

Incorporating Real-World Evidence in Regulatory Decision-Making: A Pragmatic Approach to Randomization in the Clinical Setting

Discussion Guide

Introduction

Substantial amounts of electronic health data are routinely collected from patient experiences across the health care ecosystem. As advances are being made in the electronic capture of clinical and patient-reported data, the methods for linking such data to administrative claims and other data types, and the study designs and analytic techniques used to generate evidence, new insights from patient experiences are supporting an array of health care decisions that enable improvement in the quality, safety, and value of care.

These advancements also create new opportunities to better incorporate patient experiences and outcomes from routine clinical care, or so-called real-world evidence (RWE), into a range of stakeholder decisions that can improve the quality and efficiency of evidence developed to support a broader range of more personalized questions. While many stakeholders already recognize RWE as an important, complementary component to standard clinical evidence generation activities, all parties must work together to consider opportunities to improve the value of such evidence by identifying best uses and potentially overcoming some of the limitations inherent in RWE collection and use.

This is especially true for enhancing the application of RWE in regulatory decision-making. Regulators at the Food and Drug Administration (FDA) traditionally assess clinical benefit and risk of medical products using an evidence hierarchy that consists of interventional clinical trials and non-interventional study designs. Through this approach, the FDA often relies on clinical trials to provide the basis for approval decisions while using non-interventional studies to assess larger and more longitudinal data sets – often derived from real-world settings – to review the product’s postmarket safety and effectiveness. There are well-known methodological challenges with these designs that narrow the utility of study results to certain regulatory decisions.

While the FDA has implemented numerous reforms, tools, and policies aimed at improving the quality and efficiency of evidence development – including incorporation of RWE – there are still unrealized opportunities for more firmly incorporating real-world evidence into the regulatory decision-making framework. Recent proposals in the House-passed 21st Century Cures Act and renegotiations for the sixth Prescription Drug User Fee Act (PDUFA) have highlighted these issues as a priority area for concerted policy development, and envision greater use of such evidence to both expedite drug development and ensure that safe, effective, and more personalized treatments are reaching patients.

In 2016, the Duke-Robert J. Margolis, MD, Center for Health Policy will be working in cooperation with FDA to begin tackling these issues on a broader scale. Through a series of expert workshops, white papers, and a public conference, the Center intends to engage a wide array of stakeholders to make meaningful progress toward a regulatory framework that includes opportunities for enhanced use of RWE in routine decision-making. Additional work will address and inform the broader application of RWE in other decision settings, such as routine care or coverage and reimbursement.

This initial expert workshop will kick-off these efforts by focusing on the terminology used to define and describe RWE, the data and methods for developing RWE, and exploring how such evidence might support a very specific regulatory use case – the approval of a new indication for an already-marketed medical product. To ground the discussion, participants will consider these issues within the context of a specific case study – generating RWE through a pragmatic clinical trial. What follows is a session-by-session overview intended to help guide discussion during the workshop.

Session I: The Spectrum of Evidence Development from Clinical Experience and Potential Applications in Regulatory Decision-Making

During Session I, speakers and participants will cover a range of questions related to the source and potential applications of RWE:

- What do we mean by ECE in terms of data, information, and evidence? Do different components of the data infrastructure (electronic health records, registries, claims databases, etc.) have a role in defining RWE?
- What do stakeholders gain from the use of ECE to support clinical studies and their unique decision-making processes? How is this different for regulatory decision-making?
- How can ECE support randomization in the clinical setting?
- What are the gaps in evidence remaining after traditional RCTs used in medical product development that can be addressed with ECE? What types of questions might be addressed by routinely collected data that can't be answered satisfactorily through traditional evidence generation methods?

These questions will help lay a broad foundation for workshop discussion of RWE and its potential use during regulatory decision-making.

Defining “Real-World Evidence”

Several groups and organizations have published various terms and definitions of RWE. For example, the terms real-world data (RWD) and RWE are the most commonly used, but the recently passed 21st Century Cures Act introduces a new term: Evidence from Clinical Experience (ECE).¹ Despite the varying terminology, stakeholders largely define these concepts to mean the collection of any data or evidence outside of randomized clinical trials. Table 1 provides an overview of proposed terms and definitions.

Variability in definitions may partly reflect the diverse stakeholder views toward data and evidence generated in real-world settings, which are often guided by specific organizational objectives. Additionally, this varied terminology may be the result of a changing landscape of technological capabilities to collect and analyze data. Regardless, current terminology remains overly broad and open to interpretation, and potentially conflates concepts.

For example, the terms RWD and RWE are often treated interchangeably despite an important difference between data and evidence as noted by ISPOR and others.² Data generally represents a raw measurement without meaning or context, whereas evidence connotes the synthesis of multiple pieces of information produced by the rigorous analysis and evaluation of data.³ Further, gaps in how stakeholders view data quality across data sources, and the ability to validate this data may be contributing reasons for why stakeholders feel differently about data versus evidence and how this evidence could be used.

Table 1. Proposed Terms and Definitions.*

Stakeholder	Term	Definition
House of Representatives: 21 st Century Cures Act ⁴	Evidence from Clinical Experience (ECE)	ECE means data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials, including from observational studies, registries, and therapeutic use.
Network for Excellence in Health Innovation (NEHI) ⁵	Real-World Evidence (RWE)	RWE is evidence 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.
International Society for Pharmacoeconomics and Outcomes Research (ISPOR) ⁶	Real-World Data (RWD)	RWD reflects data used for decision making that are not collected in conventional randomized controlled trials.
IMS Health ⁷	Real-World Data (RWD), Real-World Evidence (RWE)	RWD is patient-level data not collected in conventional randomized controlled trials. RWE are insights generated from RWD using appropriate scientific and/or commercial analytics.

RWE Data Sources, Standards, and Infrastructure

A number of large data initiatives are making important progress in the development of standardized and consistent ontologies across multiple data types and sources, as well as demonstrating how RWE can help address important questions related to medical product safety, patient-centered outcomes, and the value of new technologies and care delivery programs. FDA’s Sentinel Initiative, for example, is harnessing a common data model that allows data sharing across diverse data partners to enable active postmarket safety surveillance.⁸ The Patient Centered Outcomes Research Institute’s (PCORI) National Patient-Centered Clinical Research Network (PCORnet), another important data initiative, is leveraging a similar data model that allows for data linkages between multiple data collection efforts, facilitating greater access to large, longitudinal data sets reflective of broad patient populations. Many of the participants in these efforts are also routinely using these data to better understand the value of health care programs in improving quality of care and lowering costs.

In parallel to these data initiatives, ongoing efforts to develop more standardized outcomes and improve statistical techniques are needed to further establish how RWE is collected, interpreted, and used.^{9,10}

Regulatory Applications of RWE

There is a spectrum of evidence development activities, with one end occupied by non-interventional observational studies and the other represented by well-controlled, randomized clinical trials. In the middle of this spectrum, methodologies blend to varying degrees depending on the level of RWD incorporated, the evidence required to answer the question of interest, and the underlying infrastructure in place to conduct the study at hand. Where a study or evidence development activity falls on this spectrum therefore dictates its utility for any number of stakeholder decisions, especially for regulatory purposes.

*Numerous stakeholders have proposed similar definitions for RWD and RWE.

There are many opportunities in which RWE developed within this continuum could be harnessed to enhance regulatory decision-making, such as to support a label change for new dosing administration or enable postmarket safety surveillance. Other opportunities might involve using RWE in historical controls or the development and regulatory review of products intended to treat rare disease populations. These examples have been relatively well-characterized and pursued by FDA and industry stakeholders in recent years.

Session II: Utilizing ECE to Support Randomization in the Clinical Setting: A Regulatory Use Case

In this session, speakers and participants will explore a potentially more muscular application of RWE within a regulatory decision-making context: in this case the approval of a new indication for an already-approved medical product. Discussion will cover the following key questions:

- What regulatory considerations need to be made in exploring the potential use of RWE for approval of a new indication?
- How are randomized studies in the clinical setting currently being used to support other regulatory decisions?
- What are the accepted dimensions and characteristics of Pragmatic Clinical Trials (PCTs) and how might a PCT approach best support more efficient approval of new indications?
- What are the main challenges to and opportunities for utilizing a PCT approach? What key methodological, statistical, or operational issues must be addressed in order to realize the potential of PCT approaches? How could RWE infrastructure support a PCT approach?

Pragmatic Clinical Trials

Because of the established limitations of RCTs, new RWE-focused methodologies are being developed to complement traditional evidence generation activities by providing unique insight into a broader range of regulatory questions. Large simple trials, also called pragmatic clinical trials (PCTs), for example, offer a hybrid approach between traditional randomized and observational studies blending advantages from both while minimizing their limitations.¹¹ Because of this blending, these study designs could have more of a pragmatic or explanatory intention depending on the specific study aim. Consequently, PCTs should not be thought of as a specific study design, but rather a continuous spectrum of study designs. Illustrating this potential spectrum and defining the attributes of pragmatism are tools like the pragmatic-explanatory continuum indicator summary, or PRECIS, which help gauge where on the spectrum of pragmatism any one design falls.¹²

PCTs are increasingly being used to study the effects of an intervention in patient populations and clinical settings that closely reflect routine clinical care because they are often conducted in real-world settings. Because of the increasing availability and use of the nation's electronic health information infrastructure (e.g. electronic health records, registries, and other digital information systems), PCTs are also becoming more practical to implement. Efficiency advantages potentially include facilitating patient identification and recruitment through EHR phenotyping and centralized consent management, and easing the burden of data collection and reporting.¹³ Because of their potential to efficiently collect and generate RWE, a PCT design is a vehicle to further explore in developing the regulatory use case for this workshop.

Sessions IIIA-III B: Design and Conduct of a Pragmatic Clinical Trial to Support Approval of a New Indication

This session represents the bulk of workshop discussion and is intended to allow rigorous examination of the potential design and conduct of a PCT capable of contributing RWE toward a new indication approval. Through a specific use case example, participants will explore the following broad questions:

- How do we maximize the use of routinely-collected RWD as well as ensure that these data are of sufficient quality and validity to support evidence development for regulatory uses?
- What are the methodological and logistical details for conducting a full-scale PCT to support approval of a new indication?
- How should the PCT be designed and operationalized?
- How might the PCT design vary by therapeutic class, disease area, or patient population characteristics?

Individual presentations will then tackle various aspects or design characteristics of such a PCT. Each will build on the case study example, introduce key variations in statistical or methodological approaches given different study questions or type of therapy, and contribute toward a strawman PCT proposal that will be further refined for the upcoming public workshop. Additional discussion questions for each presentation are listed below.

Study Design Considerations

- When is a multi-arm, active comparison most beneficial? Are certain therapeutic areas ideal for such comparisons?
- Is there a role for using ECE and related infrastructure to support study arms or construct historical controls?
- When is cluster randomization appropriate for trials with active comparisons?
- What is the role of blinding in pragmatic designs?

Patient Identification and Selection

- What is acceptable “flexibility” in developing inclusion/exclusion criteria?
- What pragmatic elements could be incorporated into the trial’s design to streamline patient identification (e.g., electronic health record phenotyping, or other opportunities to mine large databases)?
- What innovative statistical methodologies exist to identify and accommodate subgroup heterogeneity?

Data Collection and Quality

- What are the key barriers and opportunities to improve the recruitment of practice sites in routine care settings?
- What are the opportunities to reduce data collection burden using ECE and related infrastructure? (e.g., auto-populating sections of case report forms)? Are there regulatory challenges preventing streamlined data collection?
- What are the key data challenges to ensure data quality and result validity? Are there data validation mechanisms that could be used?

Outcomes and Endpoints of Interest

- Are there certain outcomes better suited for trials using pragmatic elements? Should the outcome used depend on the pragmatic features of the trial?
- How should patient-generated data on experience and outcomes be further standardized and taken into account?
- What additional considerations should be made for study designs in symptomatic disease areas?

Session IV: Barriers to Implementation and Regulatory Use

Ultimately, the aim of this discussion is to not only provide an overview of the key challenges and opportunities in using PCT-derived RWE in a premarket regulatory approval decision, but to also identify high priority areas where improvements in the development of RWE, and the infrastructure necessary for efficient and scalable generation, are needed to enable its suitability and usefulness in a broad range of stakeholder decisions. The development of a robust evidence generation system that provides the necessary infrastructure and evidence to meet these needs will require mutual support and collaboration across the stakeholder community. The final session of this workshop will cover the remaining, larger-scale policy and infrastructure barriers to more effective, efficient generation and use of RWE.

¹ Califf, R. & Sherman, R. (2015). What We Mean When We Talk about Data [Blog post]. Retrieved from <http://blogs.fda.gov/fdavoices/index.php/2015/12/what-we-mean-when-we-talk-about-data/>

² Garrison Jr., L. P., Neumann, P. J., Erickson, P., Marshall, D., & Mullins, C. D. (2007). Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report. *Value in Health*, 10(5), 326–335. Retrieved from <http://dx.doi.org/10.1111/j.1524-4733.2007.00186.x>

³ Califf, R. & Sherman, R. (2015). What We Mean When We Talk about Data [Blog post]. Retrieved from <http://blogs.fda.gov/fdavoices/index.php/2015/12/what-we-mean-when-we-talk-about-data/>

⁴ H.R.6 - 21st Century Cures Act. (2015). Retrieved from <https://www.congress.gov/bill/114th-congress/house-bill/6/text>.

⁵ The Network for Excellence in Health Innovation. (2015). Issue Brief: Real World Evidence: A New Era for Health Care Innovation. Retrieved from http://www.nehi.net/writable/publication_files/file/rwe_issue_brief_final.pdf.

⁶ Garrison Jr., L. P., Neumann, P. J., Erickson, P., Marshall, D., & Mullins, C. D. (2007). Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report. *Value in Health*, 10(5), 326–335. Retrieved from <http://dx.doi.org/10.1111/j.1524-4733.2007.00186.x>

⁷ <http://rwdictionary.com/#R>

⁸ FDA's Sentinel Initiative. (2015, November 25). Retrieved from <http://www.fda.gov/Safety/FDAsSentinelInitiative/ucm2007250.htm>

⁹ Tunis, S., Clarke, M., Gorst, S., Gargon, E., Blazeby, J., Altman, D., & Williamson, P. (in press). Improving the Relevance and Consistency of Outcomes Reported in Comparative Effectiveness Research. *Journal of Comparative Effectiveness Research*.

¹⁰ Madigan, D., Stang, P. E., Berlin, J. A., Schuemie, M., Overhage, J. M., Suchard, M. A., ... Ryan, P. B. (2014). A Systematic Statistical Approach to Evaluating Evidence from Observational Studies. *Annual Review of Statistics and Its Application*, 1(1), 11–39. Retrieved from <http://doi.org/10.1146/annurev-statistics-022513-115645>

¹¹ Tunis, S., Stryer, D., & Clancy, C. (2003). Practical Clinical Trials: Increasing the Value of Clinical Research for Decision Making in Clinical and Health Policy. *Journal of the American Medical Association*, 290(12), 1624-1632. doi:10.1001/jama.290.12.1624.

¹² Thorpe, K.E. et al. (2009). A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *Journal of Clinical Epidemiology*, 62(5), 464-475. doi:10.1016/j.jclinepi.2008.12.011.

¹³ Mahon, E. et al. (2015). Barriers to Clinical Trial Recruitment and Possible Solutions: A Stakeholder Survey. *Applied Clinical Trials*. Retrieved from: <http://www.appliedclinicaltrialsonline.com/barriers-clinical-trial-recruitment-and-possible-solutions-stakeholder-survey?pageID=1>