DCRI THINK TANKS
FROM INSIGHT TO ACTION

Delineating Quality Standards for RWD-Enabled Trials

October 14-15, 2020

EXECUTIVE SUMMARY

BACKGROUND

Real-world data (RWD) have the potential to bridge the statistically driven world of randomized clinical trials and the traditional, and often anecdotal, practice of medicine. Concerns about RWD quality and uncertainty about regulatory expectations pose risks for drug developers, and the benefits remain unclear. In this DCRI Think Tank workshop held virtually on October 14 and 15, 2020, attendees discussed when and under what conditions a drug developer or device manufacturer might consider including an RWD-enabled trial as an element of its therapeutic strategy and regulatory filing.

SESSION I: WHEN WOULD YOU CONSIDER PUTTING RWE IN YOUR PREMARKET APPROVAL AND WHEN WOULDN'T YOU?

Moderators Lesley Curtis (Duke University) and Sastry Chilukuri (Acorn AI) introduced the first session. Mr. Chilukuri offered 2 observations: First, we have come through the first generation of RWD and have succeeded in using historical, secondary-use data to better understand how medical products are working for patients. Second, we are moving into the second generation of RWD. The quality and richness of the data are improving, enabling us to place the data in the context of the overall care of patients by combining various data sources. We are also beginning to collect RWD prospectively, allowing us to better define research questions, collect more useful data, and answer questions faster.

Panelist Kerry Jo Lee (US Food and Drug Administration [FDA]) summarized the FDA's framework and definitions for RWD and real-world evidence (RWE), interest in and optimal uses of RWD and RWE, and associated concerns.

- RWD are data pertaining to patients' health status and/or the delivery of health care that are routinely collected from a variety of sources (eg, EHRs, claims and billing, registries, patient-generated data in home use settings). RWE is the clinical evidence regarding the use and potential benefits or risks of a medical product derived from the analysis of RWD. Data that are not collected in the course of routine care do not fall

within these parameters.

- Interest in RWD and RWE relates to their potential to reflect broader and more diverse patient experience, and the ability to achieve larger sample sizes, which is especially important in studies of rare diseases.

- Use of RWD is optimal if the data are fit for the purpose of answering the research question, the end point can be ascertained from the data source, the data source includes a sufficient number of patients for sufficient duration, and patient selection in the data source is appropriate. As with evidence from traditional randomized controlled trials, RWE must address prespecified study objectives, appropriate comparison groups, bias, and trial design elements.

- In the regulatory context, there is concern about drawing conclusions about effectiveness from observational data in nonrandomized studies. Randomized controlled trials are the gold standard, because they offer robust, well-defined determinations of efficacy and safety, which serve as a benchmark for future research.

Panelist Leandro Boer (AstraZeneca) noted that his company would consider using RWD in premarket settings to define synthetic control arms and historical cohorts in studies of predictable disease for which the standard of care is well defined and stable; to select relevant and clinically translatable inclusion and exclusion criteria; and to better delineate burden of disease, cost-effectiveness, and patient and provider behavior patterns. In postmarket settings, they would use RWD for ongoing understanding of the safety profile of an approved therapy.

Technology adoption is accelerating, and a large number of clinical studies are already using connected digital technologies. Data sources today include patient registries; health care databases, including electronic health records (EHRs); pharmacy and health insurance databases; social media platforms; and online patient-powered research networks. Other sources of RWD include those used directly by patients and that generate data exponentially (eg, wearables, mobile apps, ingestibles, assessments via mobile platforms) and those not used directly by patients and that generate data less exponentially (eg, implantables). It will be important to understand the depth of the data we are collecting as data sources and technologies advance, the quality and integrity of the data, and patients' willingness to provide the data.

Panelist Rob Califf (Verily) urged attendees to focus on uses of RWD in research that relies on randomization as the key tool. Randomization is essential in determining whether treatments are effective. Dr. Califf noted that the FDA's definition of RWD and RWE includes randomization as a method. The intent was always to emphasize the use of randomization as a tool applied to RWD to make useful inferences about treatment effects.

Dr. Califf reiterated that efficacy is the cornerstone of clinical research: Do the benefits outweigh the harms in specific, controlled circumstances? Yet, what matters to patients is

effectiveness: Do the benefits outweigh the harms in usual clinical practice? Only recently, with ubiquitous access to EHRs and digital technologies, has this difference between efficacy and effectiveness became relevant for researchers. Traditional randomized controlled trials do not reflect the experiences of populations treated in clinical practice, and efficacy in these trials cannot be extrapolated to larger, more diverse populations. Moreover, most people in the United States do not have access to participation in clinical research, and most clinicians cannot or do not participate because of cost and other burdens. As the use of RWD in clinical trials expands rapidly, it will become more important to make the tool of randomization accepted in such trials so that researchers can obtain answers to clinically meaningful questions.

SESSION II: IMPRECISION IN OUTCOMES AND SAFETY: HOW MUCH CAN WE TOLERATE AND WHEN?

Moderators Rob Mentz (Duke University) and Norman Stockbridge (FDA) welcomed attendees to the next session. Dr. Stockbridge shared 2 thoughts to frame the discussion: (1) On the one hand, imprecision includes purely statistical issues that can be addressed by sample size; having a real-world component in a trial can afford access to a larger, widely distributed patient population. On the other hand, RWD can raise concerns about accurate ascertainment of events. (2) Randomization is the main tool for addressing bias.

Panelist Paul Petraro (Boehringer Ingelheim) described uses of RWD and RWE for understanding benefit-risk profiles for potential label expansions. For many years, researchers have used RWD on incidence and prevalence, background rates of disease, and mortality in developing benefit-risk profiles. Today, there is interest in using RWD to define outcomes earlier so that RWE is available at the time of product launch—much like health economics and outcomes research was once reserved for postmarket efforts but now is considered in earlier phases. Typically, RWD have come from claims and EHRs. A growing challenge, as RWD begin to emerge from social media, apps, and other platforms, is how to develop appropriate comparisons and reliable benefit-risk profiles.

Panelist Phil Sarocco (Cytokinetics) discussed a novel approach to understanding the challenge of imprecision in an effort to develop RWE in earlier phases of clinical research. Mr. Sarocco described an effort to integrate RWD on the incidence and prevalence of obstructive hypertrophic cardiomyopathy and patients' care journey in an integrated health care delivery system as inputs for a clinical trial, and to apply costs to this information about resource use in both community-based practices and centers of excellence. Clinical experts felt the data revealed greater comorbidity and concomitant medication use than they would have expected. Thus, the challenge is in understanding whether the RWD the team used was imprecise or there was a difference in how the data were entered (eg, coding, classification) in community-based practices as compared with centers of excellence.

Panelist Peter Payne (Optum) described 3 categories of gaps in knowledge related to underrepresentation: (1) trials designed to characterize biologically relevant differences in subgroups; (2) trials that leverage RWE to bolster the evidence base and explore

underrepresented populations, particularly with respect to evaluating long-term safety in diverse populations; and (3) trials that ensure access and build equity in health care and the clinical research enterprise.

Panelist Aylin Altan (Optum) posed the question of how RWD might be used to assess heterogeneity in treatment effect. Fully representative data are important for developing this work. Differential interaction with the health care system by subgroups of patients can influence how we model treatment effects. Underrepresentation of a subgroup can lead a model's inaccuracies to be underweighted. For example, facial recognition models work well at a global scale but have poor accuracy for people with darker skin tones. Likewise, financial models are known to have poorer accuracy for people who have fewer transactions. People of lower socioeconomic status have fewer transactions, so the models are biased toward people who are already well served. Likewise, issues of differential health care utilization by race/ethnicity and economic status are well known in health care.

Attendees further discussed the importance of ensuring adequate representation of subgroups and the value that RWD may add. If the goal is equitable access to participation in research, a solution is to lower barriers to access. If the goal is to accurately measure heterogeneity of treatment effect, a solution is to overrepresent subgroups of interest in the study population.

Attendees also further discussion the challenges of imprecision with RWD. Some RWD sources, such as social media platforms, may raise questions about reliability and noise.

FIRESIDE CHAT: THE COLONIZATION OF PATIENT DATA

Co-host Eric Perakslis facilitated a discussion with guest Andrea Downing, a patient advocate with the Light Collective. Topics of the discussion included:

- Patients are building and accessing communities in online social networks to find support they are not receiving in the health care system.
- Harms and concerns in these communities include privacy and security concerns, medical misinformation, advertisement targeting, and harassment.
- It is unclear how the support these communities offer and the data they generate compare with more traditional settings and sources of data.
- RWD related to social determinants of health may be more relevant to patients than data in medical records.
- Multiple digital health companies, pharma companies, and tech companies are approaching vulnerable patient groups for their data and have become savvy about appearing to align themselves with the interests of these patient groups rather than their own commercial interests.
- Patient groups are not well equipped to fairly negotiate partnerships and consider the long-term implications of uses of their data.

SESSION III: WHERE IS THE BAR FOR REGULATORY EVIDENCE?

Panelist John Concato (FDA) summarized considerations regarding the bar for regulatory evidence, citing the FDA's framework for RWD and RWE: whether the data are fit for purpose; whether the study design can provide adequate scientific evidence to help answer the regulatory question; and whether the study conduct meets regulatory requirements. The simple division between randomized controlled trials and observational studies no longer holds. Rather, FDA regulations refer to adequate and well-controlled studies that include a valid comparison with control and a method of assigning patients to treatment and control groups that minimizes bias (normally meaning randomization).

Panelist Paul Petraro (Boehringer Ingelheim) observed that it is not necessarily true that RWD-enabled research is quicker and less expensive. The important thing is to ensure data are collected correctly and that studies are planned accordingly. Randomized controlled trials are still the gold standard, and the question is how to integrate RWD on a case-by-case basis when the available data are fit for purpose.

Panelist Ken Stein (Boston Scientific) agreed that randomized controlled trials are the best design for making causal inferences from data. However, traditional randomized controlled trials have limitations, including Hawthorne effects, underrepresented populations, nonrepresentative investigators, and nonrepresentative standards of care. Beyond the practical reasons for using RWD in clinical trials and observational studies, there are scientific reasons: accessing data that are less susceptible to bias and more representative of what we expect to see from therapies in the real world. In setting the bar for regulatory evidence, we should consider which of the variables we access from RWD require thorough adjudication and which do not, and set the bar accordingly. Finally, are we measuring what's important to patients and clinicians? Often we measure what we can measure in the hope that it is important. For example, in heart failure, we use the 6-minute walk distance because we can measure it , and we hope it is a surrogate for something important to patients. We should ask ourselves and regulators to accept novel end points that may turn out to be fundamentally more important to patients and clinicians.

Panelist Sandi Siami (NESTcc) discussed the work that NESTcc is doing to develop research methods and data quality frameworks in the context of medical devices.

Moderator Adrian Hernandez (Duke University) presented a hypothetical scenario involving a new viral disease. A pharmaceutical company has identified a drug that is already approved for another indication and that has biological activity to reduce viral load. Clinicians are already using the drug in clinical practice and reporting anecdotal evidence of response. The company has a new RWD system that uses proprietary methods to link data from EHRs, financial transactions, health plan claims, and mobility data. The company has 2 options for establishing an indication: (1) conduct an observational study leveraging the new RWD system, which will

produce answers in 1 month; or (2) conduct a randomized controlled trial leveraging the new RWD system, which will produce answers in 6 months.

Dr. Hernandez asked attendees to indicate which option they would choose. There was general consensus among the attendees that randomization is important and that it can address concerns about bias, noise, and imprecision. Other considerations in choosing between the options include the novelty of the intervention, patients' risk tolerance and preferences about the certainty that the drug will be effective, and the likely amount and type of bias.

SESSION IV: GETTING REAL ABOUT RWD

In discussing patients' consent in the use of RWD, panelist Scott Lipnick (PatientsLikeMe) highlighted the importance of transparency and of aligning with patients' expectations. In one example, when the NIH approved the use of embryonic stem cells for research purposes, the review board settled on relying on what expectations people had for information at the time they gave consent. In another example, academic researchers often use deidentified data for research, but it is unclear whether the use of these data is aligned with patients' expectations. PatientsLikeMe supports letting people know exactly how their data will be used, who will use it, which elements are and are not deidentified, and giving people ownership over permissions. Dr. Lipnick proposed moving away from the model of allowing large groups to sell data without transparency or alignment with patients' expectations.

Panelist Andy Coravos (Elektra Labs) discussed the growing use of sensors and wearables and challenges related to data rights and data governance. Use of remote digital products in clinical trials is growing quickly, and these products are being used to collect patient information to support primary and secondary end points. Researchers need to reconcile informed consent with technology terms of service and end user license agreements.

Panelist Richard Schilsky (American Society of Clinical Oncology) described CancerLinQ. This RWD platform uses a common data model and allows participating practices access to identifiable data on their own patients, as well as quality measures from the data. The data are also deidentified for research purposes. Uses include evidence generation to improve quality of care; accelerated comparative-effectiveness research; postmarket surveillance; improved guidelines and measures; improved clinical trial design; and analysis of off-label drug use. Considerations for converting RWD to RWE include ambiguous and incomplete information in EHRs; the need for a common data model; the important role of human curation; access to source documents for data verification; reconciling differences in the timing of assessments; data provenance; and established policies and procedures. One important approach has been the development of common data elements.

Attendees further discussed the challenge of transparency and consent in the use of RWD. Topics included transparency about who is using and profiting from the data and whether consent should be reobtained regularly; and how health care systems can help with data literacy and making consent simpler for patients. Patients are concerned about pharmaceutical

companies and insurance companies having their data, but they generally support use of their data for quality improvement and research. It is important to inform people about how their data are being used and to engage and train providers in understanding and communicating that information to patients.

Attendees also discussed the importance of including underrepresented populations in research, including research in the digital health space.

Panelists identified the greatest challenges facing RWD-enabled research:

- Getting more patients and providers involved in research to improve the real-world applicability of clinical research findings.
- Understanding that the line between health-related and non–health-related data is becoming less clear, and developing policies for nondiscrimination in how those data are used.
- Addressing data quality in EHR systems so that these platforms can be used to capture clinically meaningful outcomes in structured data elements that are easy for clinicians to identify and enter.

WRAP-UP

Attendees will be invited to participate in drafting a white paper from the workshop.