



THE FORUM FOR COLLABORATIVE RESEARCH

TRANSLATING REAL-WORLD DATA INTO REAL-WORLD EVIDENCE

**Webinar 1: U.S. and European Stakeholder
Perspectives**

**Webinar Summary
July 20, 2021**

*1608 Rhode Island Avenue NW
Washington, DC 20036
www.forumresearch.org*



THE FORUM
For Collaborative ResearchSM

Berkeley Public
Health

WEBINAR 1: U.S. AND EUROPEAN STAKEHOLDER PERSPECTIVES

Welcome and Introduction

Jessica Weber, Lauren Fisher, Cheri Banks, Veronica Miller, Forum for Collaborative Research

Real-world data and real-world evidence play an increasing role in health care decisions across different disease areas. These types of data have the potential to optimize clinical trial design, inform regulatory decision making, and allow for the overarching medical community to address questions previously considered unanswerable. The Forum's *Translating Real-World Data into Real-World Evidence Project* brings together the Liver, PSC, and Rare Diseases Forums to explore the opportunities and challenges associated with application of real-world data and real-world evidence across a collective yet inherently nuanced medical landscape.

Subject matter experts from industry, regulatory agencies, insurers, academia, and patient organizations will consider foundational areas and key uncertainties pertinent to the operationalization of real-world data throughout the scientific community, including though not limited to the following: 1) whether real-world data are fit-for-use in generating real-world evidence; 2) data quality and curation, and 3) reliability and validity of innovative analytic tools to address questions of interest, streamline, and improve the efficiency of clinical studies for improved patient outcomes and mitigation of existing knowledge gaps.

This first webinar featured patient, industry, academic, and regulatory experts from the US and Europe. Topics discussed include: 1) overarching principles for fit-for-purpose data; 2) data quality and effective standards for the regulatory process; 3) practical application of real-world evidence; 4) lessons learned from use of real-world evidence as external controls; 5) the role of data at different stages of drug development: from Proof of Concept to confirmatory; and 6) translation of real-world data from various sources to fit-for-purpose evidence.

FDA Real-World Evidence Program

Presenter: John Concato, MD, MPH, U.S. Food and Drug Administration (FDA)

Slides: <https://bit.ly/3yMgilk>

Background: The 21st Century Cures Act (2016) called upon the U.S. Food and Drug Administration (FDA) to establish a program to evaluate the potential use of real-world evidence to support a new indication for a drug under section 505(c) and satisfy post-approval study requirements. The FDA issued a draft framework in 2018 to describe the sources of real-world evidence, challenges, pilot opportunities, and so forth. As of October 2021, the FDA has issued draft guidance for industry, entitled [Data Standards for Drug and Biological Product Submissions Containing Real-World Data](#). This draft guidance addresses challenges in real-world data standardization, appropriate documentation practices and processes for managing real-world data, conforming real-world data to data standards that are accepted by the FDA, and

provides examples for mapping health care data. Meanwhile, the standard for substantial evidence remains unchanged and commitments align with the Prescription Drug User Fee Act.

U.S. Food and Drug Administration (FDA) Real-World Evidence Framework (2018)

The 2018 framework applies to the Center for Drug Evaluation and Research and Center for Biologics Evaluation and Research. A multifaceted program to implement real-world evidence, the FDA RWE Framework focuses on internal processes, external stakeholder engagement, guidance development, and demonstration projects.

'Real-World' Definitions

Real-world data are data related to patient health status and/or delivery of health care routinely collected from a variety of sources, including electronic health records; medical claims data; product disease registries; patient-generated data, including from in-home settings; and other sources that can inform on health status, such as wearable devices.

Real-world evidence is clinical evidence regarding the usage and potential benefits/risks of a medical product derived from analysis of real-world data. Real-world evidence is generated using different study designs, including but not limited to randomized trials (i.e., large simple trials, pragmatic trials), externally controlled trials, or observational studies.

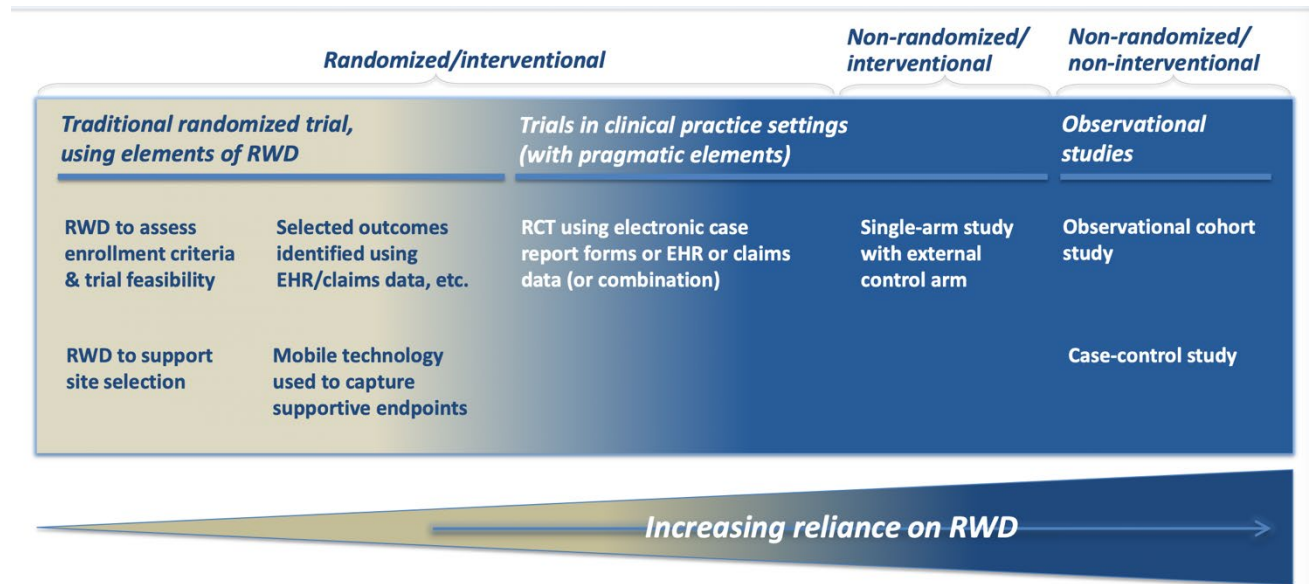
FDA Approach to Evaluating Real-World Evidence

When evaluating real-world evidence, the FDA considers whether the real-world data is fit for use, whether the trial or study design used to generate real-world evidence can provide adequate scientific evidence to answer or help answer the regulatory question, and whether the study conduct meets FDA regulatory requirements.

According to Concato et al. (2020), “in the current era of real-world evidence, the FDA is evaluating whether and how observational studies intended to evaluate efficacy can contribute persuasive results from scientific and regulatory perspectives.” Furthermore, “in this context, a ‘randomized trial versus observational study’ is overly simplistic as shorthand for strength of study design to support causal inference.” In addition to an assessment of prognostic determinism for the corresponding cause-and-effect association, clarity is needed regarding interventional or noninterventional design, primary collection or secondary use of data, and characteristics of comparison group(s).¹

¹ *Pharmacoepidemiol Drug Saf.* 2020;29:1514-1517

Figure 1: Overview of Real-World Data (RWD) and Study Design



Source: MD, MPH, Concato, John. Overview of Real-World Data and Study Design. FDA Real-World Evidence Program.

Application

Real-World Evidence for Safety: FDA Sentinel Initiative

In 2007, Congress passed the Food and Drug Administration Amendments Act, which requires the FDA to work with public, academic, and private entities to create a system using existing electronic healthcare data from many sources to assess the safety of approved medical products. The Sentinel Initiative was launched in 2008 as FDA’s response to the Food and Drug Administration Amendments Act and aims to improve how FDA monitors medical product safety issues.

The Mini-Sentinel Pilot (2009) created a data model and distributed data approach that enables the FDA to track the performance of medical products while simultaneously safeguarding patient privacy.

The Office of Surveillance and Epidemiology in the Center for Drug Evaluation and Research leads the Sentinel System and uses Sentinel to proactively assess the safety of FDA approved drugs under real-world conditions. In sum, when evaluating the safety and effectiveness of medical products, FDA is looking into real world data found in sources such as the Sentinel system.

An Example of a Demonstration Project to Improve Real-World Data: iCAREdata® Project

The ‘iCAREdata’ project is a collaboration between The MITRE Corporation (MITRE) and the Alliance for Clinical Trials in Oncology and is being conducted in association with randomized controlled trials and National Cancer Trials Network institutions. Based on Minimal Common

Oncology Data Elements, the iCAREdata project aims to enable clinical oncology research by prospectively gathering high quality real-world data².

FDA Approves New Use of Transplant Drug Based on Real-World Evidence: Prograf

In 1994, Prograf (tacrolimus) was approved for prophylaxis of organ rejection in patients receiving liver transplants based on randomized controlled trial evidence. Though widely used in clinical care – eventually for kidney and heart transplants – randomized control trials were not done for lung transplants. Subsequently, Astellas Pharma US submitted a supplemental New Drug Application to FDA.

Study data – specifically, US Scientific Registry of Transplant Recipients data on all lung transplants in the US from 1999-2017 - and design – non-interventional (observational) treatment arm compared to historical controls - were evaluated as per FDA standards. Upon review, FDA determined this non-interventional study with historical controls to be adequate and well-controlled.

EMA Approach to the Use of Real-World Evidence in Decision-Making

Presenter: Gianmario Candore, MSc, European Medicines Agency (EMA)/Committee for Orphan Medicinal Products (COMP)

Slides: <https://bit.ly/3yM25VI>

Background: Head of Medicines Agency/European Medicines Agency Joint Big Data Steering Group

To describe the landscape of big data from a regulatory perspective and to identify practical steps to leverage Big Data in support of innovation and public health in the European Union (EU), the European Medicines Agency (EMA) and Heads of Medicines Agency (HMA) set up a joint task force, ultimately leading to the creation of the Joint Head of Medicines Agency /European Medicines Agency Big Data Steering Group and the Big Data Steering Group Work Plan. The comprehensive, inclusive approach includes [the workplan itself](#) (published in January 2020); [an implementation plan \(published in September 2020\)](#) and Big Data Stakeholder Forums (the [first one](#) held in [December 2020](#)).

The Head of Medicines Agency and European Medicines Agency Joint Big Data Steering Group Workplan

Table 1: Priority recommendations of the HMA/EMA Joint Big Data Task Force:

I	Deliver a sustainable platform to access and analyze healthcare data from across the EU
II	Establish an EU framework for data quality and representativeness
III	Enable data discoverability

² icaredata.org

IV	Develop EU network skills in big data
V	Strengthen EU Network processes for Big Data submissions
VI	Build EU Network capability to analyze big data
VII	Modernize the delivery of expert advice
VIII	Ensure data are managed and analyzed within a secure and ethical governance framework
IX	Collaborate with international initiatives on big data
X	Create an EU big data ‘stakeholder implementation forum’

Source: MSc, Candore, Gianmario. EMA approach to the use of RWE in decision-making. European Medicines Agency.

The Workplan’s [10 recommendations](#) (Table 1) provides for necessary EU-wide platforms and frameworks; building and growing networks; strengthening of processes for Big Data submissions; building analytic capacity; modernizing methodologies, including advanced analytics; establishing an Omics Working Party; emphasizing secure and ethical governance; and international collaboration. Each recommendation includes critical activities to realize the full potential of Big Data in regulatory decision making. For example, as a response to Recommendation III (Data Discoverability), a [workshop](#) on real-world evidence meta data was held in April 2021. Outputs include agreed meta data by the end of 2021 and a procurement for an academic consortium to deliver a data quality framework, a draft of which is expected early 2022. A catalog of data sources and type, partnered with information on the quality of the data, will inform the EU community on data quality and availability to answer specific questions.

Under Recommendation V (Network Processes), Data Standardization Strategy was the subject of a May 2021 stakeholder [workshop](#). Recommendation V contributes to ongoing development of a Real-World Evidence Collaboration Roadmap. A Pharmacovigilance Risk Assessment Committee launched and completed a pilot study of rapid analytics of real-world data, as well as a review of 2018-2019 marketing authorizations and real-world data.

As part of the effort to make best use of big data, and to achieve greater global alignment with other regulators on big data topics, the joint task force recommends collaboration with international initiatives on big data (Recommendation IX). Of note, an international data standardization strategy is under development and was the subject of a workshop held in May 2021 with stakeholders. Notably, good progress is being made in collaboration with the U.S. Food and Drug Administration (FDA) and Health Canada on developing a Real-World Evidence Collaboration Roadmap. Linked to the modernization of expert advice delivery to the Network, this roadmap informs development of guidance on data characterization, data analysis, study methods and presentation of protocols and results, including OMICS³.

³ The term OMICS refers to collective technologies and approaches that specifically look at the differences between RNA, DNA, proteins, and cellular molecules.

Examples of Use of Real-World Data and Real-World Evidence in the EU Regulatory Process

Real-World Evidence (RWE) in marketing authorization application & extension of indications

Recommendation V in Table 1 specified a review of all submissions containing of real-world data and evidence submitted in 2018 and 2019. The motivation for this activity was the recognition that little was known about the use of real-world evidence in applications in terms of objectives, data sources, methods, and outcomes. The study explored the contribution of real-world data and evidence to benefit-risk decision making in marketing authorization applications and in extension of indication applications by looking at the outcome of the regulatory review and regulatory decisions. Seven investigators extracted data using a standard form after manual review of the final/latest version of the Committee for Medicinal Products for Human Use Assessment Report and Risk Management Plan, and if needed, other documents such as Rapporteur reports for withdrawn products. Two independent reviewers verified a sample set of the submissions.

The results demonstrate the use of real-world data and real-world evidence in 40% of marketing authorization applications – mainly post-authorization – and in 18% of extension of indication both pre-and-post authorization. Pre-authorization, real-world data and real-world evidence was used mainly to support studies looking at efficacy/effectiveness. Post-authorization constituted mainly risk management plan category 3 (for studies included in risk management plans looking at safety). For both pre-and-post authorization, the most common data sources included registries, followed by hospital data and electronic health care records.

Though there is a widespread use of real-world evidence to support marketing authorization applications and extension of indication, further work is needed to evaluate the impact and usefulness of real-world evidence in regulatory evaluation, exploring how real-world evidence is used, which characteristics are most important, and whether there is a consistent approach followed in decision making. There is a need for guidance targeted to various stakeholders as there is no existing framework nor structure for use of real-world evidence in submissions.

The Use of Real-World Evidence by EMA Committees

EMA committees have several mechanisms available to them for obtaining real-world evidence. For example, they can access data from previous studies such as request obligations to pharmaceutical companies, analysis of public information, and data analysis involving National Competent Authorities. Another mechanism is to conduct studies in-house, such as EMA studies on electronic health databases, commission studies procured through the EMA framework, and to use DARWIN EU (starting in 2022), and deliver a sustainable platform to access and analyze healthcare data from across the EU.

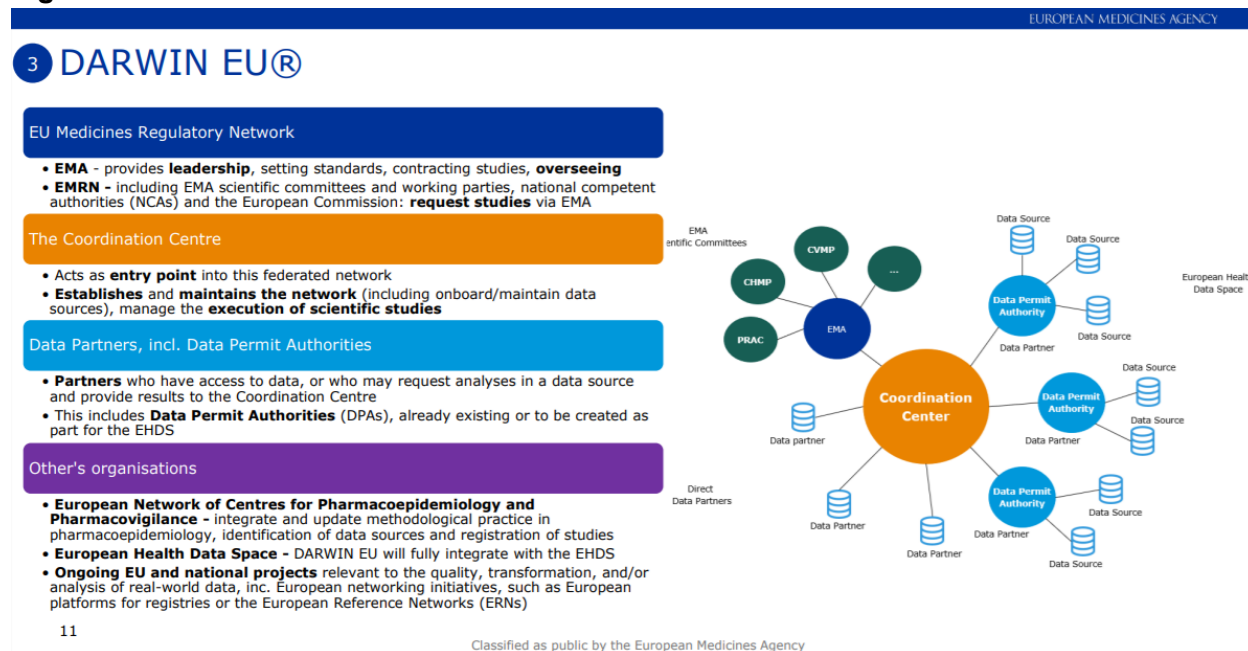
EMA has databases from the United Kingdom, France, and Germany accessible for in-house analysis, and is working on increasing geographical representation and access to hospital

prescribing. This approach was used in 98 cases since 2013, supporting evidence needs of EMA committees, primarily the Pharmacovigilance Risk Assessment Committee.

Second, studies procured through the EMA framework contracts allow access to different data sources and scientific expertise. Since 2010, there have been 30 funded studies. In September of 2021, a new framework contract with broader scope of organizations will be introduced.

DARWIN EU, an ambitious project involving many actors, allows for a European network of databases of verified quality and content with the highest levels of data security to inform regulatory decision-making with robust evidence from healthcare practice. EMA provides leadership and oversight. Other key players include the Coordination Center, Data Partners and Data Permit Authorities, and other organizations such as the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (see Figure 2). Operationally, a specific question from an EMA Committee would initiate evaluation of feasibility, protocol development, identification of Data Partners, data aggregation, analysis of aggregate data and compiling a summary report to be integrated into the assessment report.

Figure 2: DARWIN EU



Source: MSc, Candore, Gianmario. EMA approach to the use of RWE in decision-making. European Medicines Agency.

Lessons Learned from Use of Real-World Data as External Controls

Presenter: Bettina Hansen, PhD, MSc, University of Toronto

Slides: <https://bit.ly/3sdODXW>

Background: Use of Real-World Data/Evidence

Real-world data and real-world evidence can be used to describe the natural history of disease, to identify risk factors of disease, and for post-marketing surveillance of adverse events. Importantly, external controls (based on real-world data and real-world evidence) can be used as a comparator with treated patients in situations where there is unmet medical need, difficulty performing randomized control trials, or when navigating the complexity of rare diseases, pediatric populations, or extended follow-up periods. In cases in which treated patients are followed long-term without a control arm (for example, when patients on a placebo arm are rolled over after end of phase 3), external control comparisons are needed to understand if treatment improves event free survival.

Feasibility of Real-World Data as External Controls

While trial data is often marked by high quality standards and narrow inclusion and exclusion criteria, real-world data can be problematic. Real-world data often constitutes a mixed population with missing data and potential biases.

To achieve the goal of improving patient care, each stakeholder brings a unique contribution to the table. Pharmaceutical sponsors have trial data; independent clinical researchers have real world data; and regulators are responsible for guarding the integrity of the process. For data sharing, protocol, and statistical analysis planning, collaboration - marked by shared willingness, transparency, and trust – is necessary.

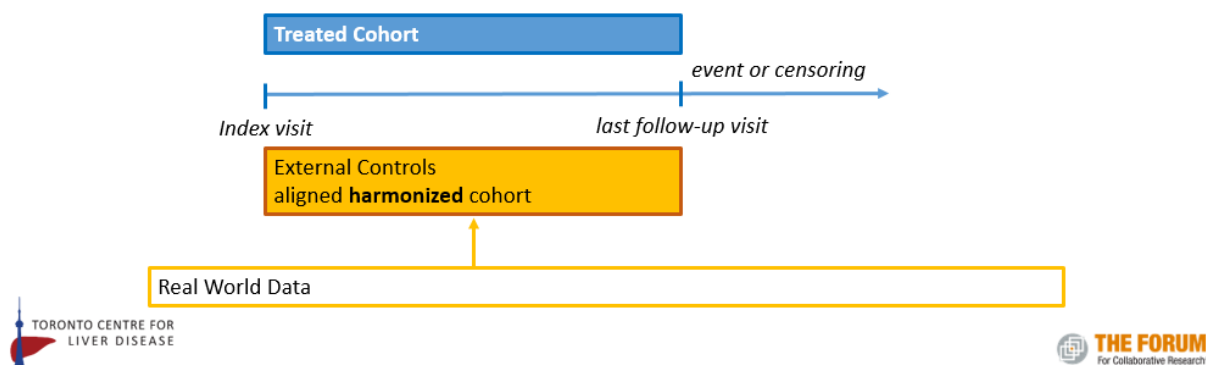
The successful use of real-world data, exemplified by the GLOBAL Primary Biliary Cholangitis Study Group (2012) and GALA: the Global Alagille Alliance Study (2018), calls for a high bar of standardization, quality, completeness, accuracy, and consistency. Both the GLOBAL Primary Biliary Cholangitis Study and Global Alagille Alliance Study aim to compare time to clinical events (in this case, liver transplantation or death) in treated patients with external controls. Use of real-world data in this setting requires the creation of an aligned, harmonized cohort extracted from the larger set of real-world data as illustrated in the figure below.

Figure 3: Primary Aim

Primary aim

To compare time to clinical event in treated patients with external controls

Examples PBC and Alagille: Event defined as liver transplantation or death



Source: PhD, MSc, Hansen, Bettina E. Lessons Learned from use of Real-World Data as External Control. Toronto Center for Liver Disease, UHN - University of Toronto.

The process of harmonization starts with a feasibility assessment, followed by the identification of patients and visits, choice of index time, and an assessment of balance. Importantly, researchers need to be blinded to outcome during these four steps.

For assessment of feasibility, researchers need to ask questions such as: is the data of sufficient quality? Do outcomes use the same definition? Are the laboratory values consistent? How similar are the patients? How complete is the data set? What confounders need to be accounted for? Will the study have sufficient power to allow drawing meaningful conclusions?

To identify and select the most appropriate patients to include in the external control, researchers apply inclusion and exclusion criteria that align with those applied to the selection of patients on treatment. Ideally, patients for the external control would be selected from the same sites and regions, observed during the same calendar time and have received the same standard-of-care treatment. Figure 4 illustrates how these principles were applied to GALA.

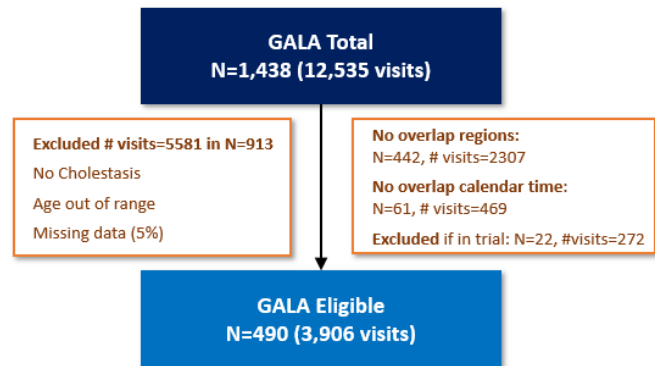
Example external controls selection Alagille

Alagille phase 2 trial: inclusion severe cholestasis, age 1-18yr

RWD = External controls from GALA

Identification of patients and visits:

- A patient may be eligible with multiple visits



Source: PhD, MSc, Hansen, Bettina E. Lessons Learned from use of Real-World Data as External Control. Toronto Center for Liver Disease, UHN - University of Toronto.

GALA includes 1,438 patients, but only 490 of these were eligible for the external control for the Alagille phase 2 trial.

Once patients are identified, researchers need to determine the best Index Time (start of follow-up). This could be a specific visit, or a range (e.g., first to last) or determined using methods such as maximum likelihood. Avoiding immortal time bias is important. For example, a cohort patient may be eligible to enter a phase 3 trial over multiple clinic visits but may be “too frail to enroll” at others, and such visits should not be used as the start of follow-up.

The last step is assessment of balance, important because of potential confounding due to the distribution of prognostically significant baseline variables differing between the treated and the external control patients in non-randomized studies. This is done using pre-specified checks and tests, and statistical methods using weighting, as in propensity scores, inverse probability of treatment weighting, or average treatment effects on the treated weights.

Once the above four steps have been completed, unblinding allows the researchers to proceed with analysis of time to event, using methods such as Kaplan-Meier and Cox regression models, conduct sensitivity analyses and subgroup analyses.

Lessons Learned

There is enormous support and enthusiasm for collaboration in the use of real-world data and real-world evidence from many stakeholders. The benefits of such collaboration include

exploring improvements in methodology, improvement of understanding of the effect size through multiple sensitivity and subgroup analyses and having more than one real-world data set available for validation. Challenges include data quality and how to assess it and the fact that relevant safety data is often missing, especially in retrospective cohorts. Immortal time bias remains an issue to contend with. It is important to ensure that all ethical and legal requirements are met. Finally, to be effective, collaborations with many investigators in many sites and regions, must be carefully managed and supported. As a field, we need to recognize and act on the strong need to create easier pathways for collaborations in order to achieve the common goal of improving patient care.

Fit-for-Purpose Data

Presenters: Satrajit Roychoudhury, PhD, MStat, Pfizer and Jerry Vockley, MD, PhD, University of Pittsburgh

Considerations in Analysis of Real-World Data

Registration of a new drug requires a well-controlled trial. One of the main concerns when using real-world evidence in the regulatory setting is whether the data meets the regulatory standard of a well-controlled experiment. If it does not, it is necessary to explore how to mitigate bias that is introduced by a non-randomized experiment.

Recommendations for use of real-world data and real-world evidence are available from The International Society of Pharmacoeconomic and Outcomes Research, the International Society of Pharmacoepidemiology, and the Analytical and Statistical Association, as well as regulatory authorities. Although they approach the topic from different perspectives, there is a common theme: pre-specification of the hypothesis, design, analysis plan, method to reduce bias, and the importance of transparency.

Real-World Evidence in the Rare Disease Setting

The Estimands Framework (ICH E9) is useful to consider while we are in the learning phase, especially in the challenging context of rare diseases with small populations. First, it is important to recognize that the standard-of-care can be diversified. Do we have the right population to address the clinical question? Have we applied the right inclusion/exclusion criteria? Second, we need to clarify how we define the endpoint and how we can appropriately measure it. Third, intercurrent events such as lost-to-follow-ups, missing data and deviation from the standard-of-care are not handled as well in real-world data compared to randomized clinical trials. Fourth, it is important to bring in causal inference at the very beginning. We need to know the confounders and pre-specify how to deal with them with methods such as propensity scores, maximum-likelihood, and Bayesian approaches.

From a practical perspective, recruitment into rare diseases trials is difficult. Heterogeneity abounds, both at the patient and provider level. Unique genotypes and phenotypes result in

unique patient journeys. Providers for patients with rare diseases are few and far between, and often bring their own unique perspective into the care of their patients. Thus, even the fact that a patient moves from their provider to a major center to participate in a trial, means that their standard-of-care may change significantly. Caring for patients involves a lot of clinical laboratory testing; biomarker data accumulating as a result should become part of what is collected under real-world data.

Real-world data in rare diseases will be inevitably imperfect and inevitably incomplete. As a field, we need to overcome these imperfections to provide useful data for clinical trials, and find a way to bring competing interests together, rather than pursue small, short-term follow up cohorts each time a new therapy is being investigated.

DISCUSSION

Moderators: Sandy Lehrman, MD, Independent Consultant and Patient Advocate and Veronica Miller, PhD, The Forum for Collaborative Research

Regulatory perspective: using real-world data and real-world evidence as an external control is indeed feasible, but it is difficult to do right, given the many issues that can threaten the validity. The bar of level of evidence remains unchanged. The data source is important; type of data and quality can vary according to region or country. The agencies remain committed to understanding the full potential of real-world data and real-world evidence in regulatory decision making.

The decision to use real-world data and real-world evidence is made at the Divisional level. Divisions will consider the disease, the drug being tested, the expected benefit of the drug, and the treatment effect. Thus, there is no “one size fits all”. Importantly, safety needs to be evaluated and that is difficult to do with no contemporaneous control arm.

In terms of design and analysis, the need to be blinded for outcome, as outlined earlier during the webinar, is extremely important.

Patient perspective: Patient organizations like PSC Partners are engaging in significant ways to generate reliable natural history data and patient reported outcome measures. Patients need to be included as one of the stakeholder groups contributing to any real-world data and real-world evidence discussions.

Researcher perspective: One approach to use natural history in rare diseases is to incorporate a run-in period on standard-of-care, followed by a roll-over into an on-treatment arm, each patient serving as their own control. The challenge with this is that natural history often progresses slowly, thus retrospective data will inevitably be needed.

Natural history studies can have different purposes. For example, the PBC Global Study Group was used to validate alkaline phosphatase as a surrogate endpoint for clinical trials. Such purpose brings different issues and challenges, compared to using the study as an external control. The Global PBC Study Group, now combining real-world data with clinical trial data has evolved over the last decade to a higher standard, including auditing of outcomes. Another consideration is that as treatments are being developed and approved, “natural history” cohorts will start following patients on treatment. How is the field preparing for this?

The panel discussion demonstrated how collaboration between academicians, patients, patient advocates, industry, and regulators will continue to inform the way we think about clinical trial designs and real-world evidence in its collection to be used as fit-for-purpose data. Thus, everyone can achieve their goals of better study designs, data, therapies and strategies for managing patients with PBC, PSC, Batten’s disease, etc.

We are aware that real world data and evidence are useful for many diseases areas. The Forum welcomes additional questions and recommendations for future topics and is interested in learning what would help stakeholders move their respective fields forward by using some of the discussed approaches.