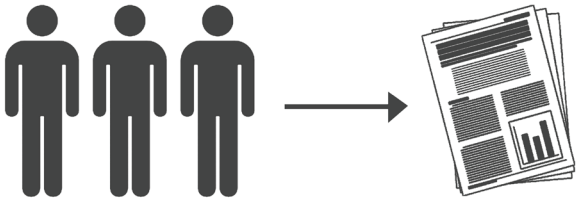

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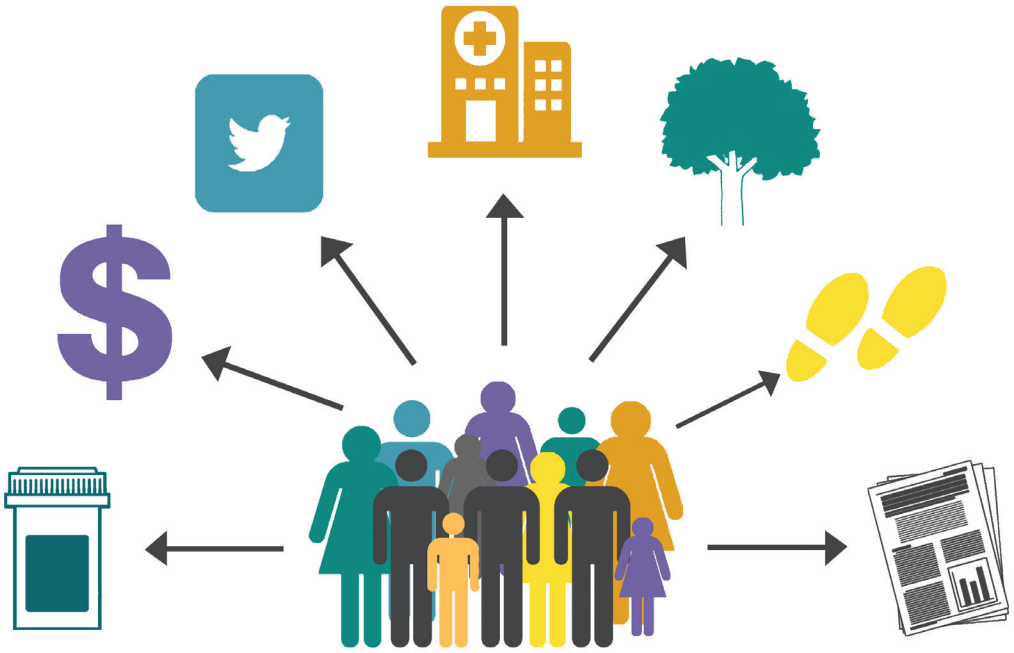

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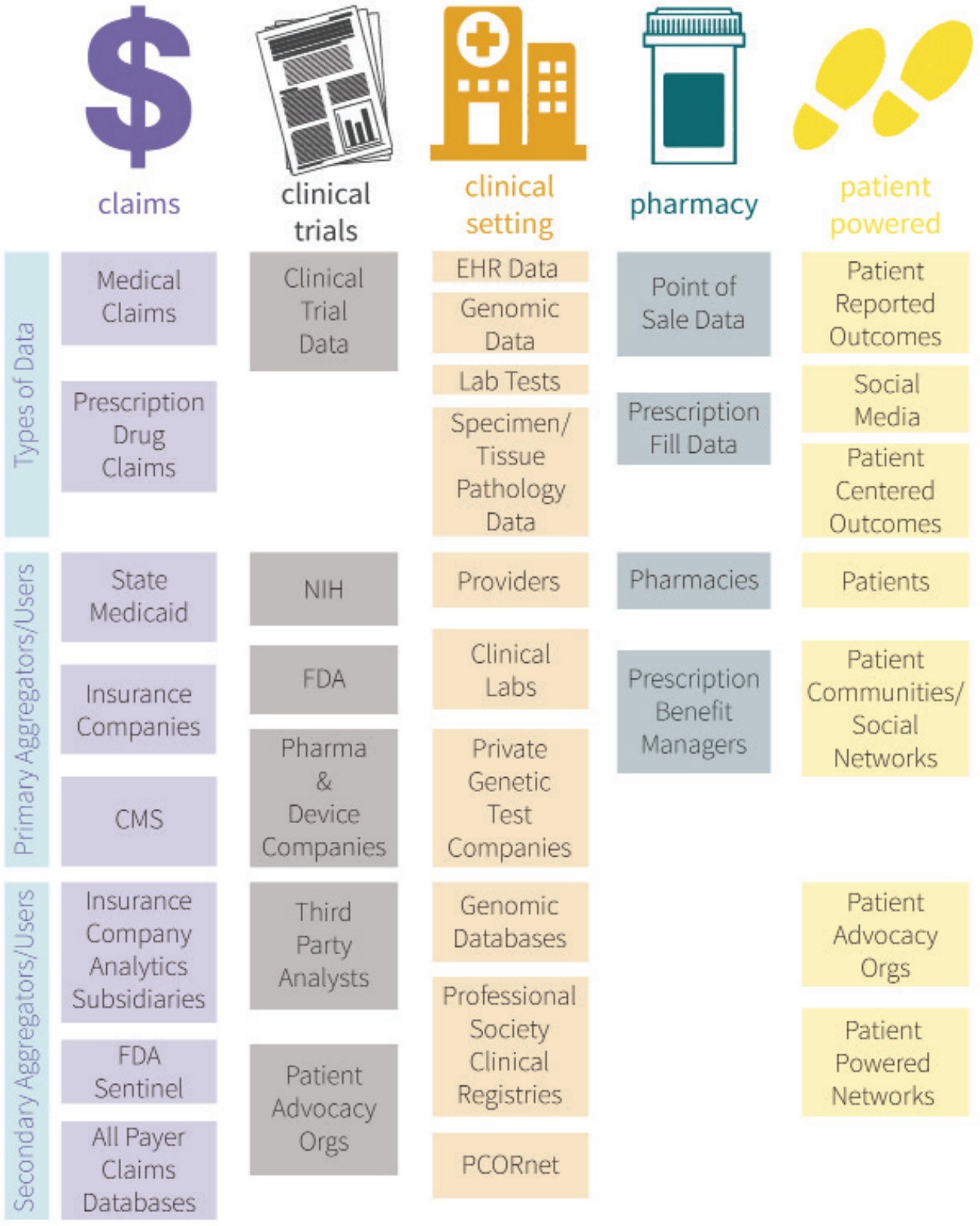

Applications of RWE

According to experts, the promise of RWE is that a rich diversity of data collected from extremely large samples of patients will yield more precise, better targeted and thus more highly effective health care at the level of the individual patient. Hypothetically, as RWE informs choices on the right care, for the right patient, at the right time, patient outcomes will improve and health care spending will be targeted towards the most valuable interventions based on individual patient needs.

There are numerous implications for health care innovation:

- ***Quality improvement***: RWD, such as patient clinical data captured in electronic health records, can be utilized for health care quality improvement. Case study 4 outlines an example in which the Hospital Corporation of America (HCA) utilized routine clinical data to identify a best practice for infection control leading to significant reductions in MRSA infections. At the December 2014 NEHI roundtable on RWE Dr. Joe Selby of PCORI noted that many health care delivery systems regard quality improvement as the most practical use of patient data under their control.
- ***Regulatory approval for new products***: : RWE may augment RCT data on the safety and efficacy of new drugs and medical devices. Data on the use of more heterogeneous (real world) sets of patients may:
  - Create greater precision and clarity as to the safety and efficacy profile of new products, thus improving the labeling and approved indications of products.
  - Improve the amount and quality of information available to patients and physicians relative to informed decision-making about new products.
- ***Demonstration of value***: Examination of post-approval, real world use of products may accelerate the rate at which products prove their value to patients, providers and payers, including:
  - More precise identification of safety risks and risk/benefit trade-offs.
  - Identification of heterogeneous responses, including identification of sub-population effects of products, the value of products when used among complex and co-morbid patients (See Case Study 2), and value derived when products are delivered in diverse practice settings.
- ***Longitudinal study***: RWE draws on data sources that are based on recurring events such as patient visits and insurance claim submissions, thus facilitating long-term study of patient outcomes and health care utilization that may generate new findings on the appropriate use and the value of innovations.
- ***Hypothesis generation***: Analysis of RWD sources is widely considered to be a valuable source for the generation of research hypotheses and research questions that can be tested in randomized trials of drugs, devices and procedures, including trials for new or expanded uses of existing products (see Case Study 3).
- ***Patient recruitmen***t: RWD sources can be utilized to expedite identification and recruitment of patients for clinical research.

"We're the richest nation in the world – and yet when our patients come into our care settings for care, the evidence base for the treatment they receive is sometimes less than 30 percent. That's no fault of the physicians, that's a lack of real world evidence."

-Ann Bonham, PhD, Chief Scientific Officer, AAMC

Case Study 2

The Salford Lung Studies:
Prospective Real World Drug Trials Utilizing Community Resources

The Salford Lung Studies are described as the world's first Phase 3 pragmatic randomized clinical trials of a novel drug therapy. The studies are located in the United Kingdom and are comparing the use of a once-per-day inhaled corticosteroid against normal course of care for both COPD and asthma patients. Patients are treated and monitored across encounters with physicians, physicians' staff and community pharmacists, through use of electronic medical records. The drug trial will test both the clinical effectiveness of treatments and their impact on patients' ability to adhere and realize long-standing benefit.[5]

Case Study 3

The Transcatheter Valve Therapy Registry:
Physicians Employ A Registry That Supports Post-Market Trials

Transcatheter aortic valve replacement (TAVR) devices are a new and innovative class of medical devices that allow treatment of patients with diseased aortic valves who are deemed ineligible or at too-high a risk for conventional aortic valve replacement. In 2011, the American College of Cardiology (ACC) and the Society of Thoractic Surgeons (STS) joined in a common strategy to "construct a new pathway for rollout" of TAVR procedures in the U.S. that would ensure the most safe and effective adoption for patients in need.[6] The centerpiece of the strategy is a new TAVR registry that builds on the pre-existing registries administered by both societies. The ACC and STS have developed common data formats and data collection methods that have expedited use of the registry to conduct prospective, randomized, post-market trials of different valve products. Evidence generated by the registry has already resulted in FDA approval of expanded indications for the Sapien Transcatheter Heart Valve, manufactured by Edwards Lifesciences.[7]

Case Study 4

The HCA MRSA Studies:
A Learning Health Care System uses RWE for Quality Improvement

Hospital-acquired infections, including MRSA, are a growing threat to hospital patients and staff. There has been limited evidence to support adoption of competing infection control strategies for MRSA, leading at least nine states to simply mandate a screening and isolation strategy for hospitals. A pragmatic, cluster-randomized clinical trial conducted by Hospital Corporation of America (HCA) staff within the HCA system, and peer reviewed for publication in the New England Journal of Medicine, found strong evidence for a single approach. The trial cost less than $3 million – substantially less than a classic randomized clinical trial, although an indication that "high-quality delivery science is not free."[8]

Hurdles in Generating Robust and Usable RWE

As Dr. Joe Selby, Executive Director of PCORI, pointed out at the NEHI expert roundtable, relatively little of what can be considered RWE available today is based on more than one data source. Reaching the full promise of RWE will mean merging or integrating sources of data from multiple sources — sources that are now controlled by disparate organizations in disparate industries. For this reason many RWE proponents see an increasing need to come together around a shared set of rules for the conduct of RWE, and shared priorities for action that will accelerate the sharing and integration of data and surmount barriers to the conduct of RWE.

Many of the barriers are fundamental.

For the most part, the data sources that are raw material for RWE are sources that are not collected or formatted for purposes of analysis or with RWE in mind. The data are collected to carry out the daily practice of medicine, for billing purposes, for other business objectives or for research purposes that are unconnected to the routine practice of medicine (e.g. genomic data).

"The problem with real world data is the real world. We thought it was going to be easy, just press the blue button."

- Marcia A. Kean Chairman, Strategic Initiatives, Feinstein Kean Healthcare

As a result, the formats for collecting and reporting data relevant to RWE still vary considerably. Gaps in reported data are common, and reported data is subject to inadvertent biases that must be corrected through adroit use of statistical methods that are themselves in need of validation and adoption. The field of health data analytics is rapidly growing but at this point it is primarily based on claims analysis, not on clinical data analysis or the integration of claims and clinical data.

Patient protection and privacy are also challenges for RWE policy. Policy and practice regarding patient consent for use of data are inconsistent. Even the use of clinical data for quality improvement has been called into question as a purpose that may be subject to traditional Institutional Review Board (IRB) scrutiny.[9] Frequent data breaches in the health care industry suggest that protection of patient privacy is inadequate and could pose a threat to both patient consent for RWE research and for public support and funding of research programs.

Experts believe that the business models necessary to sustain investment and routine maintenance of data collection and analysis are at best immature and unproven. For example, patients often face substantial barriers to access their own data or to collect and forward it to researchers, including emerging networks of patient-directed, "patient-powered" research. There are also outstanding questions as to when innovation will be best served by open access to data and unfettered research practices, or when upholding private, proprietary interests will be necessary to sustain long-term development of innovations

Hurdles to RWE Use by Biopharma and Medtech Industries

For manufacturers of innovative health care technologies, such as the biopharmaceutical and medical device industries, the emergence of RWE creates both unique challenges and unique opportunities.

Biopharmaceutical companies have longstanding interests in three areas:

- The use of safety and effectiveness data describing both approved as well as medically accepted alternative uses of previously approved drugs, such as uses not listed in the medication's labeling but for which the medication is listed in compendia and regularly prescribed by physicians.
- The comparative effectiveness of drugs in actual, real world use.
- The value or economic impact from the use of new or existing drugs, such as the impact of a medication's use on hospitalizations or other measures of health care utilization.

The medical device industry has similar longstanding interests in demonstrations of the comparative effectiveness of products as demonstrated in real world use, and in demonstrating clinical results that may have an impact on patient satisfaction as well as in long-term utilization of medical services.

Both the biopharma and the medtech industries are subject to FDA regulation in the U.S. that generally prohibits them from proactively disseminating research findings that are not strictly connected to the specific uses of the products as approved by the FDA or from commenting proactively on such data or findings made by others. In practice, this restricts manufacturers from making claims that are not derived directly from the results of the traditional RCT. Some examples of this data include:

- Outcomes among patients who are not likely to be part of the RCT patient pool, such as complex or co-morbid patients who typically excluded from traditional RCTs. Patients with co-morbid psychiatric disorders, heart and cardiovascular disease and diabetes are often excluded from RCTs.
- Outcomes derived from novel trial designs or statistical methods, such as methods that may suggest sub-population impacts from the use of drugs and devices that may not otherwise be discerned in the RCT.
- Economic impacts of the use of the product, such as impacts on patient's overall medical costs or on utilization of medical services.

FDA-approved standards for data collection, analysis and dissemination do not apply to other stakeholders, such as health care delivery systems and health insurers. Some of these stakeholders are now actively accumulating and analyzing data under their control and using it for business purposes such as decisions on adoption, coverage and reimbursement. Other stakeholders, such as networks of patients, have clear rights to analyze and make claims regarding their interpretation of their own data.

Industry analysts often describe the gap between FDA rules on communication that pertain to manufacturers and the disparate, looser standards that apply to others as an "asymmetry " of communication standards. In the coming months several factors may close this asymmetry:

- In August 2015 a federal court in New York found that pharmaceutical companies have a First Amendment right to communicate findings on off-label uses of approved drugs if their claims meet a standard for "truthful and non-misleading information." As of this writing, it is unclear whether the FDA will appeal the ruling or announce plans for issuing clarifying guidance on the standard of truthful and non-misleading information.

- Congressional action may direct the FDA to augment evaluation of RCTs with development of standards for evaluating findings from Real World Data and from novel, non-RCT trials. The 21st Century Cures legislation recently approved by the House of Representatives includes such directives, and would also direct the FDA to issue guidance on appropriate communication of information defined as "truthful" and "non-misleading" outside of the FDA-approved labeling of approved drugs, and expand the freedom of biopharma firms to communicate with payers regarding pharmacoeconomic claims. Senate and presidential approval of these directives is not certain but Senate action on similar legislation is expected by the end of this year.
- The FDA indicated early in 2015 that it might release guidance under the FDAMA 114 rule regarding standards for permissible communication of economic claims for the use of approved pharmaceuticals. The 1997 FDA Modernization Act directed FDA to issue guidance, but the FDA has declined to promulgate standards up to this point.
- The most potent force in clarifying biopharma's rights of communication may prove to be the ongoing shift in health care payment models underway in the U.S. As noted previously, the interests of biopharma and payers in establishing more precise evidence on the value of products may be converging as payers shift reimbursements towards value-based payment models. Medical device manufacturers share this interest as well. Moreover, both biopharma and medical device manufacturers share an interest in demonstrating the contribution of their products to the overall costs of patient care as payers shift providers towards reimbursement based on annualized total-costs-of-care for patient populations, towards episode-based or bundled payments for procedure, and towards similar models.

The practical effect of clarifying both manufacturers' rights and their mutual interest with payers might then prove to be clarification of priorities for improving data collection and methods of analysis in RWE. Data collection and analysis would re-focus on data points and findings that are most important to proving value, including measurable patient outcomes and measurable improvements in utilization and total costs of care. Potential examples might include:

- Patient medication adherence: real life use of medications in actual practice is subject to high rates of discontinuation and variability, affecting patient outcomes and total costs of care over time. Integration of pharmacy data with claims and clinical data offers new capabilities to track medication use with costs of care, to offer targeted medication adherence interventions, and potentially to offer new or redesigned drugs that enhance good patient adherence.
- Hospitalization: inasmuch as hospitalizations remain among the highest cost services in the health care system, integration of data to show the impact of products on reducing hospitalization rates is becoming a higher priority.
- Diabetes care: as successful treatment of diabetes is highly-dependent on individual patient characteristics, evidence from real world use of diabetes medications can prove to be extremely valuable in demonstrating the highest and best use of medications among sub-populations of diabetic patients.

Exhibit 3 outlines major high-level questions that must be resolved by stakeholders in order to fully exploit the potential of RWE.

Exhibit 3: Major questions in supporting the generation of RWE

Legal and Regulatory Compliance

- What standards and principles of evidence should stakeholders endorse for inclusion in regulatory procedure so as to:
  - Promote open, transparent and replicable real world analysis (e.g. standards of truthful and non-misleading information)?
  - Enhance public health and the efficiency of the health care system overall?
- What standards and data formats will allow RWD researchers to appropriately match patient data from disparate sources while respecting patient privacy and patient consent? Can stakeholders develop safe and secure patient identifiers?
- How will disparate rules on researcher access to state government-sponsored All Payer claims Databases (APCDs) be reconciled?

Terms of access to data

- What should be the rules for public access to the data?
  - Should access granted through the data holder or through a third-party?
  - Are specific professional qualifications (e.g. a degree) required for access?
  - Is pre-clearance required for research topics, analytical methods or research strategies?

Costs

- How should costs be assessed to researchers for access to data?
- What could be the business/sustainability model for maintenance of the data source?

Patient Rights

- What should be the policy on protection of patient privacy as regards use of patient data?
- What should be the policy on securing patient consent for use of data, and for repeated consent if warranted?
- How will the patient's ownership rights in his/her own data be defined and enforced?

Data Sharing

- What should be the policy on sharing data with external organizations or with data networks?

Publication and Dissemination of Analysis

- What should be the rules on publication of studies and on disclosure of data and methods?
- Should studies be subject to peer review or other external review?
- What policy, if any, should promote or govern reproducibility of studies? What standards should this include?

Rights to Comment and Rights of Rebuttal

- What should be the policy regarding the ability of the public, external organizations or competitors to comment on or challenge studies and study findings?

Drivers of RWE Policy and Practice

The ongoing shift towards value-based payment models in the U.S. may prove to be one of the most powerful forces for encouraging use of RWE, and thus for driving consensus on standards of data collection and analytical methodologies. Several other current policy developments should also be seen as potential drivers for consensus in RWE practice.

Open Data Policy

- The Obama Administration has set broad goals for opening access to government-held health data. In May 2015 the Administration announced plans to open Medicare data for use by qualified researchers, including commercial researchers and entrepreneurial firms – a step towards sparking more innovation in health care analytics and RWE. The National Institutes of Health have strengthened policy regarding mandatory disclosure of data and analysis by NIH-funded researchers, and the FDA has taken steps to open up access to FDA-held data. Meanwhile the VA health system's "Million Veteran Program" (MVP) had enrolled almost 400,000 veterans by mid-year in an effort to link veterans' genomic data with VA clinical data for studies to improve care and treatment for veterans.
- In the past two years the pharmaceutical industry has expanded access to clinical trial data by qualified researchers who submit their plans to independent reviewers or custodians. Examples include the Clinical Study Data Request Initiative supported by life science firms including GlaxoSmithKline, Sanofi, Astellas, Bayer, Boehringer Ingelheim, Lilly, Novartis, Roche, and Takeda and the Yale-based YODA project that offers access to Johnson & Johnson data.
- Third-party access to payer-held claims data is also now available through a number of payer claims databases established or implementation by over a dozen states around the country, although the timeliness, the extent and the usability of the data varies, and state-level Medicaid data is not routinely available.

PCORnet

- The Patient Centered Outcomes Research Institute (PCORI) has committed over $240 million to development of PCORnet – a network-of-networks that encompasses 111 existing clinical data research networks and over 20 Patient Powered Research Networks, organized by patient groups to pool data and accelerate analysis to support better treatment for specific disease states. PCORnet's central coordination is managed through the Harvard Pilgrim Healthcare Institute, which also serves as central coordinator for FDA Sentinel and the NIH Research Collaboratory, creating a major opportunity to harmonize RWE standards and practices across these national networks.

Meaningful Use

- The federal Meaningful Use program has set national objectives for electronic health record (EHR) and health data exchange adoption, and serves as the major policy force behind the technology that will power routine collection of clinical data. Compliance with Meaningful Use continues to be a difficult process for many providers, particularly as providers cite barriers to interoperability among EHRs and resulting failure to routinely share data. Timely resolution of and compliance with federal interoperability policy could be a significant factor in making RWE a reality in U.S. health care policy, as was recently re-enunciated through the Office of the National Coordinator's Interoperability Roadmap.

The FDA Sentinel Program

- The FDA Sentinel network is focused on detecting signs of adverse events from the use of FDA-approved drugs by drawing on medical claims data offered on a voluntary basis by four major national health insurers who cover up to 150 million lives throughout the U.S. While Sentinel is designed to enhance drug safety, FDA and Sentinel leadership has also stressed that Sentinel data and network capabilities can be used more expansively to support generation of Real World Evidence.

Blue Button

- Federal HIT policy calls for health care providers to guarantee patients the ability to download a file with their personal health information via Blue Button capability as an element of Meaningful Use Stage 2 requirements. For patients opting to pool data through patient networks or to volunteer for clinical research, the Blue Button file represents a means to volunteer data despite ongoing problems with EHR interoperability and electronic health data exchange. Blue Button originated in a Veterans Health Administration program is generally viewed as a success, but as a result of low levels of provider attestation to Stage 2 Meaningful Use capabilities the Office of the National Coordinator (ONC) has been forced to push back the program's deadlines for provider compliance.

Consensus Principles for Data Sharing

- Stakeholder groups have convened under various auspices to outline principles of research conduct that address various aspects of data collection and analysis. Major models or suggested codes of conduct include:
  - The January 2015 report of the Institute of Medicine Panel on Strategies for Responsible Sharing of Clinical Trial Data.[10]
  - The April 2015 statement of the World Health Organization on public disclosure of clinical trial results. [11]
  - The GRACE Principles (Good ReseArch for Comparative Effectiveness), most recently updated in 2010, for evaluation of the quality of observational studies comparing the effectiveness of various medical products and services, including evaluation of non-randomized studies.[12]
  - Joint adoption by PhRMA (Pharmaceutical Research and Manufacturers Association) and the European Federal of Pharmaceutical Industries and Associations (EFPIA) in July 2013 of principles for responsible clinical trial data sharing.[13]

Exhibit 4: Opportunities to Develop Consensus on RWE over the Next Two to Three Years

Several major legislative proposals are pending that could prove to be major vehicles for advancing public policy that will influence data collection and analysis, as well as stakeholder collaboration on Real World Evidence. Other opportunities will arise as existing law comes up for reauthorization over the next two to three years. Among the leading opportunities:

21st Century Cures: As previously noted, the 21st Century Cures legislation recently passed by the House of Representative as includes authority for the FDA to develop standards for considering Real World Data and findings from novel trial designs in evaluation of new products, as well as directing the FDA to provide guidance on truthful, non-misleading manufacturer communication of research findings for information and data not contained in the FDA-approved labeling. The Senate Health, Education, Labor and Pensions (HELP) Committee is now formulating a Senate version of the 21st Century Cures bill. [14]

The Precision Medicine Initiative: The Obama Administration's FY 2016 budget calls for a $215 million Precision Medicine Initiative to accelerate scientific discovery that will promote development and use of therapies tailored to the characteristics of individual patients. The initiative will promote both expanded use of genomic data and analysis from large data sets of patient-specific data that will allow for precise identification of patient needs and targeting of health care interventions. A central feature of the initiative is recruitment of a million patient volunteers and inclusion of their data within existing and expanded research networks.[15]

Reauthorization of PDUFA and MDUFA: TThe Prescription Drug Users Fee Act (PDUFA) and the Medical Device Users Fee Act (MDUFA) are reauthorized every five years, and are due for reauthorization in 2017. PDUFA and MDUFA authorize user fees paid by drug and medical device companies that support regulatory review by the FDA. Past reauthorizations have been a vehicle for establishing regulatory performance improvement goals at the FDA. The FDA has signaled increasing willingness to test use novel endpoints and outcomes measures (including Real World Data sources) and flexible trial designs from the standpoint of patient safety and clinical effectiveness. The PDUFA and MDUFA reauthorizations could be vehicles for authorizing further steps.

PCORI Reauthorization: The Patient Centered Outcomes Research Institute (PCORI) was created under the 2010 Affordable Care Act, with a sunset provision due to fall at the end of federal fiscal year 2019. PCORI is supported by a dedicated stream of revenue from assessments on health insurers and employer-sponsored health plans until that date. PCORI Executive Director Dr. Joe Selby has stated that PCORI's signature PCORnet research network will become financially self-sufficient by 2017, but observers expect an active debate over the reauthorization and continued operation of PCORI leading up to its 2019 sunset date.

Conclusion

Recently PatientsLikeMe, one of the earliest sponsors of online patient communities, announced a new service that portends a direct-to-consumer form of Real World Evidence. PatientsLikeMe will provide medication experience data from its patient communities to Walgreens and the Walgreens Health Dashboard, part of the Walgreens customer web portal, on an ongoing, continuously updated basis. This is only one of many signals that the proliferation of patient health data through an equally rapid proliferation of data aggregators and data networks will change the face of health care decision-making in the years ahead.

Not all stakeholders enjoy equal access to data or the ability to evaluate or communicate results of analyses using it, but public policy and private sector initiative is beginning to address these gaps. although entrepreneurial firms such as Patients Like Me and publicly-funded programs such as PCORI's Patient Powered Research Networks are enabling patients to assert a more active role, patients continue to face obstacles in accessing their data and on terms they can afford. FDA-regulated industries face unique restrictions on their ability to communicate findings, but pending congressional and court action may alleviate those barriers.

> ***"On a clear day you can see a learning health care system."***
>
> *- Dr. Richard Platt, Chair of the Department of Population Medicine, Harvard Pilgrim Health Care Institute and Principal Investigator, FDA Mini-Sentinel program*

Nevertheless, most experts believe that the full promise of RWE can only be achieved if all sources of data are available for integration and analysis, through formats, networks and methods that are widely supported and accepted for their validity. What the RWE landscape lacks today is a widely shared framework that defines what good and appropriate collection, integration, analysis and use of data means.

A widely shared framework should allow each stakeholder group to achieve their own particular goals, whether the goal is quality or process improvement for health care providers, value-based coverage decisions for payers or expanded communications between manufacturers and healthcare professionals.

Achieving all these disparate goals will require the fundamental support of patients. Every data point that builds Real World Evidence is a data point that originates with a patient. As Harvard Pilgrim Healthcare Institute and PCORnet director Dr. Richard Platt said during the NEHI RWE Roundtable, "patients need to understand that (RWE) is an appropriate use of their data." Patients will not only expect a future of better, person-centered, precision medicine, but use of patient data that will support their values as citizens and taxpayers: a sustainable, cost-effective health care system that respects their privacy and priorities.

Endnotes

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NEHI is a national health policy institute focused on enabling innovation to improve health care quality and lower health care costs. In partnership with members from all across the health care system, NEHI conducts evidence-based research and stimulates policy change to improve the quality and the value of health care. Together with this unparalleled network of committed health care leaders, NEHI brings an objective, collaborative and fresh voice to health policy.