NATIONAL HEALTH COUNCIL

Real-World Evidence Roundtable: Pre-Read
July 31, 2017

Introduction

The stakes for identifying value in health care have never been higher. With ever-rising health care costs, pressures resulting from an aging population and increasing chronic illness burden, a growing focus on patient-centeredness, and burgeoning data available to inform decision-making, we need clarity about what interventions work, for whom, and in what setting. While the randomized-controlled clinical trial remains the gold standard for creating evidence on what can work, there is growing consensus among researchers, policymakers, payers, and patients about the relevance and usefulness of other sources to understand how things work in the "real world." Such data and the "real world evidence" it generates can offer insights on disease for innovation, inform coverage and payment policy, and enhance comparative effectiveness research. While vigorous consideration of appropriate context, methods, and applications of such evidence have occurred in recent years, the National Health Council is concerned that patient community perspectives about the scope and appropriate use of real-world evidence (RWE) have not been fully considered.

This pre-read offers background and context for participants in the July 31, 2017 National Health Council **Roundtable on Real-World Evidence from the Patient Perspective**. The Roundtable will convene members of the patient community and stakeholders from regulatory, payer and industry sectors to gather views on RWE from patient representatives. Meeting participants will engage in general session and small group dialogue to:

- Gather, from the patient community, its perspectives on RWE, including but not limited to issues of: definition, transparency, privacy/security, sources, and use;
- Identify opportunities for improving the communication and dissemination of RWE to the patient community by identifying the characteristics RWE needs to have, including but not limited to issues of rigor, trust, reputation of the data source, etc.; and
- Capture from the patient community the skill set, tools, or trusted source they need to understand and make the best use of RWE in decision-making.

The Roundtable will inform a National Health Council white paper in early Fall 2017. The paper will reflect perspectives about patient's' level of knowledge and concerns about RWE, and challenges to the collection and application of such evidence, and identify the skills and tools that patients need to understand and make the best use of RWE in decision-making. It will summarize the discussion, identify patient views on or reactions to the definitions of RWE and highlight areas of importance that may guide industry and regulatory agencies and other stakeholders as they formulate future policy and practice in collecting, disseminating and applying RWE.

Background

RWE: Common Definition Needed

In general, proponents agree that "real-world data" (RWD) refers to using a wide array of existing data sources, rather than solely randomized-controlled studies, to interpret outcomes and patterns in health care. RWE studies may interpret information and data from electronic health records, medical claims data, genomic and socio-economic data, observational studies, patient registries, as well as other sources (Hubbard and Paradis, 2015). By reviewing these data sets on a macro scale which means that individual patients cannot be identified and privacy is preserved, researchers can tailor studies to identify the individualized needs of patients, payers, and policy makers.

Though consensus continues to build for the use of RWE, the details of how to structure standards and methodologies for conducting analyses remain inconsistent and are still emerging (Morton, 2015). The purpose of the Roundtable is to examine these details with the patient perspective in mind.

RWE and RWD Definitions

Experts and officials are working with similar, but not exactly the same definitions of RWE.

National Health Council Working Definition of RWD and RWE (Proposed). "*Data and data-derived interpretation that is based on sources other than conventional, randomized, controlled studies[1] and offers insight to clinical, coverage, payment, and patient decisions.*

Food & Drug Administration (FDA) Definition of RWE per 21st Century Cures Act. "*Data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials.*" 21st Century Cures Act.

International Society of Pharmacoeconomics and Outcomes Research Definition of RWD (ISPOR). **"***Data used for clinical, coverage, and payment decision-making that are not collected in conventional randomized controlled trials (RCTs). Real-world data could be characterized in a number of different ways, e.g., by type of outcome, by location in a hierarchy of evidence, or by type of data source*." (ISPOR Real-World Data Task Force, 2016).

FDA Center for Drug Evaluation Research (CDER) "Working Definitions" of RWD and RWE.

- **Real-World Data (RWD)** are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.
- **Real-World Evidence (RWE)** is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Examples of RWD include data derived from electronic health records (EHRs), claims and billing data, data from product and disease registries, patient-generated data including in home-use settings, and data gathered from other sources that can inform on health status, such as mobile devices. Sources of RWD include registries, collections of EHRs, and administrative and healthcare claims databases, among others. RWD sources such as these can be used as data collection and analysis infrastructure to support many types of trial designs, including, but not limited to, randomized trials, such as large simple trials, pragmatic clinical trials, and observational studies (prospective and/or retrospective).

Data with a Purpose

In its best form, increased use of RWE can augment randomized, controlled studies in a generalizable and cost-effective approach and provide information about groups that are not traditionally included in clinical trials (Jarow, 2017). For this Roundtable, the National Health Council seeks to focus on four main areas where the application of RWE can benefit patients.

Individualized Evidence. RWE can enhance the understanding about a patient's trajectory of disease and the impact of comorbidities as well as non-medical factors in care. Such evidence can reveal "signals" within specific disease states or sub-populations (e.g., ethnic groups, aging populations, children) that identify opportunities for bench research or therapeutic modification. Moreover, RWE can identify treatment effects, benefits or harms that may be overlooked or confounded in a rigid clinical-trial setting, or provide information on treatment effects among patients more representative of the general patient population than was included in clinical trials. For example, researchers conducted a prospective study and reviewed the records of 73,124 patients through the CathPCI Registry of the National Cardiovascular Data Registry and found early and convincing evidence that demonstrated that a medical device was associated with significantly higher vascular complications than other similar devices (Resnic et al, 2017). In a second example, researchers used a prospective registry[1] to determine risks associated with receiving an MRI for patients with different types of pacemakers (Russo, 2017).

Changes in Regulatory Policy. RWE has a vital role in regulatory review and decision-making, both at the approval phase for new products/innovations, as well as post-market safety monitoring. Such evidence can clarify treatment gaps; confirm or refute expected effectiveness in subpopulations or in patients not eligible to participate in clinical trials (e.g., elderly and children); and identify safety signals or patient outcomes which enhance clinical understanding of both label and expanded use of treatments.

Under the 21st Century Cures Act, the FDA has been charged with establishing a program and protocol to evaluate the potential use of RWE in the process of approving or reviewing the effectiveness of medications and drugs under the FDA.[2] In addition, the Prescription Drug User Fee Act (PDUFA VI) for fiscal years 2018-22, which is currently up for reauthorization, provides guidance on how the FDA can enhance the use of RWE in the process of regulatory decision-making, and charges the FDA to use stakeholder comments and pilot studies to offer draft guidance by 2021.[3] The National Health Council will use the output of this Roundtable to provide input into this process.

Improved Interventions. RWE can identify new opportunities for clinical pathways and identify important treatment factors and risk/benefit considerations that may be valuable to patient decision-making. Such evidence may highlight comparative value of certain treatment interventions in practical settings and give insight to concurrent therapy approaches or service bundles (e.g. a therapeutic product with another clinical intervention or service) in a way that is meaningful and effective for patient

[1] **Patient Registry.** A patient registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves a predetermined scientific, clinical, or policy purpose(s).

[2] Under the 21st Century Cures Act, the FDA must: Create a framework for use of RWE in the approval of drugs under the FDA; Identify the sources of RWE, including ongoing safety surveillance, observational studies, registries, claims, and patient-centered outcomes research activities; Identify the gaps in data collection activities; and Establish the standards and methodologies for collection and analysis

[3] Key milestones under PDUFA VI include: 1-2 Workshops with all stakeholders to review RWE availability, quality, and challenges, and the best methodologies and context for using RWE by the end of FY 2018; Conduct multiple pilot studies or assessments to test the use of RWE by the end of 2019; and Issue draft guidance on how RWE can contribute to assessment of safety and regulatory submissions by the end of 2021.

outcomes. For example, in a review of Medicaid claims data, researchers determined that use of antidepressants did NOT lead to congenital cardiac defects (Huybrecht, 2014).

Treatment Factors. RWE can offer insight into the constellation of factors that influence patient response to treatment, drive decision-making about risks and benefits of various treatment options, and yield net benefit to specific patient populations or subpopulations. For example, researchers reviewed nationwide databases of patients with schizophrenia and found that long-acting injectables were associated with lower re-hospitalization rates than other antipsychotic medications (Tiihonen, 2017). This type of insight is imperative to the future design of value-based coverage and payment policies and systems that are evidence-based and personalized for the patient (Avalere and NPC, 2017).

Understanding the Challenges of RWE

Despite growing enthusiasm for the possibilities inherent in RWE, significant challenges remain. On the most basic level, the sheer volume of RWE studies may overwhelm and challenge the ability of stakeholders to discern valuable insight from "noise." Consensus about parameters of generating and using RWE needs to address the following challenges:

- **Data Integrity**. One of the chief debates about using RWE in conducting safety or comparative research is its quality. "Is it good enough?" is a lingering refrain as the scientific community debates the rigor of RWE study design and the methods for data collection and analysis. For example, most sources of RWE data are not collected for research purposes or in any standardized form, and researchers must "clean" inconsistencies in the data and reconcile different formats across data sets. Such methodological issues include sample size, reliability of coding (as in claims data sets), statistical models, and approaches to derive meaning and evidence of "effect."
- **Patient privacy**. Given privacy breaches and cyber-terrorism, maintaining patient privacy is of utmost concern. Privacy breaches may impact patient willingness to participate in such analyses. While many accept the emergence of patient registries, are there certain uses of such data resources where privacy issues are a concern?
- **Research Methodology.** Without consistent definitions and methodological standards, researchers can dredge data to "find" the outcome they are seeking, may find a misleading outcome due to outside factors, or may attempt to report general outcomes for small sample sizes.
- **Determining the Best Uses of RWE.** There are many potential domains for using RWE, including to supplement the current information included in new product approval, safety monitoring, quality improvement, changes to indication or labeling of a product, development of clinical practice guidelines or care pathways, and coverage and payment determinations, (Hubbard & Paradis, 2015). Another challenge in the RWE frontier is to define the scope of appropriate use for such evidence. For what decisions is RWE best suited or most relevant? What are instances when RWE use is methodologically inappropriate and when might it be socially or ethically considered inappropriate from the patient's view?

It is also important to point out that many patient advocacy organizations are generators of RWE. Through interviews, focus groups, surveys, and registries many patient groups collect, analyze, and disseminate RWE routinely. Experiences in that realm are valuable to capture and contribute to the dialogue on RWE.

During the Roundtable, the National Health Council seeks patient community input about areas of greatest concern, additional questions that need to be addressed, and information and tools most needed by patients in order to understand and apply RWE to their decision-making.

Patient Perspectives on RWE Are Vital

Patients and patient representative organizations are vital contributors to further dialogue about RWE. The National Health Council Real-World Evidence Roundtable is an important forum to distill and convey patient perspectives on RWE to the scientific and regulatory community. Moreover, the dialogue will add an important element by defining opportunities to improve dissemination of RWE to patients for their meaningful use in navigating coverage and treatment options.

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