



Patient Perspectives on Real-World Evidence: A Roundtable to Gather Views, Needs, and Recommendations



NATIONAL HEALTH COUNCIL

1730 M Street NW, Suite 500
Washington, DC 20036
202-785-3910
www.nationalhealthcouncil.org

Executive Summary

The topic of real-world evidence (RWE) has gained considerable attention recently. As health researchers, policymakers, and regulators establish standards and structure for using real-world data (RWD) as evidence in regulatory and clinical decision making, patients must be the primary focus. Since the idea of RWD is new to many in the patient community, it is important to explore the patient community's needs, concerns, and potential contributions and uses of RWE to ensure the patient voice is considered.

On July 31, 2017, the National Health Council (NHC) brought together a multi-stakeholder roundtable, with patient advocacy organizations comprising the majority of participants. The objectives were to elicit patients' views on RWE: 1. Definitions and uses; 2. Characteristics needed for RWE to be understood and trusted; and 3. Skillsets and tools needed by patients. The purpose of this report is to describe the Roundtable, discussions, and findings.

Key findings include:

1. Patient Views on RWE Definition and Uses:

- a. Most patients have little understanding of RWE or that controversies exist with respect to selection of types of evidence used in decision-making.
- b. The ultimate focus of RWE should be to answer the questions: "Does this work for me? Is this safe for me?"
- c. Acceptable uses of RWE must be linked to the context of its use.

2. Questions that Aid in Patient Understanding and Trust of Real-World Evidence:

- a. Who or what group conducted the study(ies)? Was the study(ies) co-developed with patients?
- b. What is the purpose/objective of the study(ies)? Does it have pre-specified study aims versus post-hoc (i.e., data mining to "see what we find")?
- c. What are the key findings and how are they meaningful to patients ("Why is it relevant to me")?

3. Skill Sets and Tools Needed by the Patient-Advocacy Community to Make the Best Use of and Communicate About RWE to Constituents:

- a. Standardized, concise RWE definition, universal to all stakeholders that is understandable and useable by patients;
- b. Guidance to assist organizations with creating a scientific advisory council or identifying a medical director resource to help with community understanding of RWE studies and findings; and
- c. Patient-organization education materials/program on RWE uses, sources, and key issues (e.g., 15-minutes with Q&A; offer at patient advocacy organization conferences).

The findings and recommendations from this Roundtable will be used by the NHC to inform discussions with policy makers and others about the views and needs of the patient community with regard to RWE.

Patient Perspectives on Real-World Evidence: A Roundtable to Gather Views, Needs, and Recommendations

Introduction

Real-world evidence (RWE) has the potential to provide patients, clinicians, and policymakers information that more traditional scientific studies cannot. While randomized, controlled trials (RCTs) will continue to be the standard for assessing new medical treatments for use, they have distinct limitations. RCTs often require researchers to exclude many patients (who may have a need for the treatment), are expensive, may be slow to yield results, and may be infeasible for disease states that impact very few people. Emerging sources of data that capture the “real world” in terms of treatment settings and patient populations (e.g., subgroups, people with co-morbidities, etc.) offer enormous opportunity for deeper understanding of why treatments work (or not) and for whom. Evidence generated from such data, can help clarify best use of treatments for individuals and populations, and care value. RWE is a complement to the evidence derived from traditional RCTs, filling gaps by, for example, providing information relevant to small populations, or particular types of patients or clinical scenarios. However, standards vary for the quality, format, interpretation, dissemination or use of such a wide variety of real-world data (RWD) sources.

“ Since the idea of RWD is new to many in the patient community, it is important to explore the patient community’s needs, concerns, and potential contributions and uses of RWE to ensure the patient voice is considered.”

Patients, in particular, are at a disadvantage because they are not the primary drivers in the discussion and do not have a full understanding of the complexities of generating RWE. Most patients are unaware there is a debate about the types of evidence used as evidence of safety and effectiveness of medical treatments, let alone have awareness of the complex discussions about using different types of studies for different kinds of decisions. Patients often assume their providers have an ongoing feedback loop, and that patient data is typically available for providers to use in choosing the right course of action. Some patients also assume RWD is already being incorporated into treatment decisions. This is an important point of needed clarification about current research standards (e.g., gold standard RCT) and their benefits and limitations, so that a deeper discussion on the value and role of RWD can take place.

As health researchers, policymakers, and regulators establish standards and structure for using RWD as evidence in regulatory and clinical decision making, patients must be the primary focus. Since the idea of RWD is new to many in the patient community, it is important to explore the patient community’s needs, concerns, and potential contributions and uses of RWE to ensure the patient voice is considered.

On July 31, 2017, the National Health Council (NHC) brought together a multi-stakeholder roundtable, with patient advocacy organizations comprising the majority of participants. The purpose was to discuss the level of patient knowledge on RWE and elicit from the patient community its needs to be able to fully contribute to the important dialogue about how to use RWE to improve innovation, treatment approval, and use at point of care. The purpose of this report is to describe the Roundtable, discussions, and findings.

NHC Roundtable and Objectives

The NHC convened 50 individuals representing industry, research entities, federal regulatory agencies, and patient advocacy organizations for a discussion on RWE and consideration of patient perspectives and needs that contribute to future dialogue about appropriate use of such data (see [Appendix A](#) for a list of participating organizations). More than half of the participants directly represented the patient community as advocates, family members, and patients themselves.

Objectives

The objectives of the Roundtable were to:

- Gather from the patient community **perspectives on RWE**, including but not limited to issues of: definition, transparency, privacy/security, sources, and meaningful use.
- Identify opportunities for improving the communication and dissemination of RWE to the patient community by identifying **key characteristics of RWE**, including but not limited to issues of rigor, trust, reputation of the source, etc.
- **Capture from the patient community** skill sets and tools needed to understand and make the best use of RWE in decision-making.

Format and Methods

Prior to the Roundtable, all participants received a brief pre-read document that outlined objectives and provided a basic overview of key issues (see [Appendix B](#)). The day-long Roundtable was designed to maximize opportunities to learn from the participants, and to ensure all had a basic conceptual understanding of RWE before moving to working discussion sessions.

Participants were organized in small working groups, pre-assigned to ensure representativeness across stakeholder groups and to emphasize patient leadership within each group. Each group selected a leader to report out key comments to the full group and participants were asked to prioritize patient perspectives, questions, and viewpoints. Representatives of other stakeholder communities were asked to use their expertise to answer questions, provide examples, and support patient participants in engaging during each session, to maximize the representation of patient perspectives. All individual group discussions were documented and key points captured during the group report out sessions.

Definitions of Real-World Evidence

As part of the pre-read activity, the NHC shared working definitions of RWE to serve as a foundation for the discussion. RWE has been defined by regulatory bodies in the U.S. and internationally with an emphasis on the setting from which the data are derived. The NHC offered a short, plain-language definition for use at the meeting (see [Table 1](#)).

Context and Background: Level-Setting Discussion

Participants heard context-setting remarks and background on RWE. The NHC has conducted qualitative research on patient perspectives on RWE, including focus groups, and patient and caregiver interviews to gauge patient awareness and identify patient comfort level with the definition and potential uses of RWE. Preliminary findings were shared: With a clear description of RWE, patients support use of such information for quality improvement, to enhance knowledge of side effects or post-market safety issues with a treatment,

and to improve how treatments are used clinically (e.g., for sub-populations). They are moderately comfortable with RWE being used to assess new uses for an approved, marketed product. Patients are less comfortable with using RWE for payer coverage decisions. They are not in favor of RWE as the sole basis for approving a new product.

The context setting remarks also emphasized that RWD has unique and distinguishing features as compared to typical “gold standard” sources of evidence, such as RCTs. [Figure 1](#) delineates these features and clarifies the value RWD offers in complementing RCTs. The strengths and limitations of RWD, the importance of understanding and clarifying patient perspectives on appropriate use, and utility of RWE were also discussed. High-quality RWD offers the opportunity to understand how treatments are used and work in diverse populations (e.g., by age, ethnicity, disease stage) and in real-world settings, which, in turn, improves our knowledge about outcomes and optimal clinical pathways to achieve them. Moreover, methodologies for generating RWD have the potential to yield knowledge faster and at lower cost than traditional RCTs. At the same time, it was acknowledged RWD may not answer all patient questions (see [Figure 2](#)), since many factors affect treatment decisions (e.g., access and payment, stage of disease), individuals may have complex clinical conditions that are not reflected in such evidence, and data may not always be representative (e.g., missing data, unbalanced groups, differences in follow-up, unreliable coding).

It was discussed that in any effort to understand and overcome these challenges, there is a need to define the parameters for how and when RWE can be used to support patient and other decision-making. There must be better and ongoing inclusion of patient perspectives in order to prepare patient communities to engage in both generation of RWD and use of RWE. All stakeholders must be informed to ensure RWD is included in the robust evidence that serves as the basis for defining value in health care in the future.

Setting the Stage: Stakeholder Perspectives on Real-World Evidence

The NHC invited a multi-stakeholder panel to share with participants their perspectives on RWE to initiate dialogue and frame the break-out sessions. Presenters represented a government regulator, health policy research center, large US payer with research capabilities, and large patient advocacy organization. All panelists emphasized the importance and opportunity inherent in the emergence of RWE, while acknowledging significant challenges posed by the complexity and absence of clear standards for conduct and communication of RWE to patients.

Panel participants identified key messages to help frame RWE for the patient community:

- RWE is about “learning from your everyday care” to identify benefits of a treatment, combinations of care, or sequences of treatment that may help you and others;
- RWE is derived from data (pieces of information) on others that are “similar” to you in terms of physical characteristics, disease experience, or treatment setting. This may be useful to identify treatments that may benefit you; and
- RWE could help you and your doctor decide what treatment can help you optimize your quality of life and minimize the likelihood of adverse events or complications.

Noteworthy discussion points from the panel session included:

- The Food and Drug Administration (FDA) has interest in and a statutory mandate to explore the parameters and application of RWE in regulatory decision-making. This focus offers a catalyst for collaboration and progress that can integrate patients into the research lifecycle and expand the opportunity for a true learning health care system.

- Data standardization, integration, and methodologies for the conduct of RWE studies are a primary focus of the FDA and a vital step to standardizing the generation and use of RWE.
- Timely access to RWD is a challenge, but it is an important driver for fundamental shifts in the infrastructure and environment for research using such data.
- Patient-directed and generated data will drive new directions in RWE generation. To date, the focus and emphasis have been on electronic health records (EHR), insurance claims data, and the ability of researchers to aggregate, share, and mine that data. Today’s typical RWD sources are often missing crucial data that, while not essential to payment or clinical treatment, offer important insights into progression of disease, treatment of comorbidities, treatment adherence, and important patient outcomes. These absent RWD points are important missed opportunities, especially from the patient point of view.
- The ultimate focus of RWE should be to answer the question: “Will this work for me? And “Is this safe for me?”
- Patients would like to see RWE generated from patients experiences be incorporated into value-driven decision making and policy discussions ensuring the outcomes most important to them are considered. Patients want more control of their data and how it is used; they want their data used for research, but do not want it used for only commercial purposes and not for patient benefit.
- Patients need robust decision support tools to enable them and their providers to parse and evaluate the credibility and utility of RWD.
- All stakeholders are concerned that rigid legal and business barriers lock data in proprietary systems, with little incentive to open and harmonize them. Thus, costs and time required to create a sustainable backbone for collection, research, and dissemination of RWE are significant barriers.

The patient advocacy organization representative speaker summarized the complexity well by saying that RWE is exciting and frustrating. It is exciting because of all the promise and possibility it brings, e.g., use of artificial intelligence. But, it is frustrating because though it is supposed to speed up the process, it still is taking a long time. Meanwhile, patients are waiting.

The panel presentations and the ensuing conversation underscored the importance of bringing patients into the RWE discussion, and that the Roundtable can serve as a starting point to bring patients to the decision-making table.

Breakout Session 1: Patient Perspectives on RWE

During the first breakout session, participants were asked to describe their understanding of RWE and areas where they need additional information and context. In addition, they were asked to share their perspectives and concerns about RWE and its appropriate use.

Opportunities and Concerns

Patient advocates believe that better defining RWE is important to increasing their confidence in the data collection methods (e.g., registries, PCORNet), use of RWE for treatment protocols, clinical pathways, study design for new therapies, and quality improvement initiatives.

The small-group and general discussion distilled a number of themes, which emphasized the need to develop a “critical mass” of understanding to build trust and to define standards for such evidence. The discussion of views and understanding of RWE by patients is summarized in [Figure 3](#).

Breakout Session 2: Characteristics RWE Must Have for Improved Communication and Dissemination

The second breakout session of the day focused on identifying opportunities and barriers to communication about RWE, and on defining key components that such communications should contain in order to promote trust and use of RWE.

Challenges and Opportunities for Communicating to Patients

Roundtable participants grappled with the complexity of defining and understanding RWE and identified important principles to guide the approach and content that would best communicate the value and opportunities. Recommendations regarding communication of RWE to patients are summarized on [Figure 4](#).

Characteristics Necessary for Decision-Making

The small groups considered the characteristics that should be clarified for patients to facilitate understanding, trusting, and using RWE. Participants noted that these characteristics were both important elements of and potential barriers to effective communication about RWE. This is primarily due to the complexity of the emerging field of RWE (i.e., such detailed characteristics may not be universally available), as well as the lack of consensus about what metrics connote good quality RWE, and uncertainty about what roles should be played by federal regulators, industry stakeholders, researchers, and patient advocacy organizations to disseminate RWE. Participants agreed that the goal should be to create accessible, trustworthy information about RWE to facilitate decision making and promote transparency of data. [Figure 5](#) highlights the characteristics of RWE needed in communication with patients.

Breakout Session 3: Skills and Tools Needed by Patient Advocacy Organizations

During the third breakout session, participants considered the tools and skill sets patients need in order to review, understand, and incorporate RWE into their decision-making. The groups were charged with developing recommended resources to support patients regarding RWE. Participants universally agreed that the complexity of the topic required basic tools geared toward patient advocacy organizations, to enable them to help their individual patient constituencies understand RWE. Patient advocacy organizations need accurate and non-misleading information about RWE and help in understanding credible study characteristics and sources. Tools should come in a “bite-sized format.” That is, capture RWE concepts, parsed into small, easy-to-understand, brief formats, and created with patient input, to ensure accessibility and usability. The discussion highlighted that the goal is not to make patients or patient advocacy organizations RWE “method experts,” but rather to support patient advocacy organizations in discerning the between good quality RWE and “junk science” and to provide context to RWE to identify how it may be relevant to their disease and treatment choices.

Roundtable participants noted that an important challenge for patient advocacy organizations is the question of at what point do they intervene in conveying RWE when sorting the rigorous findings from anecdote. Many organizations believe this is their role and an obligation, especially if patents are being endangered and/or are financially at risk (high cost, no benefit scams). Others pointed out that it is hard to draw a line when “junk science” is harmless and might make people feel good (e.g., Foot baths may be unproven to do anything medically, but do no harm and may make the patient feel better. But, highly overpriced foot bath salts may cause financial harm with no benefits.). Any tools for RWE communication by patient advocacy organizations must balance risks and benefits.

It was suggested that one way patient advocacy organizations might create capability to identify and communicate such top-line context is establishing a robust scientific advisory council and/or engaging an affiliated medical director, medical school faculty, or academic researchers to assist with understanding and honing the assessments and communications. Participants recognized that not all patient advocacy organizations are sized or structured for such capability; organizations, such as the National Health Council and other collaborative partnerships within disease communities or between patient advocacy organizations and academia, may offer solutions.

Tools and Resources for Patient Advocacy Organizations and Other Stakeholders

The Roundtable participants identified a wide array of tools and resources ([Figure 6](#)) that could contribute to improved understanding and use of RWE. The common factor to establishing the value of such tools should be their contribution to the patient experience and the ability of patients to identify relevance of the research to their own journey and needs.

The final session ended with general agreement that patient advocacy organizations have an important role, but the organizations require support and some standardized tools and resources that can assist them in educating their patient constituencies and preparing them to apply RWE in the complex and “noisy” scientific-evidence environment. Moreover, participants agreed that communication and capacity building must target patient and clinician communities to ensure that both value the role and potential benefit of RWE. Finally, participants supported centralized repositories of information, tools and communication to share existing materials, case studies, and resources for the benefit and replication by patient advocacy organizations. Such a collaborative resource would foster common understanding of the definition and sources of RWE and promote a learning community among patients, clinicians, researchers, innovators, and regulators.

Next Steps

The Roundtable concluded with a brief summary of the day's findings as well as of the value and importance of collaboration amongst the diverse stakeholders moving forward.

Key findings include:

1. Policymakers and advisory groups need to invest in significant education efforts to inform and fully include the patient community in initiatives to establish standards for RWD and to use RWE more effectively. Patients need a better understanding to both use and contribute to RWE.
2. Patients see the possibility of using RWD to understand how a treatment works in diverse patient populations – to find someone that “looks like me” as an assurance of how a treatment might benefit them.
3. The primary source of accessible evidence for patients and clinicians is typically via clinical guidelines. However, physicians are usually the core audience for such data syntheses and often the focus is randomized-controlled trial data, which often doesn't reflect the diversity of patients, real world settings, or real care scenarios (e.g. comorbidities) that directly impact treatment choices and outcomes. Therefore, clinicians must understand and accept RWE in order for patients to benefit from RWE. Patient understanding alone is necessary but not sufficient.
4. Internet/social media-based opportunities for sharing experiences provide patients the opportunity to see commonalities that they can apply to their own treatment decisions. At the same time, such enterprises can generate real-world data on a consistent basis, particularly for rare disease or conditions where fewer robust research studies exist or are likely to yield timely data. However, evidence from these data sources must be readily discernible from anecdotes and “junk science.”

The findings and recommendations from this Roundtable will be used by the National Health Council to inform policymakers and others about the views and needs of the patient community with regard to RWE.

The findings and recommendations from this Roundtable will be used by the National Health Council to inform policymakers and others about the views and needs of the patient community with regard to RWE. This is an important time in discussions about uses of RWE. For example, the 21st Century Cures legislation requires the FDA to investigate how it can make the best use of RWE in regulatory decisions. This report will provide input into these and other efforts and policy proposals.

Table 1. Widely Used Definitions of Real-World Evidence

National Health Council Working Definition (Proposed)	Data and data-derived interpretation that is based on sources other than conventional, randomized, controlled studies and offers insight to clinical, coverage, payment, and patient decisions.
Food & Drug Administration per 21st Century Cures Legislation. <u>21st Century Cures Act</u>	Data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials.
International Society of Pharmacoeconomics and Outcomes Research Definition of RWD (ISPOR). (<u>ISPOR Real-World Data Task Force, 2016</u>)	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.
Food & Drug Administration, Center for Evaluation Research (CDER) “Working Definitions” of RWD and RWE (FDA, 2017)	<p>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.</p> <p>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.</p> <p>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 health care 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).</p>
Jarrow, Lavange, Woodcock, (2017)	The analysis of RWD in a study designed with a high degree of pragmatism, regardless of study type. A wide variety of study designs can be used to generate this evidence including pragmatic RCTs.

Figure 1. Characteristics of Real-World Evidence

1. Typically generated via everyday interactions with the health care system
2. May but does not typically result from methods that used randomization
3. Treatment choice is up to the patient and provider
4. Patients typically reflect general patient population
5. Comes from a variety of data sources, including:
 - a. Insurance claims
 - b. Electronic health records
 - c. Patient registries
 - d. Wearables

Figure 2. Patients Have Questions about RWE

1. What is the critical mass of data needed to establish “evidence”?
2. How do we identify the rigor and credibility of real-world studies?
3. Does my medical data belong to me? How can patients provide permission to share data with researchers?
4. How can I ensure that when I share my data it gets used for research that helps patients, and not solely for a company’s profit?
5. How can privacy best be protected?
6. How can clinicians be educated about importance of RWD sources and how to incorporate RWE into shared decision making? (e.g., Patients can’t benefit if clinicians don’t buy in.)

Figure 3. Patient Views, Questions, and Concerns Regarding Real-World Evidence

1. **Most patients have little understanding of RWE** or that controversies exist with respect to selection of types of evidence used in decision-making about availability of treatment, payment based on its value, or choice among various treatment options. It must be recognized that patient advocacy organization education is needed to further this understanding.
2. **A common definition of RWE is vital.** The definitions in use today are broad and vary. Efforts must clearly define RWD, its sources and how such data can be interpreted to yield useful RWE.
3. **Acceptable uses of RWE must be linked to the context of its use.** RWE may serve different purposes for different diseases, e.g., inform surrogate outcomes for future clinical trials, help define improved treatment protocols or clinical pathways, or improve adherence to treatment. Patients generally agree that RWE should not be used for clinical evaluation of new, unapproved therapies. Patients see opportunity for the use of RWE to inform new uses of existing therapies in, for example, new patient sub-groups (e.g., children, the elderly), for treatment of co-morbid conditions, and to achieve patient-defined endpoints not part of clinical studies.
4. **Privacy must be protected and data ownership clear to promote trust.** Patients often lack clarity about who owns data about their health, and often struggle to access their own medical records. Access to an individual’s data and ability to influence how it is used remains an evolving issue and advocates favor transparent, open access. Websites such as [OpenNotes.org](https://www.opennotes.org) and [HealthIT.gov](https://www.healthit.gov) (Blue Button) are two examples of efforts to increase patient access to their medical information. While HIPAA may allow for data sharing, privacy issues remain a concern for patients and standards of protection to ensure anonymity must be clarified. Patients are concerned about efforts that seek to commoditize data about them, without a clear focus on improving their care or their ability to engage in collaborative decision-making about treatment options.
5. **RWE should include authentic sources of real patient data (patient-provided information).** Electronic health records and claims data, two primary sources of real-world data, may not accurately reflect real

patient diversity,¹ disease experience, preferences or outcomes due to missing data and the clinical and payment emphasis of such sources. RWE should aggregate these types of sources with additional real-world sources, including patient-generated data (e.g., registries, patient advocacy organization sources, wearables, PCOR networks) and include patient-reported information.

6. **Clinicians must be champions for dissemination and use.** To make the most of RWE, physicians need to buy-in to its value in identifying potential treatment options and supporting patient decision-making. Providers who are not supportive of such use may create a barrier to important knowledge and uses of RWE. Education efforts on RWE must target the clinician community as it is a primary conduit of information to patients and to mitigate clinician biases.
7. **Patient advocacy organizations need clear quality standards for RWE.** Distinguishing between sources of good quality RWE and “junk science” or anecdotes is a challenge to the effective use of such information. Navigating the universe of data requires education about characteristics of good studies and sources of data, as well as identification of trusted sources and/or arbiters of such evidence (e.g., FDA, USPSTF, patient advocacy organizations, clinical societies²). Despite the fact that there are methods standards for most observational study designs, there are no universal standards for real-world studies per se, which leaves a field of variable data and data quality, and opens the door for anecdotal information to be erroneously labeled as RWE.
8. **RWE is intended for action – RWE should support informed decision making.** Thus, it is intended to discern how a treatment works in real-world settings and in diverse patients to help us apply such treatments in practice.

Figure 4. Communicating RWE to Enhance Understanding, Trust, and Empowerment

1. **Keep it simple.** Simple language (no acronyms or scientific jargon), emphasizing the applicable user (is it relevant to me?), and presenting actionable data (what can I do next with this information?) should drive the format and content of communication with patients.
2. **The messenger is important.** Patient advocacy organizations are key arbiters and communicators of what good real-world evidence looks like. Participants stated that patient advocacy organizations have an obligation to serve in this role. They can be educators of patient populations on the concepts and sources of RWE; and they can develop key questions and other “litmus tests” to assist with discerning value of RWE for their constituencies. Patient advocacy organization communication can be an effective method to build trust and convey information in language that is understandable and relevant to the audience.
3. **Empower the patient.** Communication should enable actions for decision making and helps patients see a role for their contribution to studies that generate RWE.
4. **Emphasize high standards for methods and qualities of RWE.** It is important to establishing expectations for “good quality” in RWE.
5. **Address limitations of RWE.** Similarly, communications should identify where studies are missing data, contain comprehensive versus only new data, include positive and negative studies, or are outright “junk science” masquerading as RWE.
6. **Use varied communication methods tailored to the needs of the audience.** Such methods may include patient focus groups, peer-facilitated listservs, or discussion groups, etc. Patient advocacy organizations can build on the narrative already at play in the community and find peer champions to convey messages and combat misinformation or junk-science threads within the patient community. Collaborate within disease state communities to ensure consistency and to optimize resources.

1 As one participant said, “RWE should look like America.”

2 One participant commented that ISPE/ISPOR task force recommendations may contribute to increasing reliability of RWE.

7. **Clarify potential uses of RWE.** Communication should identify potential application of RWE for patients.
8. **Clinicians/providers can be a resource regarding RWE.** While patient advocacy organizations are one important source about emerging evidence – clinicians provide another opportunity to convey such information. Clinicians can help with translating RWE for their patients to understand and use RWE in decision-making. In turn, patients should seek their doctor’s opinion about theories and information they are finding.

Figure 5. Questions that Aid in Patient Understanding and Trust of Real-World Evidence:

1. Who or what group conducted the study(ies)? Was the study(ies) co-developed with patients?
2. What is the purpose/objective of the study(ies)? Does it have pre-specified study aims versus post-hoc (i.e., data mining to “see what we find”)?
3. Who owns (or holds) the data (e.g., government data, insurer-owned)?
4. How many people were included? What were their characteristics (e.g., subgroups, co-morbidities, treatment-resistant patients, rare disease)?
5. Over what time period did the study(ies) take place?
6. Did the methods align with question/objective?
7. Who interpreted the study(ies)? What are their qualifications (e.g., clinicians, publication peer-review group, peer-patient, scientific body, government agency)?
8. What are the key findings and how are they meaningful to patients (“Why is it relevant to me?”)?
9. Who is the evidence most likely to interest or benefit?
10. How are the findings actionable for patients and clinicians?
11. How does the study(ies) fit into the larger realm of science on this topic? Is it data (singular study, “raw” pieces of information) or evidence (repeated findings, signs of a pattern/trend, validated by replication, readily applicable to treatment dialogue)?
12. How is this a novel finding, or how does it replicate or refute past work? Where does the RWE fall on the spectrum of understanding -- ranging from “confirms current thinking” to “changes current thinking?”
13. How does it deal with the reality that, for some treatments, there is no clear consensus on a given treatment?
14. What are the identified limitations, including barriers/challenges, especially for patients?

Figure 6. Skill Sets and Tools Needed by the Patient-Advocacy Community to Make the Best Use of and Communicate about RWE to Constituents

1. Standardized, concise RWE definition, universal to all stakeholders;
2. Guidance to assist organizations with creating a scientific advisory council or identifying a medical director resource to help with community understanding RWE studies and findings;
3. Patient-group education materials/program on RWE uses, sources, and key issues (e.g., 15-minutes with Q&A; offer at patient advocacy organization conferences);
4. Case-study database providing examples of RWE, explaining potential impact on patients;
5. Brief summaries of real-world studies for patient advocacy organizations to use in communications;
6. Resource that clarifies current rules on patient data ownership/rights;
7. Resource of sources of patient-generated RWE (e.g., registries);
8. Fact sheet or tool that assists patient advocacy organizations with evaluating credibility of RWE; tools to support patient-group data literacy, (e.g., what good studies look like; synthesizing the volume of evidence);
9. Education and tools to build capacity for patient co-development in real-world studies or initiatives;
10. Education and tools on shared decision-making using RWE;
11. Tools to help understand alignment of study rigor with the context of decision-making; and
12. Tools for clinicians to use in interpreting and discussing RWE with patients.

Appendix A - Participating Organizations

PATIENT GROUPS

Alpha- 1 Foundation	National Blood Clot Alliance
Alzheimer's Association	National Eczema Association
American Cancer Society, Cancer Action Network	National Health Council
American Diabetes Association	National Multiple Sclerosis Society
Foundation for Ichthyosis & Related Skin Types	National Psoriasis Foundation
Hydrocephalus Association	Osteogenesis Imperfecta Foundation
Immune Deficiency Foundation	Parent Project Muscular Dystrophy
Lung Cancer Alliance	PKD Foundation
Myasthenia Gravis Foundation of America	Research!America
National Alliance on Mental Illness	WomenHeart: The National Coalition for Women with Heart Disease

INDUSTRY ORGANIZATIONS

Amgen	Janssen
Biogen	Merck & Co.
Biotechnology Innovation Organization	National Pharmaceutical Council
Eli Lilly and Company	Nestle Health Science
GlaxoSmithKline	Sanofi
HealthCore	QuintilesIMS

ACADEMIC/RESEARCH ORGANIZATIONS

Duke-Margolis Center for Health Policy
Patient-Centered Outcomes Research Institute (PCORI)
University of Maryland School of Pharmacy

GOVERNMENT

U.S. Food and Drug Administration

OTHER PARTICIPATING ORGANIZATIONS

AcademyHealth
FasterCures – A Center of the Milken Institute
Momentum Health Strategies

Appendix B

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 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 registry¹ 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 FDA². 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.

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.

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 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.

References

1. [21st Century Cures Act](https://www.congress.gov/114/bills/hr34/BILLS-114hr34enr.pdf) (2016). United States House of Representatives and Senate. <https://www.congress.gov/114/bills/hr34/BILLS-114hr34enr.pdf>
2. Avalere Health and National Pharmaceutical Council. Health Plan Use of Patient Data: From the Routine to the Transformational. April 2017. Available at: http://www.npcnow.org/system/files/research/download/npc-avalere-health-plan-data-use2017_0.pdf
3. Food & Drug Administration (2016). PDUFA REAUTHORIZATION PERFORMANCE GOALS AND PROCEDURES FISCAL YEARS 2018 THROUGH 2022. <https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm511438.pdf>
4. Food & Drug Administration (July 27, 2016). Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices: Draft Guidance for Industry and Food and Drug Administration Staff. <https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf>
5. Hubbard, T., and Paradis, R. Real World Evidence: A New Era for Health Care Innovation (September 2015). The Network for Excellence in Health Innovation (NEHI). http://www.nehi.net/writable/publication_files/file/rwe_issue_brief_final.pdf
6. Huybrechts, K., Palmsten, K., Avorn, J., Cohen, L., Holmes, L., Franklin, J., Morgun, H., Levin, R., Kowal, M., Setoguchi, S., Hernandez-Diaz, S. (June 19, 2014). Antidepressant Use in Pregnancy and the Risk of Cardiac Defects. *N Engl J Med* 2014; 370:2397-2407 June 19, 2014 DOI: 10.1056/NEJMoa1312828. <http://www.nejm.org/doi/full/10.1056/NEJMoa1312828>
7. Jarow, J., LaVange, L., et al. Multidimensional Evidence Generation and FDA Regulatory Decision Making Defining and Using “Real World” Data (July 13, 2017). *JAMA*. <http://jamanetwork.com/journals/jama/fullarticle/2644655>
8. Morton, S.C., Costlow, M.R., Graff, J.S., Dubois, R.W. Standards and Guidelines for Observational Studies: Quality is in the Eye of the Beholder. *J of Clin Epidemiol* 2016;71:3-10. Infographic available at: <http://www.npcnow.org/issue/defining-high-quality-observational-studies>
9. Resnic, F., Majithia, A., Marinac-Dabic, D., Robbins, S., Ssemaganda, H., Hewitt, K., Pohirakis, A., Loyo-Berrios, N., Moussa, I., Drozda, J., Normand, S., Murray, M. (February 9, 2017). Registry-Based Prospective, Active Surveillance of Medical-Device Safety. *N Engl J Med* 2017; 376:526-535. <http://www.nejm.org/doi/full/10.1056/NEJMoa1516333>
10. Russo, R., Costa, H., Silva, P., Anderson, J., Arshad, A., Biederman, R., Boyle, N., Frazbizzio, J., Birgersdotter-Green, U., Higgins, S., Lampert, R., Machado, C., Martin, E., Rivard, A., Rubenstein, J., Schaerf, R., Schwartz, J., Shah, D., Tomassoni, G., Tominaga, G., Tonkin, A., Uretsky, S., Wolff, S. (February 23, 2017). Assessing the Risks Associated with MRI in Patients with a Pacemaker or Defibrillator. *N Engl J Med* 2017; 376:755-764. <http://www.nejm.org/doi/full/10.1056/NEJMoa1603265>
11. Sherman, R.E., Anderson, S.A., Dal Pan, G.J., Gray, G.W., Gross, T., Hunter, N.L., LaVange, L., Marinac-Dabic, D., Marks, P.M., Robb, M.A., Shuren, J., Temple, R., Woodcock, J., Yue, L.Q., Califf, R.M. Real-World Evidence — What Is It and What Can It Tell Us. *N Engl J Med* 2016;375:2293-2297.

12. Tiihonen, J. Mittendorfer-Rutz, E., Majak, M., Mehtala, J., Hoti, F., Jenedius, E., Enkusson, D., Leval, A., Sermon, J., Tanskanen, A., Taipale, H. (July 2017). Real-World Effectiveness of Antipsychotic Treatments in a Nationwide Cohort of 29,823 Patients With Schizophrenia. *JAMA Psychiatry*. 2017;74(7):686-693. <http://jamanetwork.com/journals/jamapsychiatry/article-abstract/2629295?resultClick=1>