2022 Global Conference on Regulatory Science

CONFERENCE PROCEEDINGS

October 11-12, 2022

Hosted by the Harvard-MIT Center for Regulatory Science

ABOUT THE HARVARD-MIT CENTER FOR REGULATORY SCIENCE

The Harvard-MIT Center for Regulatory Science was established in 2018 to advance research and education in regulatory science. The Center serves the broad community of biomedical research scientists and physicians in academia, industry, and regulatory agencies who seek to improve the development and evaluation of medical products. The primary principle underpinning these activities is that scientific discoveries will most benefit patients if accompanied by an efficient, rigorous, and adaptable approach to evaluating the many rapidly emerging biotechnologies. The Center functions as a platform to foster interdisciplinary and multi-stakeholder discussions on scientific and infrastructure needs. The Center offers a Regulatory Science Fellowship, hosts local and international conferences, and manages a portfolio of research collaborations with regulatory agencies, industry, and other academic institutions.

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I. INTRODUCTION

What is Regulatory Science?

Rapidly evolving areas of science are promising new approaches to improve health while also demanding new tools, standards, and approaches to evaluate innovative products. Regulatory science comprises a range of scientific disciplines that are applied to the quality, safety and efficacy assessment of medicinal products and that inform regulatory decision-making throughout a product's lifecycle. Effective regulatory science requires dialogue and collaboration between academic investigators active in the field, and the government and industry groups for whom the evaluation, regulation and marketing of medical products is a central concern.

Conference Description

Hosted by the Harvard-MIT Center for Regulatory Science (CRS), the 2022 Global Conference on Regulatory Science was held virtually over 2 days, October 11-12, 2022. This annual event convenes academic scientists, international regulators and industry experts to explore emerging topics in the development and regulation of medical products. This year's theme was the Evolving Use of Real-World Evidence in Therapeutic Development and Regulation, and conference participants discussed how real-world evidence (RWE) is informing regulatory decision-making and advancing knowledge throughout the product lifecycle.

Regulatory science *comprises a range of scientific disciplines that are applied to the quality, safety and efficacy assessment of medicinal products and that inform regulatory decision-making throughout a product's lifecycle.*

These Proceedings summarize the invited speakers' presentations, panel discussions, and related Question and Answer sessions. The conference also included a working group and a special session, reported separately.

Conference topics included RWE frameworks and use cases in several areas:

- Drug development and approval in rare conditions
- Demonstration projects
- Post-market evidence generation for medical devices
- The patient community perspective

Definitions

RWD

- Real-world ***data*** are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources, such as *EHRs, claims, registries, wearables*

RWE

- Real-world ***evidence*** is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.

Conference Context and Focus

Opening remarks by **Florence Bourgeois**, Co-Director of the Harvard-MIT CRS

Bourgeois noted that the Conference was occurring in the context of a decade-long rapid acceleration in the interest in and use of real-world data to support regulatory activities. An ever-increasing volume of digital health information is available, from the more traditional sources of electronic health records (EHR), insurance claims, and disease registries, to newer sources such as mobile devices, wearables, and other sensors that gather and store huge amounts of health-related data. These data hold the potential to improve the design and conduct of clinical trials and to support clinical investigations previously deemed infeasible.

Recent legislative activity aims to hasten use of RWE in medical product development and regulation. In response to the 21st Century Cures Act[1], the FDA launched a multifaceted program to develop guidance documents, conduct demonstration projects, and evaluate use of real-world data to support regulatory decision-making. There have already been tangible successes, including the approval last year of Prograf® for organ rejection prevention in patients with lung transplants. This approval relied on registry data to demonstrate the improvement in outcomes among patients treated with Prograf as compared with historical controls. Real-world data was also in the limelight as part of the most recent renewal of the Prescription Drug User Fee Act[2] (PDUFA) which incorporates changes to the accelerated approval program, including language requiring drug sponsors to conduct an appropriate post-approval study which may be augmented or supported by RWE.

But despite the promise of real-world data, a number of critical issues warrant further consideration and were addressed by conference speakers. They include:

- Most existing real-world data were not generated with regulatory standards in mind and therefore significant challenges remain to ensure these data are of sufficiently high quality and fit-for-purpose to be reliably used in regulatory decision-making.
- While these data may be sufficient to complement clinical trial data, or be acceptable alternatives when confirmatory trials are not feasible, it is premature to consider RWE as the sole source for determining clinical benefit.
- A number of investigations have demonstrated considerable challenges with conducting FDA-required post-approval studies using real-world data.
- There are important tradeoffs with traditional randomized controlled trials (RCTs). Considerable work is needed to understand: 1) exactly how real-world data needs to evolve to be fit-for-purpose, and 2) its place alongside other sources of clinical evidence.

***Real-world data studies are not a replacement for randomized controlled trials**, and they are not always faster, easier, or cheaper.*

The 2022 Global Conference brought together a distinguished group of experts to explore some of these issues including the COVID-19 Evidence Accelerator as an approach to rapidly sharing real-world data, the need for global coordination on standards and requirements for RWE use, integrating patient experiences into evidence generation to better understand what endpoints are most relevant to patients, and developing the infrastructures and analytical tools required to help realize the full potential of real-world data to accelerate medical product development.

II. KEYNOTE ADDRESS: THE EVOLVING USE OF RWE IN DRUG/DEVICE DEVELOPMENT: TOWARDS TOTALITY OF EVIDENCE

Keynote Speaker:
***Carla Rodriguez-Watson**, Director of Research, Reagan-Udall Foundation for the FDA*

Rodriguez-Watson began by exploring the critical role RWE played in measuring effectiveness of COVID-19 treatments. With thousands dying daily at the pandemic's peak, waiting years for clinical trial results wasn't an option. The Reagan-Udall Foundation, in collaboration with Friends of Cancer Research, created the COVID-19 Evidence Accelerator where leaders from across the healthcare ecosystem collaborated to explore urgent questions about COVID-19 through the lens of real-world data and RWE generation. Lessons learned were summarized in a COVID-19 Real-World Evidence Primer[3] that provides insight into core pharmaco-epidemiologic methods for RWE study conduct.

"COVID-19 really was the catalyst that forced us all to think about how we can disrupt the current discovery process to get safe and effective products to market faster, but with a high level of rigor to engender trust."

Pandemic responses illuminated the distinct role for real-world data and RWE along with RCTs in the totality of evidence. This is particularly true for monitoring the safety and effectiveness of drugs and devices used during pregnancy as RCTs typically exclude pregnant persons. A recent series of FDA guidances summarize frameworks resulting from the progress made in methods to use, evaluate and report RWE for regulatory decision-making. The foundation aims to operationalize these frameworks, modernizing medical and product development and safety, via public private partnerships like the Innovation in Medical Evidence and Development Surveillance (IMEDS) Program.[4] COVID-19 further exacerbated pre-existing disparities. Despite this, and although one-fifth of new drug approvals show differences in exposure and/or response by racial and ethnic groups, many data systems sill lack race/ethnicity information. The Foundation is launching an evidence accelerator-style project—RACE: Real-world Accelerator to evolve the standard of Care and Engagement in clinical studies for communities of color—to help improve capture, retention and protection of race/ethnicity data.

Q&A excerpt:
How is race handled in real-world data?

"Along the whole data cascade, as data are moved from their native source to be integrated into larger networks, the reporting of race, the capture of race, the curation of race and ethnicity data is low in real-world data. There's a need for standardization in the categories we present folks to answer, but also a need for those categories to be reflective of the population so that people see themselves in those categories and can report."

Rodriquez-Watson acknowledged a disconnect between the attention to RWE on a policy level and lack of RWE familiarity among reviewers of regulatory submissions. Real-world data is messy and inherently biased because much of it comes from sick people seeking care. The current workforce needs training to recognize whether submitted real-world data can actually generate evidence. But she also envisions a future where these data do not just reflect a doctor's panel or the information needed for reimbursement, but instead could improve patient care, or help generate evidence for drug safety and effectiveness, or where healthcare utilization data could be used in a meaningful way to conduct decentralized clinical trials. This could

look like a learning health system, or even an evidence-generation system nested within a learning health system.

III. STAKEHOLDER PERSPECTIVE ON THE USE OF REAL-WORLD EVIDENCE

Including the Patient Experience in Evidence Generation

Speaker:

***Jennifer King**, Chief Scientific Officer, GO2 Foundation for Lung Cancer*

King shared insights on patient experience from the perspective of a non-profit advocacy group aiming to transform lung cancer survivorship.

FDA GUIDANCE ON PATIENT-FOCUSED DRUG DEVELOPMENT

Incorporating patient experience includes considering patient views, needs, feelings, actions, preferences, and interactions regarding their disease and its treatment.[5] It also includes impacts on patient caregivers and loved ones. Real-world data provides information about the patient's experience, but doesn't necessarily mean that information is important to the patient.

THE VALUE OF ADVOCACY GROUPS

Advocacy groups have expanded beyond patient and caregiver support programs to encompass:

- Political advocacy and informing or helping pass legislation
- Providing navigation programs to help patients find treatment options and clinical trials
- Performing their own clinical research in partnership with key investigators
- Nominating patients and caregivers to speak or serve on advisory boards

THE PATIENT VOICE IN STUDY DESIGN

Key recommendations for study design from advocacy group navigators include providing patient-friendly informed consent forms and a 1-2 page summary of the trial. Patients want to know whether the drug has been used before and what happened. Be transparent about what a participating patient can expect and will have to do. Provide flexibility and remote participation options when possible, and contact information for someone who can answer questions about the trial.

MEANINGFUL ENDPOINTS

Some data suggests that the endpoints that can be obtained from real-world data may not always be those that are most important to patients, and that rates of side effects and adverse events in patient-reported data may be much higher than that in clinical trial data. When comparing similar medicines, we should compare key side effects impacting patient experience as well as overall symptom reduction.

TAKE-HOME MESSAGES

1. Remember to consider patient experience in clinical trial design for regulatory approvals, e.g. why would the patient want to go on this study and what would be most meaningful to them?

2. Consider what are the most meaningful endpoints to the community your drug or device is intended to serve.

3. Develop partnerships with advocacy groups. They know a lot about the community they serve and are willing to help you design the best trial for your shared community.

Panel: Perspectives of Global Regulators on the use of RWD/E in Rare Conditions

Moderators:
Gracy Crane, International Regulatory Policy Lead for RWD, Roche
Elodie Aubrun, Group Head, Quantitative Safety & Epidemiology, Novartis

Panelists:
Kathleen Donohue, Director, Division of Rare Diseases and Medical Genetics, FDA
Catherine Cohet, Pharmaco-epidemiology/RWE Senior Specialist, Data Analytics & Methods Task Force, European Medicines Agency
Tobias Polak, Director of Real-World Data, myTomorrows
Fabricio Carneiro de Oliveira, Head, General Management of Biological Products, Brazilian Health Regulatory Agency (ANVISA)

Panelists identified a range of issues related to rare diseases and rare disease products including:

- small patient populations
- limited knowledge of the natural history of the disease, hindering identification of relevant outcome measures
- potential heterogeneity in disease phenotypes or genotypes.

They discussed challenges in using RWD/E in rare disease drug development due to data scarcity. To achieve sufficient numbers of patients may require pulling data from varying origins, and each source requires feasibility assessment. Real-world data, including from patient registries, can complement evidence generated pre- and post-authorization, but there is a need for harmonization across registries or other data owners, and issues around data sharing, technical considerations and data quality persist.[6] Research questions of interest and the associated data elements should be defined early to prepare for reliable analysis. Multi-stakeholder collaboration is also needed.

Scientific method issues, including availability of appropriate controls, are also significant challenges. There may be no credible path forward for certain single-arm trials, but designs such as Bayesian adaptive borrowing may allow reductions in the size of a control or placebo group while maintaining randomization. Real-world data may also be useful to "fill gaps" in data that were collected for approvals and pharmacovigilance.

Data collected as a part of expanded access treatment programs may represent a very specific type of real-world data, coming from the preapproval access setting vs. from products already on the market. Rare diseases may particularly benefit from information derived from treatment of patients in an expanded access setting. However, European legislation varies across individual member states as to whether data collection is allowed under expanded access or compassionate use. U.S. regulations regarding extrapolation of efficacy or safety would also apply to expanded access data.

Q&A excerpt:
Validating biomarkers

"Biomarkers are one of our most powerful tools for advancing drug development, and often the piece we're missing in rare diseases is that correlation with clinical outcomes. One of the big opportunities for real-world evidence in rare diseases is going to be in validating biomarkers…that's probably going to be the area where we see the most progress."
- Katie Donohue

KEY CONSIDERATIONS FOR A RIGOROUS REAL-WORLD DATA PROPOSAL

REGULATOR'S PERSPECTIVE

1. Define a clearly formulated research question
2. Demonstrate an understanding of the natural history of the disease
3. Provide a deep description of external controls, including demographics, key factors that might predict disease course, extent of missing data, the strategy for matching
4. Include objective endpoint(s)
5. Assess feasibility of data source(s) including any registries
6. Include a plan to generate confirmatory data if conditional authorization is granted

Finally, the panelists stressed that early collaboration between industry and regulators will help to "bridge" regulatory and industry views regarding the use of real-world data in rare conditions.

FDA and Real-World Evidence

Speaker:

John Concato, Associate Director of Real-World Evidence Analytics, Office of Medical Policy, FDA

THE FDA REAL-WORLD EVIDENCE PROGRAM

In response to the 21st Century Cures Act,[1] FDA established a program to evaluate use of RWE to support a new indication for a drug already approved or to satisfy post-approval study requirements. In 2018, they published a framework for the program that applies to the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, and the Oncology Center of Excellence.[7] Draft guidances issued for industry in 2021 clarify key considerations in use of RWE.[8,9,10,11] They also encourage sponsors to engage early when designing non-interventional studies so that FDA can be convinced they were done in a rigorous, fair way. The FDA is also supporting a number of RWE research projects, including to improve quality of EHR data, develop statistical methods for RCTs with hybrid control arms, and evaluate confounded treatment effects.

CURRENT STATUS OF REAL-WORLD EVIDENCE

Over five years after the Cures Act, the terms real-world data and RWE are being used inconsistently and interchangeably.[12]Real-world data and RWE are not new concepts, as the sources of data and types of study design haven't fundamentally changed. However, there is electronic access to more detailed clinical data and the data are becoming more relevant and reliable. It is also not the case that a simple dichotomy of randomized trials versus observational studies exists. Rather, study designs include:

Randomized, Interventional Study		Nonrandomized, Interventional Study	Nonrandomized, Noninterventional Study
Traditional randomized trial using real-world data in planning	Trial in clinical practice settings with pragmatic elements	Externally controlled trial	Observational study

Reliance on real-world data increases moving left to right; all designs but traditional RCTs generate RWE.

Across RWE submissions for drugs and biological products, key FDA considerations are:

- Whether the real-world data are fit for use
- Whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question
- Whether the study conduct meets FDA regulatory requirements

REMAINING CHALLENGES

Concato concluded with some representative problems for use of RWE. Real-world data sources may have issues of reliability or clinical relevance. Even the most pristine dataset can only go so far if it lacks information on the variables of interest. Other issues include lacking linkages to other data sources, missing or mistimed data. And not all endpoints of interest are equally detectable in real-world data sources. Non-randomized study designs bear a risk of residual confounding, especially when the signal of interest is weak. Other study design concerns include problems with an index date ("zero time"), as well as use of inappropriate comparators. Protocols and analysis plans should be *pre-specified*.

> *"The FDA remains committed to robust policy development aligned with the 21st Century Cures Act, while maintaining evidentiary standards and honoring our obligation to protect and promote public health."*

Faster, Better, Cheaper: The Increasing Role and Opportunities for Real-World Evidence in Information Regulatory Pathways

Boone shared wide-ranging perspectives on the current and future state of using RWE derived from big data sources to accelerate the discovery, development and delivery of 21st-century therapies in a post-COVID world.

Speaker:

Christopher Boone, Vice President, Global Head of Health Economics & Outcomes Research, AbbVie; Adjunct Assistant Professor, NYU Wagner School

Currently, biopharma is a very risky business and the clinical trial system is broken. The average time and cost needed to develop a drug is 14 years and $2.6 billion. Less than 10% of therapies entering human trials make it to the pharmacy. Few patients participate in clinical research, many that do drop out, and trial populations are not representative of the U.S. population. In this context, RWE is appealing because of an emphasis on value and costs, a desire to move toward precision medicine, and overall public demand for higher quality. But increased regulator openness to RWE for regulatory decision-making has made it much more incentivized for industry.

"The ability to generate compelling evidence through the life cycle of an asset is increasingly important as we move from a world where evidence generation is predominantly from RCTs prior to launch, to one where generation of the right evidence, including RCTs, RWE, or patient experience data, is critical to delivering on a drug's full potential."

Boone identified a number of current use cases for RWE including for indication prioritization, and for post-market studies of safety and effectiveness in a real-world context after initial conditional accelerated approval (as was done with COVID-19 vaccines).

Going forward, Boone asserts that the era of precision healthcare is upon us, represented in three dimensions:

- Tailored prevention and treatment to individuals
- Precision reimbursement--decision-making based on the clinical and economic value to patient sub-populations or clusters
- Precision public health that targets interventions for certain populations around the world, including trying to control future pandemics

Four trends will shape the future of the role of RWE in drug development: 1) reaching a "tipping point" where biopharma and all life sciences invest more in talent, governance and data analytics to support RWE strategies, 2) the pursuit of health equity to increase patient and investigator diversity and ensure equitable access to diagnostics and medicines, 3) reaching more patients with virtual clinical trials to address recruitment and retention issues, and 4) accelerating drug development with platform trials.

For biopharma to accelerate the use of RWE, it must increase understanding and communication of relevant endpoints using RWE to all key stakeholders, including policymakers, providers, patients, and payers; create organization and operating models and culture that drive integration of RWE; build stable platforms that manage and analyze real-world data in a rapid, low-cost fashion; and advocate for global harmonization of regulatory guidance for RWE acceptability.

IV. BUILDING THE INFRASTRUCTURE TO ADVANCE EVIDENCE GENERATION

RWE Reproducibility and Validity with Implications for Expanded Effectiveness Claims

Speaker:

Sebastian Schneeweiss, Professor of Medicine and Epidemiology, Harvard Medical School; Chief, Division of Pharmaco-epidemiology, Department of Medicine, Brigham and Women's Hospital

The largest difference between RWE studies and RCTs is the lack of baseline randomization. Also, RCTs work with primary data, while RWE studies use secondary data. Given these differences, Schneeweiss identified four areas to address to instill confidence in RWE studies for decision-making.

1. Transparency and reproducibility of implementation: Although greater transparency is needed about study parameters used to create RWE datasets,[13] published papers often lack sufficient detail to attempt reproducibility. Analytic software platforms are built for transparency but sharing programming code does not ensure a protocol was implemented as the investigator intended. Improvements in transparency and reproducibility are possible through consistent use of study registration, audit trails, and structured templates to plan and report database studies of RWE.[14,15]

2. Fit-for-purpose data: Tested strategies exist to improve measurement characteristics for 4 key variable types of interest (study population, exposure, outcome, and confounders) but the question of how good is good enough remains. With secondary data, they will never be perfect, but it is important to assess and to apply appropriate modeling strategies.[16]

3. Validity of findings: Non-valid study findings cannot support effectiveness claims. RCT-DUPLICATE, a FDA-funded methods demonstration project, sought to test a process to emulate RCTs in a RWE study with U.S. claims data. In trials where it was possible to closely emulate the design and measurements of the RCT, there was high correlation between the conclusions of the RCT and the RWE.[17] While not demonstrating all RWE are valid, RCT-DUPLICATE's findings are encouraging and point toward an important potential use case for RWE trial emulations. In this approach, a RWE study would not only be submitted for consideration for supplemental indication approval, but also demonstrate that the RWE study design and measurements came to the same conclusion as the original RCT.

4. Facilitating decision-maker review: As RWE studies are increasingly considered for regulatory, coverage, and other clinical decision-making, reviewers used to making assessments based on randomized trial evidence will need training[18] and tools[19] to feel comfortable evaluating RWE studies. Regulators will also need to be able to re-analyze patient-level data from RWE studies like they do for RCTs, as the ability to do sensitivity analysis, or change inclusion criteria or outcomes will build confidence in the data. This will require identifying new ways to share third-party data and data analytics environments.

Schneeweiss believes the influence of RWE in regulatory and coverage decision-making will increase:

- As we follow principles of causal inference (which we know how to do)

- As we reduce human error and increase transparency (which we know how to do)
- As data sources improve (which they do rapidly)

Preparing for the Future of Evidence Generation

Speaker:

Joe Franklin, Product Counsel, Verily Life Sciences

Franklin summarized his goals that modern evidence generation be:
1) of greater depth, including more diverse participants and richer data sources
2) more generalizable, by including participants traditionally excluded from research, including those with comorbidities
3) more longitudinal, with data about timepoints before and after the clinical trial.

Despite great progress in developing novel data analytical approaches and in global consensus in regulatory expectations for novel data, considerable last mile challenges persist.

DOCUMENTATION OF DATA QUALITY

Data for longitudinal evidence generation are coming from many different sources to complement clinical trial data. And those data sources have markedly different data integrity and quality. There is an important role for regulatory science to develop consensus around how to document data quality, communicate about it, and to improve it for use in decision-making, including in the regulatory context.

"'We can think about applying the same type of scale, momentum and overall effort as in the 1960s moon landing into understanding how to use modern evidence generation… it's a very exciting time."

VALIDATION OF NOVEL MEASURES

Interest in novel measures is high, especially for data collected directly from participants. Some frameworks exist for novel monitoring technology or digital biomarkers (e.g., analytical validation that a physiological or behavioral trait of interest is being measured, validation that the trait is clinically relevant). Challenges remain to increase the scale and speed at which decisions can be made and consensus reached between product developers, regulators, and others using data from sensors.

Q&A excerpt:

Data quality

"The demand for data is going to come back to the quality and reliability of the data and the scientific methods for evaluating it. We are seeing over time as regulators get more experience with evaluating data sources, there's a lot more sophistication around how we can design systems to ensure data quality."

LONGITUDINAL EVIDENCE GENERATION

Several regulatory use cases demonstrate remaining challenges for longitudinal evidence generation.

- Machine learning/artificial intelligence-based software as medical device algorithms. The FDA and others have developed best practices for designing and training algorithms and the data they contain. But significant issues remain in how to monitor real-world performance of algorithms over time, including prioritizing the questions to ask about how an algorithm is performing, determining how data relevant for real-world monitoring is collected, and how regulators and others doing the monitoring share information about how algorithms are performing.
- Self-care consumer products. Better data are needed to understand how over-the-counter (OTC) products perform in post-market settings. In addition to safety monitoring, RWE generation could assess whether consumers know how to correctly select or use OTCs. A proposed

FDA rule would establish an additional condition for nonprescription use,[20] such as answering a questionnaire via an app, to determine eligibility to purchase an OTC product. These additional data could be used to monitor performance of this condition of use over time, and also be an opportunity to connect with patients for recruitment to studies assessing how drugs are performing.

- Post-approval longitudinal evidence generation. Programs such as Medicare coverage with evidence development,[21] used successfully to collect post-approval data about monoclonal antibodies for Alzheimer's disease, and about transcatheter aortic valve replacement, and the Medicare drug price negotiation components of the 2022 Inflation Reduction Act, also represent opportunities for longitudinal evidence generation.

Building and Validating Real-World Data Cohorts to Support Regulatory Use

Speaker:

Jessica Franklin, Principal Consultant, Epidemiology and Real-World Evidence, Optum

Franklin outlined four potential regulatory uses of real-world data:[22]

- Support a primary approval decision with studies using external or historical controls derived from real-world data
- Support a secondary indication or a supplemental approval
- Adaptive pathways, expanding from a small initial approval to a larger full approval decision
- Post-marketing safety assessments of potential issues known at the time of initial approval, as well as response to a safety signal identified via continued monitoring

An example of using a pure RCT to assess safety on cardiovascular events of a newly-approved diabetes drug illustrates the size, time, and cost challenges of the RCT design. A hybrid study design would derive some patients from a real-world data source to augment the placebo-controlled patients from the RCT. This approach requires fewer patients to be enrolled with resulting faster accrual time, fewer study sites, lower cost, and likely a quicker path to obtaining evidence on safety.

The advantage of this hybrid design over a purely RWE approach is the ability to maintain randomization. However, questions remain as to how to determine whether the real-world data for a particular study and specific data set are valid. Methodologic approaches, including assessment of balance on partially measured covariates and negative control analyses, are useful and should be encouraged. But they require having committed to a RWE approach before assessing whether RWE is going to succeed. What is really wanted is an approach that allows assessment of a potential augmented real-world data control group before committing to a hybrid design.

What can be done in the pre-approval phase to set up for using real-world data in the post-approval phase? Franklin proposes comparing real-world data and RWE cohorts against the phase two and phase three trial populations. If the real-world data cohort is a good match to the trial cohorts in phases two and three, particularly if they are a good match for the placebo group, this provides increased confidence that the control cohort will be valid during the post-marketing safety study. The eligibility criteria from the RCT would be applied to construct a cohort of real-world data controls. Then within the population of eligible real-world patients, propensity score matching or a similar technique would be used to create a real-world data cohort that can be compared against the trial population. If the RCT placebo patients and the matched real-world data control patients are similar, that strengthens confidence in the ability of the real-world data controls to be useful in a post-marketing safety study.

Although it has promise, questions remain about many of the details of this approach, including how to reconcile a global trial population against a more limited real-world data population, do data vendor data protection policies prevent sharing patient-level data, how to power a study utilizing an augmented real-world data control group, what pre-planned steps are necessary if the real-world data assessment shows poor agreement with the RCT, and how to ensure that blindedness of study data is not compromised at interim analyses.

Panel: Real-World Evidence Generation for Medical Devices

Moderator:
Sanket Dhruva, Assistant Professor of Medicine, University of California, San Francisco School of Medicine

Panelists:
Joseph Ross, Professor, Department of Internal Medicine, Yale School of Medicine, Professor, Department of Health Policy and Management, Yale School of Public Health, Center for Outcomes Research and Evaluation, Yale-New Haven Hospital

Natalia Wilson, Executive Director, Center for Healthcare Delivery and Policy, Arizona State University, Adjunct Faculty, College of Health Solutions, Arizona State University

Flora Sandra Siami, Senior Vice President, NEST Coordinating Center

Paul Coplan, Vice President and Global Head of Medical Device Epidemiology and Real-World Data (RWD) Sciences, Office of the Chief Medical Officer, Johnson & Johnson

Panelists highlighted the status of several issues specific to use of RWE for devices. The multistakeholder National Evaluation System for health Technology (NEST)[23] ecosystem is focusing on research methods and data quality of pre-market evidence generation for regulatory decision-making. Coplan's industry team is using RWE for safety assessments, regulatory decisions, market access purposes, and innovating new data sources. Since the FDA established the Unique Device Identification (UDI) System final rule in 2013, the vast majority of class II and class III devices have UDIs, as do an increasing number of lower-risk (class I) devices. However, only some health systems document UDIs. The FDA identified 90 examples of RWE used in medical device decisions between 2012 and 2019. Going forward, because of changes to data, informatics and infrastructure, and the collaborative efforts via NEST, opportunities exist to leverage EHR data and other data sources in new ways for medical device RWE studies.

There was broad agreement that challenges exist for greater use of RWE to inform regulatory decision-making for devices as well as decision-making by payers and ultimately by clinicians and patients. Academics, industry and health service system researchers are all working together to define what good quality data looks like. Considerations include degree of missingness, inclusion of patient and geographic diversity, maintaining privacy when data are aggregated, and data standards (e.g., using the same common data model or being able to transform to a common data model).

Ideally, a checklist or framework can be constructed to make it easy for a company or academic center who wants to do a study and take it to FDA for a regulatory decision. This could represent the start of a pre-certification effect where certain databases become known as meeting the data quality standards, with resultant greater certainty for those proposing the study to use that data source for that application. An additional consideration is how to address uncertainty in a regulatory environment, as RWE will never be perfect. The FDA has a framework for interpreting uncertainty for clinical trials on medical devices, and a similar framework could be developed for how to interpret uncertainty for RWE.

Q&A excerpt:
Scarcity of RWD

"On the pharma side, we're already into applied research because we have such good databases and sophisticated methods. On the medical device side, the availability of real-world evidence is much less. And so there needs to be a lot more work into the basic research to identify feasibility, method, data quality."
- Paul Coplan

RWE CONSIDERATIONS SPECIFIC TO MEDICAL DEVICES

1. Availability of unique device identifiers (UDIs) in real-world data

2. Limited exemplars of publications in the peer-reviewed literature of RWE in medical devices

3. Governance and other methods for medical device companies to be able to access data to rapidly respond to questions from the FDA

V. SPECIAL GUESTS

Interview with Dr. Aaron Kesselheim

Moderator:

Laura Maliszewski, Co-Director, Harvard-MIT CRS

Interviewee:

Aaron Kesselheim, Professor of Medicine, Harvard Medical School; Director, Program on Regulation, Therapeutics, and Law, Brigham and Women's Hospital

Kesselheim discussed the Prescription Drug User Fee Act (PDUFA) reauthorization. The conversation covered the origin of PDUFA, which was passed by the U.S. Congress in 1992 to provide funding from drug manufacturers to the FDA in order to ensure firmer review deadlines after lack of funding led to years-long delays during the 1980s. Renewed every five years, PDUFA represents a relatively uncommon mechanism where the regulated entity provides the budget for the regulator.

While PDUFA has led to improvements in meeting FDA review timeline deadlines, it has also evolved considerably over the last 30 years. The amount of coordination, and therefore negotiation, between the FDA and industry increases with each successive round of revisions. Deadlines have become even shorter. And user fees have expanded to other areas of the FDA, including for medical devices and for generic and biosimilar drugs. As a result, PDUFA now helps define a major part of the FDA's budget.

Therefore, PDUFA has become a must-pass piece of legislation, giving advocacy groups and lobbyists the opportunity to get additional policies passed through Congress. As Kesselheim explained it, "You can kind of think of them as ornaments on a Christmas tree that industry lobbyists or other lobbyists hang on to the User Fee Bill, knowing that unless Congress passes the bill, the FDA is going to have to start furloughing people and shutting down major divisions, which would totally disrupt the pharmaceutical and other product markets."

> *"PDUFA has evolved from a way of offsetting the expense of regulation to shorten the timeline into a pretty powerful tool for modifying how the FDA actually does business."*

Some of the PDUFA add-on policies have been substantial, including creation of a breakthrough therapy designation that provides expedited review and additional resources for potentially promising drugs, and provisions giving the FDA encouragement to study surrogate measures that manufacturers use to study their products. As they are quite variable, it is hard to assess whether PDUFA modifications have been to the benefit of the public.

More broadly, Kesselheim noted that it is very important that the FDA have the necessary funding to do its essential work, and that insufficient resources don't cause unnecessary delays and inefficiencies in new product development and availability. However, having industry fund the FDA raises concerns about perceived or real conflicts of interest. Therefore, he hopes that going forward we can move towards full government funding for the FDA.

(Editor note: Subsequent to this conversation with Dr. Kesselheim, PDUFA was reauthorized. PDUFA VII[24] will provide FDA with funding for federal fiscal years 2023-2027.)

Harnessing Connections to Build a Regulatory Science Collaborative Community

Speaker:

Tina Morrison, Director, Office of Regulatory Science and Innovation, FDA

The Office of the Chief Scientist (OCS) is one of several offices hosting cross-cutting efforts across FDA's six product centers (e.g., Biologics Drug Center, Devices Center) and focuses on increasing scientific coordination across the FDA. The OSC's Office of Regulatory Science and Innovation (ORSI) is charged with ensuring FDA has a robust regulatory science foundation. ORSI manages intramural and extramural funding programs to drive innovative regulatory science research, and facilitates training and education with academic partners through the Centers of Excellence in Regulatory Science and Innovation (CERSI) program.

ORSI PROGRAMS AND RECENT ACCOMPLISHMENTS

1. FDA Senior Science Council. A) Formed a committee to focus on research impacts; B) Published a 2022 update to the Focused Areas of Regulatory Science (FARS) Report.

2. Twelve cross-cutting scientific topical working groups. Currently including artificial intelligence, emerging sciences, and modeling and simulation, discussions are in progress about adding a group to focus on real-world data and the science surrounding it.

3. CERSI cooperative agreement grant program. Among the current collaborations between the funded CERSI institutions and FDA subject matter research experts, a number are collecting, analyzing or using real-world data.

4. Broad Agency Announcements (BAA) via a research and development contracts mechanism. The regulatory science priority areas for BAAs are being updated but almost a dozen projects funded through the BAA mechanism have focused on real-world data / RWE.

As a part of the *Unleashing the Power of Data* strategic initiative highlighted in the FARS Report, FDA is working to use RWE to support biologic, device, and drug development and regulatory decision-making, acknowledging RWE can help fill knowledge gaps in product safety, effectiveness, and risk reduction.

Morrison shared that going forward FDA is balancing extreme resource constraints, given the scope of its responsibilities and the rapid pace of innovative technology coming through the agency, with concurrent demands for faster timelines and new flexible pathways. They would like to partner more aggressively with research universities, institutions, scientific teams and centers that already focus on FDA-related areas of study. They plan to work with the Reagan Udall Foundation who hosted the COVID-19 Evidence Accelerator, and leverage the accelerator model to build a connected, strong, engaged regulatory science pilot scientific community, with the CERSI program at the heart of the collaboration. An initial deliverable would be a roadmap for regulatory science for each of the focus areas outlined in the FARS Report, including the existing science gaps, key priorities, and an action plan and an implementation strategy.

"'We need you all now more than ever to work alongside us to advance our regulatory science mission. We aim to engage the community to help us identify regulatory science gaps and priorities for our crosscutting areas of regulatory science."

VI. CLOSING REMARKS

Although use of real-world data to inform clinical knowledge is not new, there is considerable excitement, interest and also some controversy in the use of real-world data. A continued challenge remains in extracting valid endpoints that will improve a patient's life, and to convert these endpoints into measures that are acceptable from a regulatory perspective. Any advancements in building measurable endpoints for outcomes that matter most to patients but are often overlooked in clinical trials, would open up important areas for patient-centered therapeutics development.

Going forward, incorporating real-world data and evidence offers opportunities to integrate additional information on the benefits of therapeutics from the perspective of the patient or their broader caregiving group, including family and physicians. These assessments could inform the process by which a therapy is reviewed or potentially approved.

Closing remarks moderated by: **Peter Sorger**, Co-Director, Harvard-MIT CRS

Panelists:
Florence Bourgeois, Co-Director, Harvard-MIT CRS

Mark Namnchuk, Executive Director of Therapeutics Translation, Harvard Medical School

Recurrent conference topics included:

- It is not real-world data and RWE *versus* data and evidence generated by an RCT; there are distinct complementary roles for each of these data types
- Use of real-world data is not new in the regulation of therapeutics and devices, but approaches, methods, and data types are expanding rapidly
- To date, potential benefits of the patient voice and experience in real-world data and evidence generation are only partially realized
- Race and ethnicity data are lacking or under-reported in many real-world data sources

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