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REVIEW

Advancing the utilization of real-world data and real-world evidence in clinical pharmacology and translational research—Proceedings from the ASCPT 2023 preconference workshop

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Abstract

Real-world data (RWD) and real-world evidence (RWE) are now being routinely used in epidemiology, clinical practice, and post-approval regulatory decisions. Despite the increasing utility of the methodology and new regulatory guidelines in recent years, there remains a lack of awareness of how this approach can be applied in clinical pharmacology and translational research settings. Therefore, the American Society of Clinical Pharmacology & Therapeutics (ASCPT) held a workshop on March 21st, 2023 entitled "Advancing the Utilization of Real-World Data (RWD) and Real-World Evidence (RWE) in Clinical Pharmacology and Translational Research." The work described herein is a summary of the workshop proceedings.

INTRODUCTION

Real-world data (RWD) and real-world evidence (RWE) have been routinely used in epidemiology, clinical practice, and post-approval regulatory decisions.[1] Since the introduction of the 21st Century Cures Act (2016), which required the United States (US) Food and Drug Administration (FDA) to establish a program to evaluate the potential use of RWD and RWE to support drug approvals, the methodology has received increasing attention.[2] While it is recognized that RWD/RWE has application in regulatory decision-making,[3,4] it is lesser known that RWD/RWE can also be used throughout the drug development process to inform decision-making. A survey conducted in 2022 among the members of the American Society for Clinical Pharmacology and Therapeutics (ASCPT) indicated both the lack of understanding and strong interest in learning RWD/RWE and how this approach can be applied in clinical pharmacology and translational research. As part of the cross-ASCPT Network and Community collaboration initiative, the 2023 ASCPT pre-conference Workshop on RWD and RWE in clinical pharmacology and translational research was proposed, in collaboration with the Innovation and Quality in Pharmaceutical Development (IQ) RWD Working Group,[5] which has recently published a comprehensive review of current applications of RWD/RWE in clinical pharmacology, particularly from an industry perspective.

On March 21, 2023, the ASCPT Pre-conference Workshop on "Advancing the Utilization of Real-World Data (RWD) and Real-World Evidence (RWE) in Clinical Pharmacology and Translational Research" co-sponsored by the IQ Consortium took place. It was aimed to address the necessary framework for the application of RWD and RWE in the scope of clinical pharmacology, translational research, drug development, and regulatory approval. The workshop started with four state-of-the-art lectures on RWD/RWE and the perspectives from academic, industry, and regulatory as well as on RWD sources, quality considerations, and analytics considerations for generating RWE. Five case studies were presented including four cases from the publication by Zhu et al.,[5] to reflect the current practices for RWE/RWD in drug development and approval. The workshop participants participated in an exercise to discuss opportunities for implementing RWD and RWE in the development of a hypothetical Drug X for the treatment of Duchenne muscular dystrophy (DMD) in a hands-on exercise. The workshop was concluded with a forward-looking panel discussion on a necessary framework for the application of RWD and RWE in the scope of clinical pharmacology, translational research, drug development, and approval and followed by poster presentations by participants. This paper summarizes the proceedings and key learnings from the one-day workshop.

INTRODUCTORY LECTURES

Lecture 1: Introduction of RWD and RWE and advancing utilization of RWD and RWE in clinical pharmacology and translational research—an academic perspective

The US FDA defines RWE as the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD. RWD in turn are the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.[6] While RWD could be analyzed within clinical trial frameworks and, thus, within a study design that includes randomization and protocol-based outcomes ascertainment and adjudication, the more common approaches to RWE generation are retrospective observational designs where neither of these methodological features are available. Common applications for such studies are (a) post-marketing commitments, typically with a focus on a specific safety concern, (b) use of RWD to construct external control arms for single-arm trials, (c) studies on new indications (e.g., drug repurposing), and (d) studies on treatment effect heterogeneity. While the focus is different, these applications share the goal to make causal inferences about drug effects and must therefore focus on design and analytical approaches that minimize bias, following similar considerations as clinical trial designs. The discipline that designs, conducts, and develops methodology for such studies is pharmacoepidemiology.

Both trials and observational pharmacoepidemiologic studies aim to create a counterfactual, that is, a scenario that measures the outcome among study patients had they *not* been exposed to the study medication of interest. The counterfactual approach is in essence what allows a study to make causal inferences rather than reporting an association and what distinguishes seeing from doing. Observing an association between a certain exposure and outcome does not imply that implementing that exposure will produce this outcome. In a trial, counterfactuals are created via randomization and strict treatment and outcomes ascertainment protocols that create control data that are as close to the exposure data as possible. In RWD scenarios, however, nothing happens at random or per protocol. Instead, medications are introduced based on certain conditions, the severity of such conditions, patients'

health history, social determinants of health access and affordability, and so forth. Medications are switched for similar reasons as well as disease progression, medication effectiveness and safety, and emerging life or clinical events. Capture of health outcomes, in turn, depends commonly on patient's decision to seek healthcare, what diagnostic testing is considered, the validity of diagnoses, and the documentation. In such cases, patients are not randomized, they do not take placebo, treatment (neither initiation, discontinuation, or concomitant medications) does not follow protocol, outcomes are not captured per protocol and data are not missing completely at random. Thus, the key challenge in pharmacoepidemiologic study design is to establish comparable treatment groups with similar risk for manifestation and similar probability for the detection of a meaningful end point to allow for causal inferences.

There are scenarios where these challenges are insurmountable and no RWD source will fit for purpose, for example, in the evaluation of a new medication that is the first treatment option for a previously untreatable disease. No appropriate counterfactual would be available in such a scenario. In other scenarios, the study drug and comparator medications might be truly exchangeable, creating comparison groups with baseline characteristics that approach a similar balance in baseline risk typically only achieved with clinical trials, for example, considering the comparison of rosiglitazone and pioglitazone in the assessment of major cardiovascular events.[7] There are other examples where the selection of the control group carefully considered relevant confounders and achieved well-balanced comparison groups,[8] even when constructing external controls for single-arm trials.[9]

Importantly, when designing a study using RWD, we must (1) understand the process (clinical and administrative) that generated the data, (2) identify a data source that fits the study purpose, and (3) identify a study design that best addresses potential bias (Table 1). Analyses should not commence before these three steps have been completed. Analyses cannot replace design.

TABLE 1 Requirements for causal reasoning in real-world evidence (RWE) studies.

Solid understanding
• Treatment pattern and medical decision-making
• Reimbursement and other policy that affects health care
• Patient preferences and behavior
• Disease etiology
• Pharmacology
• Strength and weakness of available RWD
Data fit for purpose
• Capture outcomes equally and sufficiently among comparison groups and with adequate specificity
• Provide comparable exposure groups with adequate capture of confounders
• Adequately capture exposure
Appropriate design
• Minimizes selection bias and confounding
• Avoids immortal time bias, measurement of reverse causation, or inappropriate adjustments
• Considers time-varying hazards
• Considers missing data
• Offers sensitivity analyses and bias analyses that address potential bias

Lecture 2: Industry perspective on using RWD to inform internal decisions throughout product development

The 21st Century Cures Act, FDA framework on RWE, and related guidance documents outline a future in which RWE is integrated into regulatory decisions.[2,10–16] This proposed use for RWE has spurred the development of new sources, types, and use cases for RWD (e.g., tokenization of clinical trial participants to enable passive follow-up with RWD). Biopharma companies are investing heavily in the resources needed to prepare for a future with a greater role for RWE.[17] Although it is likely too soon to determine the return on investment (ROI) for investments in RWE based on regulatory approvals alone, biopharma companies can maximize this ROI by also using RWD to inform on internal decisions. This presentation reviewed a few examples of how RWD could be used in clinical pharmacology at biopharma companies.

RWD to understand the target population

If a patient population can be defined using diagnosis codes in medical claims, RWD can be used to understand disease epidemiology. For example, researchers analyzed RWD to estimate the prevalence of neuroendocrine tumors (NETs) in the United States.[18] Their findings suggested that the annual prevalence rate of NETs nearly doubled from 2009 to 2014. While NETs remained rare (25–30 per 1 million person-years), such insights from RWD could be critical to informing a go/no go decision early in product development.

Similarly, researchers analyzed claims databases from Optum, Kaiser, Veterans Affairs (VA), the Centers for Medicare and Medicaid (CMS), and MarketScan to estimate the number of individuals with multiple sclerosis.[19] By combining multiple sources of RWD that cover

different segments of the US population, researchers estimated there were 727,344 individuals with multiple sclerosis, nearly doubling previous estimates of 300,000 to 400,000. Such changes informed by RWD can have a profound impact on product development since estimates of the target population are used to inform clinical trial recruitment (e.g., number of sites and amount of time needed for enrolment), market access and pricing (e.g., number of patients covered by specific payers), health economics and outcomes research (e.g., budget impact model), and commercial forecasting (e.g., peak annual sales models). Using more precise estimates of the target patient population for a medication under development can facilitate informed decision-making for all stakeholders.

RWD to uncover unmet needs

RWD can also be used to uncover unmet needs in a target patient population. For example, researchers analyzed the Symphony Health claims database in the US to understand the diagnostic journey for individuals with eosinophilic gastrointestinal diseases (EGDs).[20] Using RWD, researchers determined there was an interval of 8.1 months between presenting to a health care provider with EGDs and referral to a gastroenterologist, an additional 12.9 months before obtaining an esophagogastroduodenoscopy, and a further 22.8 months until a diagnosis of EGDs was made. These findings suggested that delayed diagnosis could be a barrier to accessing new therapies.

Similarly, researchers analyzed RWD to examine how four biologic therapies (adalimumab, etanercept, infliximab, and ustekinumab) were currently used by individuals in the United States with chronic psoriasis.[21] After identifying those using these biologic therapies in claims, electronic health record (EHR) data were used to classify psoriasis as mild, moderate, or severe based on physician global assessment, patient global assessment, and body surface area affected. Adherence and persistence to these biologic therapies were then compared as proxies for real-world effectiveness and tolerability. These analyses found that adherence and persistence were lower among those with moderate or severe psoriasis, identifying an unmet need for an effective and well-tolerated therapy in this subgroup.

RWD to inform efficient clinical trials

RWD can also be used to identify specific patient subgroups of interest, inform disease progression models, and improve the efficiency of clinical trials. For example, researchers interested in amyotrophic lateral sclerosis (ALS) related to SOD1 mutations analyzed RWD by reviewing medical charts for 175 individuals from 37 sites in the United States and Canada.[22] Based on changes observed in RWD for forced vital capacity (FVC) and the ALS functional rating scale (FRS), researchers determined that individuals with SOD1 A4V mutations had a more rapid decline in function over time. Using these insights about disease progression derived from existing RWD, researchers estimated that clinical trials focused on the subgroup of patients with ALS who have SOD1 A4V mutations could enroll ~40% fewer subjects than trials that ignored this subgroup. The smaller sample size for a trial focused on patients with ALS and SOD1 mutations was based on a power calculation that assumed a steeper decline in FVC and ALS FRS in the control group, and therefore, a larger projected effect size for an experimental therapy aimed at this subgroup, assuming equal efficacy across ALS mutations. These examples highlight how RWD can be used to inform routine internal decisions that arise in biopharma companies during product development, which are not governed by regulatory guidance.

Lecture 3: Utilization of RWD in clinical pharmacology—regulatory perspectives

Regulatory agencies, such as the US FDA and the European Medicines Agency (EMA), recognize the value of RWE in supporting regulatory decisions. FDA have developed frameworks and guidances to help realize the full potential of fit-for-purpose RWD to generate RWE that will advance the development of therapeutic products and strengthen regulatory oversight of medical products across their life cycle.[6] The Office of Clinical Pharmacology (OCP) at the Center for Drug Evaluation and Research (CDER), FDA, has been committed to leveraging RWE to advance the mission of the Office of Clinical Pharmacology[23] (e.g., advancing drug development and promoting therapeutic optimization/individualization) and to improve patient care. Scientists in OCP have realized both opportunities and challenges for the use of RWD in clinical pharmacology, and therefore, they have been conducting regulatory research in this area and establishing collaborations with internal and external experts as well as various stakeholders.

In 2019, Liu et al. published a perspective on RWD and clinical pharmacology, to highlight some opportunities and challenges in utilizing RWE to address clinical pharmacology issues and to promote therapeutic individualization.[24] The opportunities include, but are not limited to, dose/dosing regimen optimization,

evaluation of benefit/risk in specific populations and optimization of treatment for intrinsic and extrinsic factors, filling the gap between traditional clinical trials and real-world clinical practice, and end point and biomarker development. This vision was later confirmed by regulatory review cases and demonstrational regulatory research projects. For example, in 2021, FDA approved a new dosage regimen of 500 mg/m^2 intravenous infusion every 2 weeks (Q2W) for cetuximab for patients with K-Ras wild-type, EGFR-expressing colorectal cancer (mCRC), or squamous cell carcinoma of the head and neck (SCCHN). The approval was based on population pharmacokinetic modeling analyses, supported by pooled analyses of overall response rates, progression-free survival, and overall survival (OS) from published literature in patients with CRC and SCCHN, and OS analyses using RWD in patients with mCRC who received either the weekly cetuximab or Q2W regimens.[25]

OCP has also been working on many collaborative research projects to identify where RWE can be most helpful and to develop best practices to advance RWE for clinical pharmacology. In one collaborative research project, both RWD and pooled clinical trial data were used to assess the association between OS and baseline organ function in patients with advanced NSCLC treated with PD-1/PD-L1 blocking antibodies.[26] Both RWD and clinical trial data suggested that baseline renal impairment did not appear to be associated with OS, while patients with baseline liver impairment had shorter OS. In addition, RWD included patients over a broader range of renal and hepatic function than was enrolled in clinical trials. In another collaborative research project, both RWD and pooled clinical trial data were used to evaluate the incidence of treatment-associated pneumonitis (TAP) among patients with advanced non-small cell lung cancer receiving immune checkpoint inhibitors (ICI) or chemotherapies.[27] This study identified that the past medical history of pneumonitis was associated with TAP in both ICI and chemotherapies in both RWD and trial data.

RWD/RWE can be used to advance the mission of the ODP at FDA and clinical pharmacology more broadly. Although opportunities exist to incorporate RWD/RWE into drug development, more research and collaborations are needed to learn where RWD can be most helpful and to develop best practices on how to use RWD to inform decisions.

Lecture 4: RWD sources, quality, and analytics considerations for generating RWE

RWD sources are typically contained in siloed environments; direct access is not usually permitted necessitating agreements and data transfer. Metadata describing these sources and facilitating data integration must often be retrofitted after ingestion requiring financial investment from the acquiring institution. Most often, data standards are lacking, making integration of RWD with traditional, structured data sources problematic. Data quality is not guaranteed for most RWD sources. It is up to the data acquirer to investigate, assess, and ultimately decide whether the data are useful for the intended purpose. Regulatory authorities will request justification for the context of use (COU). Analytics can provide solutions and/or tools to accelerate drug development. Analytics that are intended to be used for regulatory purposes need to be validated with underlying source code to be used to support decision-making (e.g., patient, end point, and dose selection) transparently provided to regulatory authorities.

RWD can inform decision-making for various modalities in development benefiting local and global health initiatives. Positive use cases exist with more stakeholders investing in integrating RWD sources into their R&D decision-making activities. While many of the global RWD types resemble data from high-income countries (HIC's) that inform R&D in the developed world, much of it is not and the conditions of the data and mechanism for access are dramatically different. Country-level data are hard to obtain, and EHR data are not available in the quantities available in developing countries. Moreover, it is difficult to obtain data from many countries of origin because privacy laws and data governance are complex, and significant legal support to obtain and maintain data from different countries is often required. Collaborative "honest broker" arrangements and modern digital research environments (DREs) are urgently needed to ensure data sharing and improve the quality of the underlying source data. Improved data quality would also ensure that integrated data potentially used for regulatory submission can be trusted along with the code, models, and solutions derived from the data.[28]

CASE STUDIES RWD/RWE APPLICATIONS IN DRUG DEVELOPMENT AND APPROVAL

Five case studies of RWD/RWE applications in the scape of clinical pharmacology and translational research to support drug development and approval were presented. For case studies 1–3 and 5, the reader is also referred to a recently published comprehensive review of current applications of RWD/RWE in clinical pharmacology, particularly from an industry perspective.[5]

Case study 1. RWD applications in informing study design/dose selection in organ impairment population and pediatrics

RWD can be used to assess the organ impairment patients' prevalence and inform the feasibility of a dedicated organ impairment study. Lu et al.[29] demonstrated it in the clinical development of polatuzumab vedotin (pola), an antibody drug conjugate (ADC), in diffuse large B-cell lymphoma (DLBCL) patients. To inform the label of pola dosing, an integrated RWD and pharmacokinetic (PK) assessment of pola was conducted in DLBCL patients with organ impairment. In the Flatiron Health EHR database, less than 6% DLBCL patients had a moderate-to-severe hepatic impairment, indicating that enrollment for a dedicated hepatic impairment PK study can be challenging. Also, applying the same exclusion criteria related to hepatic function in pola clinical trials to the RWD population, it would only exclude <9% of DLBCL patients, meaning pola clinical trial population covers the vast majority of the target DLBCL population and a dedicated hepatic study would be of limited added value. Similar results were shown in the DLBCL patient population with renal impairment. Taken together, dedicated organ impairment studies were waived by health authorities and clinical development of pola was accelerated. Of note, there are several limitations to this RWD application. For example, only first-line DLBCL patients' data were available from Flatiron Health EHR, while the target population (for the initial filing of pola) was the relapsed/refractory patient population. Also, instead of the commonly used Child–Pugh score criteria, NCI criteria were used to characterize the hepatic impairment severity, which was due to the availability of the RWD laboratory results data. From a clinical pharmacology point of view, given the lack of dedicated organ impairment studies, the impact of the organ impairment on pola PK was assessed using the population PK approach. Due to limited data, no solid conclusion could be drawn for patients with moderate or severe hepatic impairment. Therefore, the US Prescribing Information for pola recommendation was to avoid treatment in patients with moderate-to-severe hepatic impairment.

Moreover, RWD can also be used to guide the dose selection and study design of pediatric clinical trials. This was illustrated in the research project by Zhang et al.[30] Etrolizumab, a humanized monoclonal antibody, was under clinical development for inflammatory bowel disease (IBD). One of etrolizumab's mechanisms of action is shared with vedolizumab, which has already been approved in adults with IBD. At that time, vedolizumab's pediatric clinical trials were ongoing, and RWD (ImproveCareNow [ICN] registry) included pediatric patients with off-label use of vedolizumab. Results indicated that around 70% of pediatric patients were treated with the equivalent vedolizumab dose to that used in adults, and pediatric patients (2–17 years) have similar or slightly better efficacy compared with efficacy from adult clinical trials. The knowledge gained from RWD was leveraged for the dose selection and study design for etrolizumab pediatric clinical trials. The limitations/challenges of this RWD application include unstandardized dose regimens (fixed and body-weight based), disease severity confounded dose selection (sicker patients may be given higher dose), and very limited sample size of pediatric patients with off-label use of vedolizumab in RWD.

Case study 2. RWD/RWE applications to inform drug–drug interaction decision-making

In routine clinical practice, patients will likely receive more than one drug (i.e., polypharmacy) to treat a disorder or multiple diseases. Concurrent administration of multiple medications may result in drug–drug interactions (DDIs), which may affect the PK and pharmacodynamics (PD) of the investigational drug and alter the efficacy and safety of the concomitantly administered drugs. DDIs may be associated with increased morbidity, hospitalization, prolonged hospital stays, or deteriorated outcomes. Avoiding drug interactions would improve treatment outcomes and compliance. Therefore, before administering an investigational medication to patients, it is essential to understand its elimination profile in the presence of potential DDIs, how the investigational product's affects and is affected, in terms of PK and PD, by the presence of other comedications.

In that respect, early translational medicine investigations may benefit from RWE on the number and frequency of medications used by patients with the target disease. RWE describing patients' profile comorbidities and concomitant medications could facilitate treatment choices and administration route. Currently, in phase I and II studies, patients receiving concomitant medications are commonly not eligible for enrollment. RWE on patients' profile comorbidities and concomitant medications could better inform those studies' inclusion and exclusion criteria, thereby enhancing the recruitment process for clinical trials.

The value of this approach was presented for psoriasis and therapy. Psoriasis is a systemic immune-mediated inflammatory disease affecting at least 100 million patients worldwide. Anti-inflammatory topical and systemic medications and phototherapy are used to treat psoriasis

depending on the disease severity and comorbidities at diagnosis. Patients with moderate-to-severe psoriasis are administered biologic medications, mainly injectable monoclonal antibodies that target highly specific immune pathways. Furthermore, a significant amount of development for effective orally bioavailable small molecule therapies is being pursued. Psoriasis involves patients of all ages, and it is associated with significant comorbidities such as cardiovascular diseases and mental disorders. Consequently, polypharmacy is a frequent phenomenon making DDIs complicated in psoriasis treatment and a major concern in the development of medicines, especially small molecule modalities.

Knowledge of comorbidities and concomitant medications in patients with psoriasis is important to address potential complex DDIs of the new oral small molecule therapies. In the presented case study, strong or moderate inhibitors and inducers of CYP3A4 were evaluated. The investigational psoriasis medication of interest is a small molecule delivered orally, that was identified within in vitro studies as a potential strong CYP3A4 autoinducer, thereby acting both as a CYP3A4 substrate and a CYP3A4 perpetrator. As such, there were two primary DDI considerations: (i) strong/moderate CYP3A4 inhibitor or inducer concomitant medications administered with the investigational molecule could potentially alter the exposure of the molecule and thus confound the evaluation of the molecule's exposure–response relationship and safety profile, and (ii) the investigational molecule as a potential strong/moderate CYP3A inducer could lower the exposure of CYP3A4 substrate concomitant medications, which may reduce their efficacy.

In the absence of previously published research in this field, the objectives of RWD/RWE were to assess the frequency of prescription claims for drugs that may interact with inhibitors or inducers of CYP3A4 in the US population of adults with psoriasis by leveraging RWD from IBM Marketscan (a large, administrative US claims database) to derive the frequency of prescription claims for drugs that are considered strong/moderate CYP3A4 inhibitors/inducers and CYP3A4 substrates in the target patient population. The findings showed that in patients with psoriasis, the majority of prescriptions of CYP3A4 substrates included corticosteroids, contraceptives, statins, and antibiotics, of which $>50\%$ were used for >90 days. These data indicated a risk for the investigational molecule as a DDI perpetrator with the potential to limit the pharmacokinetics and efficacy of these CYP3A4 substrates. RWD findings also indicated that up to 15% of patients with psoriasis had claims for at least one drug with CYP3A induction or inhibition potential; however, the CYP3A4 victim DDI potential of the investigational drug was of relatively less concern since the incidence of chronic use of strong/moderate CYP3A4 inducer/inhibitor concomitant medications is low (<1%).

Taken together, the real-world concomitant medication data was used to inform the DDI evaluations of the investigational drug's CYP3A4 victim and perpetrator potentials. Within the early development of the investigational product, these DDI evaluations were strategically integrated into the design of a first-in-human healthy volunteer trial. The clinical findings of these evaluations in healthy participants showed molecule was not a strong CYP3A4 inducer, but that it was a CYP3A4 victim with a significant impact on the investigational product's exposure. Taking the real-world polypharmacy results and the clinical DDI study findings together, data-driven decisions were made to exclude concomitant medications that were strong CYP3A4 inducers/inhibitors in clinical trials of this investigational molecule in patients with psoriasis. This case study highlights how RWE/RWD can be leveraged to accelerate and strategically streamline clinical pharmacology study designs within early development (i.e., inclusion of DDI within a cohort of a first-in-human trial, and a saving of approximately 8 to 9 months of timeline by avoiding a standalone DDI study) as well as inform trial investigators and participants of concomitant medication inclusion and exclusion criterion in subsequent patient trials.

Case study 3. Alzheimer's disease progression modeling using RWD

There is great interest in developing predictive longitudinal models to better understand individual heterogeneity and disease progression in various therapeutic areas. In addition to leveraging data collected from clinical trials, RWD provides valuable insights to help characterize disease progression because RWD usually includes a large sample size of patient data with a longer follow-up period, contains a much wider range of disease severity across the patients, and consists of a more diverse patient population.

Over the years, several groups have developed disease progression models in Alzheimer's Disease (AD). Various covariates, such as baseline cognitive and/or functional scores (e.g., Alzheimer's Disease Assessment Scale-Cognitive Subscale and Clinical Dementia Rating Scale—Sum of Boxes [CDR-SB], Alzheimer's Disease Assessment Scale—Cognitive Subscale [ADAS-Cog]), apolipoprotein E ε4 allele (APOEε4) genotype, sex, fluid biomarkers, measures of brain volume (hippocampal and intracranial volumes), and education level, were assessed for their impact on disease progression.

Using the nonlinear mixed-effect approach, a longitudinal AD progression model was developed to predict

CDR-SB progression.[31] A separate longitudinal AD progression model was also developed to predict ADAS-Cog11 progression.[32] Data from Alzheimer's Disease Neuroimaging Initiative (ADNI)[33] and placebo arm data from four interventional trials ($n = 1093$) were used for model building. Placebo arm data from two additional interventional trials ($n = 805$) were used for external model validation.

Model diagnostics demonstrated that the AD progression model for both CDR-SB and ADAS-Cog11 progression performed adequately in predicting AD disease trajectory for the RWD from ADNI and the placebo arm data from the interventional trials. By leveraging the AD progression models to assess other internal molecules that are currently in development, we were able to confirm that patients in the placebo arms progressed as expected based on their natural disease progression. In addition, the AD progression models were able to help confirm the treatment effect observed in the treatment arm.

RWD is a valuable data source for the development of disease progression models. However, pooling RWD and clinical trial data can be challenging due to differences in data processing or the assessment of disease activities. Nevertheless, the longitudinal disease progression models can be used to assess treatment effects for molecules in development and can be leveraged to help aid the study design of future clinical trials.

Case study 4. RWD to inform decision-making about kidney function in clinical trials

Clinical trials sponsored by biopharma companies routinely measure kidney function to assess participant eligibility at baseline and monitor changes during follow-up. Kidney function is often assessed by estimating glomerular filtration rate (GFR) based on serum creatinine (Scr), age, sex, height, and weight using various equations (e.g., modified Schwartz for children, Cockcroft-Gault for adolescents).[34–36] The use of age-specific equations for GFR can result in clinical trials having to use different equations as participants age. For example, the bedside Schwartz equation might be used at baseline in a 12-year-old, but the Cockcroft–Gault must be used once that participant turns 13. This makes it difficult to determine whether changes noted in GFR signify true (and potentially worrisome) changes in kidney function or are a byproduct of using different equations.

In 2021, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) proposed a new equation for GFR in adults calculated from both Scr and serum cystatin C (Scys). To explore whether this new equation could also be used in children, de-identified EHR data from 48 healthcare organizations in the United States were obtained from TriNetX (Cambridge, MA). Individuals with Scr and Scys within 1 day of each other with height and weight measurements within 30 days (infants) or 60 days (non-infants) identified and categorized into six age groups: infants (1–24 months), younger children (2–5 years), older children (6–11 years), adolescents (12–17 years), younger adults (18–64 years), and older adults (65+ years). In each age group, GFR using currently recommended age-specific equations was compared with GFR using the 2021 CKD-EPI Scr/Scys equation; "Kidney Disease: Improving Global Outcomes (KDIGO)" grades based on GFR were also compared.

The RWD population included 378 infants, 1191 younger children, 1891 older children, 3174 adolescents, 16,367 younger adults, and 9727 older adults. When comparing GFR from different equations within each age group, the intraclass correlation coefficient was 0.62 for infants, 0.41 for younger children, 0.44 for older children, 0.31 for adolescents, 0.89 for younger adults, and 0.89 for older adults. When comparing KDIGO grades based on GFR within each age group, Cohen's weighted kappa was 0.46 in infants, 0.70 in younger children, 0.75 in older children, 0.59 in adolescents, 0.75 in younger adults, and 0.73 in older adults. These findings suggest that using the 2021 CKD-EPI Scr/Scys equation could result in different estimates of GFR vs. currently recommended age-specific equations but similar KDIGO grades. This study demonstrates that large sample sizes can be readily assembled from existing RWD to answer novel research questions.

Case study 5. RWE as part of "Totality of Evidence" to support regulatory decision-making

RWE can complement RCT data and as part of the totality of evidence, can support and inform regulatory decisions. RWE was utilized along with other evidence to support the approval of a prolonged release (PR) formulation of tofacitinib in the European Union (EU), as part of such an approach to bridge efficacy and safety data from a previously approved immediate release (IR) tablet formulation. Tofacitinib is an oral Janus kinase (JAK) inhibitor that was initially approved globally as an IR oral tablet, at a dose of 5 mg twice daily, for adult patients with moderate-to-severe active rheumatoid arthritis (RA), based on a traditional development program that included confirmatory phase III RCTs. The PR osmotic tablet formulation of tofacitinib was developed, at a dose of 11 mg, to provide a more convenient once-daily dosing alternative for patients, that in turn could lead to improved adherence and therefore improved treatment outcomes. This once-daily formulation of tofacitinib 11 mg was first approved by the

FDA for use in RA patients, in 2016, based on comparative phase I PK data between the IR and MR formulations and a quantitative (model-informed) approach to bridge efficacy and safety in RA patients.[1] Data from completed phase I PK studies demonstrated that the desired PK profile was achieved and a set of several exposure–response analyses established that AUC was the PK parameter most relevant to response.[37] Following this approval, the PR formulation was included in the ongoing US registry (CorEvitas®, formerly Corrona®) initially used for the IR formulation, which enabled the generation of RWD designed to provide robust, direct comparative effectiveness evaluations between the IR and PR tofacitinib formulations, using established analytic approaches that paralleled RCTs and achieve balance in a nonrandomized setting. These key evaluations from the CorEvitas® registry therefore served as an important component of the total evidence in the demonstration of comparable effectiveness between the two tofacitinib formulations that subsequently resulted in product approval for the PR formulation in the EU.[38]

PROCEEDINGS FROM THE HANDS-ON WORKSHOP ON DRUG X FOR THE TREATMENT OF DMD

During the afternoon of the ASCPT Pre-conference Workshop, a hands-on exercise was introduced to the participants. The participants were divided into groups and requested to identify opportunities for applying RWE and RWD in the development of the hypothetical Drug X for the treatment of DMD. The participants were encouraged to identify RWE opportunities to address knowledge gaps in quantitative target product profile, translational

TABLE 2 Key learnings from the hands-on workshop on the potential opportunities of using RWD/RWE in drug development and approval of Drug X for treatment of DMD.

Drug development question	Opportunities for RWE/RWD
Quantitative target product profile	• Identify unmet medical needs and subpopulations (e.g., age groups may benefit from drug X) • Inform quantitative differentiation criteria on efficacy/safety vs glucocorticoids (SOCs)[45]
Translational research/ Biomarker identification	• Identify biomarkers that demonstrate dystrophin production • Identify biomarker/DMD and biomarker/efficacy relationships, specifically regarding long-term benefits • Identify a biomarker for early disease and/or treatment effect read-out • Identify biomarkers that correlate with safety/toxicity
Disease progression	• Characterize the natural history of DMD disease progression using longitudinal data and modeling and simulation to support clinical trial design and interpretation of trial results[46] • Understand the effects of disease onset time/stage on disease progression, biomarker, and efficacy end points • Identify more sensitive end points to predict DMD disease progression and long-term efficacy • Complement clinical trial data
Clinical trial design	• Leverage modeling and simulation to establish external/synthetic control • Include suitable and diverse patient populations • Incorporate sensitive and novel end points for efficacy and safety • Design adequate trial duration based on learnings from disease progression • Incorporate more realistic inclusion/exclusion criteria informed by RWD-based DDI liability assessment
Clinical DDI (glucuronidation & CYP3A metabolism, moderate inducer of CYP3A4)	• Identify concomitant medication use and the potential DDI liability, specifically regarding CYP inducers • Establish PBPK model using probes identified from RWD and Phase II data to identify the magnitude of interaction • Identify which drug metabolism enzymes/transporters should be addressed for DDI early on in drug development
Special populations	• Identify the prevalence of renal impairment and hepatic impairment in DMD to inform clinical trial inclusion/exclusion criteria and need for conducting the organ impairment studies • Identify alternative marker for renal function in DMD as creatinine may be confounded with muscle dystrophy • Inform pediatric patient age group to be studied • Generate evidence for extrapolation from older to younger pediatric patients if supported by RWE from SOCs

Abbreviations: CYP, cytochrome P450; DDI, drug–drug interaction; DMD, Duchenne muscular dystrophy; PBPK, physiologically based pharmacokinetic; RWD, real-world data; RWE, real-world evidence; SOC, standard of care.

research/biomarker identification, disease progression, clinical trial design (with a focus on efficacy), clinical DDI, and special populations. The background on Drug X and DMD can be found in the Supplement. In addition to the background, the participants received a list of references on RWD in DMD. This list can also be found in the Supplement. The key learnings from the hands-on exercise on the potential opportunities of using RWD/RWE in drug development and approval of Drug X in DMD are summarized in Table 2.

PANEL DISCUSSION AND OVERALL SUMMARY

It was acknowledged that the application of RWD in clinical pharmacology and translational research and in drug development and approval is still in its infancy. The panel discussion provided additional insights on how to further advance the application of RWD/RWE in these areas.

RWD/RWE can be applied as early as the program concept stage and across all stages of drug development for internal decision-making. Low-hanging fruit for RWE applications in clinical pharmacology include the prevalence of concomitant medications and specific populations to inform the need for DDI and organ impairment studies. Modeling and simulation could be applied in RWD analysis. It was pointed out that the application of RWE should also be considered in the context of questions/knowledge gaps to be addressed along with other evidence generation approaches. There are precedents of RWE as primary evidence for drug approvals in rare/life-threatening diseases, as supportive evidence for drug approvals and as post-marketing requirements in other disease areas. RWE as primary evidence for drug approval in major disease areas requires additional research with collaboration among all the stakeholders. There have been efforts ongoing to cross-validate outcomes from RWD/RWE and randomized clinical trials in a few major disease areas, for example, RCT DUPLICATE.[39]

It was highlighted that the key to the successful application of RWD/RWE is to define the right questions, understand the RWD databases and their limitations, and agree on RWE study design. There are many different sources of RWD such as EHR, medical claims data, data from product or disease registries, and data gathered from digital health technologies. Different RWD sources may provide different insights/end points, but may also have different challenges associated with them, including accessibility and rapid evolvement. It is better to define the research questions first and then identify the fit-for-purpose RWD for analysis. RWD data quality, biases in data collection, selection, and analysis are other key considerations. It was recommended that data quality matrices should be established prior to RWD analysis and sensitivity analysis should also be evaluated in RWD analysis.[40,41] RWD best practices for epidemiology have been well established and can be referenced for RWD applications in clinical pharmacology, translational research, drug development, and approval. FDA and EMA have also published guidelines on RWD/RWE for regulatory decision-making.[13,14,42–44]

Another important aspect for the successful advancement of RWD in clinical pharmacology and translational research is cross-functional collaboration, especially with stakeholders from RWD scientists, and cross-organization/sector collaborations to share the RWD/RWE best practices and learnings. In summary, the 2023 ASCPT preconference workshop provides an educational opportunity to advance the RWD/RWE application in clinical pharmacology and translational research.

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CONFLICT OF INTEREST STATEMENT

J.L., S.D., and S.M. are employees of Pfizer Inc. and hold stock/options in Pfizer. K.R.Y. is an employee of Certara UK Limited (Simcyp Division) and holds shares in Certara. A.W. has received consulting fees from Genentech Inc, Ipsen, Arbor Pharmaceutical, and Bayer KG. She has received research funding from Merck, and Sharp Dohme. R.Z. and J.H. are employees of Genentech Inc., members of the Roche group, and are Roche shareholders. A.D.M. is an employee of Lilly and is a stock recipient. C.B. was an employee of Lilly and is a stock recipient. M.A. is an employee of Takeda Development Center and holds a share in Takeda. P.M. is an employee of Astellas Pharma Global Drug Development Inc. P.R. is an employee of Affimed GmbH and holds stock options. All other authors declared no competing interests in this work.

DISCLAIMER

The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by FDA/HHS or the US Government.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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