Integrating real-world data to accelerate and guide drug development: A clinical pharmacology perspective

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Abstract

Pharmaceutical products in the current accelerated drug development landscape can benefit from tools beyond data generated from randomized control trials. We have seen an abundance of real-world data (RWD) and real-world evidence, driven by the digitalization of healthcare systems and an increased awareness that has inspired a heightened interest in their potential use. Literature review suggest leveraging RWD as a promising tool to answer key questions in the areas of clinical pharmacology and translational science. RWD may increase our understanding regarding the impact of intrinsic (e.g., liver, renal impairment, or genetic polymorphisms) and extrinsic (e.g., food consumption or concomitant medications) factors on the clearance of administered drugs. Changes in clearance may lead to clinically relevant changes in drug exposure that may require clinical management strategies, such as change in dose or dosing regimen. RWD can be leveraged to potentially bridge the gaps among research, development, and clinical care. This paper highlights promising areas of how RWD have been used to complement clinical pharmacology throughout various phases of drug development; case examples will include dose/regimen extrapolation, dose adjustments for special populations (organ impairment, pediatrics, etc.), and pharmacokinetic/pharmacodynamic models to assess impact of prognostic factors on outcomes. In addition, this paper will also juxtapose limitations and promises of utilizing RWD to answer key scientific questions in drug development and articulate challenges posed by quality issues, data availability, and integration from various sources as well as the increased need for multidimensional-omics data that can better guide the development of personalized and predictive medicine.

INTRODUCTION

In recent years, there has been an increased interest in the use of real-world data RWD and real-world evidence (RWE) to facilitate drug discovery, development, and regulatory decision making. The increased utilization of RWD is a result of a few key factors. First, the Affordable Care Act (ACA) mandated digitization of health records resulting in democratization and commercialization of hundreds of millions of pieces of patient data, including billions of records and data points. Recent estimates determined around 2314 exabytes of new healthcare data

were generated in 2020 and a single patient can generate as much as 80 megabytes of health data each year.[1,2] Second, technological advancement in the form of cloud computing and machine learning have made storage, manipulation, and analysis of large-scale data efficient and feasible. Finally, increased encouragement by regulatory policies (Prescription Drug User Fee Act [PDUFA] VI, 21st Century Cures Act) resulted in improvements to data interoperability and data quality that further has translated to first use of RWD/RWE for regulatory submission.[3] The US Food and Drug Administration (FDA) defines RWD as "data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources" and RWE as "the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD."[3] Sources of RWD include administrative/insurance claims data, patients' electronic health records (EHRs), disease/product registries, health data linked with genomic data, etc. (Figure 1a). Although development and advancement in RWD has been discussed in this paper mostly in the context of the United States, there are important initiatives underway by global regulatory agencies to further integrate RWE in drug development outside of the United States as well.[4]

Historically, RWD has been applied primarily to address gaps and questions related to safety and efficacy of a treatment in later stages of development and/or in post-marketing evaluations. However, with advances in digital technology and analytics, emergence of large population-based data sources that include both clinical and genomic data combined with increased interoperability between data platforms have allowed for a new era of integration of RWD throughout the product's lifecycle. These efforts have generated further interest across the pharmaceutical industry to address questions beyond safety and efficacy.[5,6]

Clinical pharmacology plays an essential role in advancing the development of safe and effective drug treatments and optimization of dose and dose regimens specific for different strata of patient populations. This paper highlights some of the potential applications of RWD/RWE to address clinical pharmacology questions throughout the life cycle of a therapeutic product. Additionally, the authors also discuss a few opportunities and challenges pertaining to RWD/RWE.

INTEGRATION OF RWD/RWE IN CLINICAL PHARMACOLOGY THROUGHOUT DRUG DEVELOPMENT

Clinical pharmacology can help improve decision making at critical drug development milestones. Innovative clinical pharmacology tools (e.g., quantitative or mechanistic) are increasingly leveraged from discovery of new target molecules to determine the effect of drugs to accelerate the development of safe and effective drugs across the therapeutic landscape. RWD can also be used by clinical pharmacologists to bridge potential information gaps between clinical trials and daily clinical practice. Figure 1b provides an overview of critical clinical pharmacology questions at different stages of early and late drug development and highlights opportunities to utilize RWD for functional characterization of disease, facilitating biomarker development, informing drug–drug interactions, and drug usage in special or understudied populations, as well as optimizing treatment and dosing regimens. In the following sections, we provide examples with a focus on the value of RWD to inform clinical pharmacology knowledge in three areas: (1) improving and optimizing dosing regimens; (2) facilitating pharmacogenomic biomarker development; and (3) informing drug usage in understudied subgroups, and finally we discuss some challenges and opportunities.

Improve and optimize dosing regimens

One key task for clinical pharmacologists is to determine the safe and effective doses and dosing regimens for drug products. Clinical pharmacologists use integrated pharmacokinetics (PKs), pharmacodynamics (PDs), safety, and efficacy data to establish exposure–response relationships that can impact dosing regimens with optimum benefit–risk profile. A drug can be determined to be safe and effective only when the exposure–response relationships are well-understood.[7] Dose and regimen recommendations for the new drug product usually reflect the dosing schema tested in the pivotal phase III clinical studies, where patients are selected based on specific inclusion and exclusion criteria and treatment arms are well-defined and controlled. However, these pivotal clinical trials have a limited number of study participants that are not a representation of the overall patient population or specific subgroups. As a result, initially approved drug dosing regimens may not be optimal for a more heterogeneous real-world population commonly excluded from the strictly controlled clinical efficacy and safety trials or have multiple characteristics likely to influence treatment outcomes (e.g., patients with organ impairment or pediatric population). Inclusion of RWD from routine clinical practice experience provides an enhanced opportunity to continuously improve drug dosing recommendations even after treatment is approved. Examples of studies from the literature based on RWD to inform alternative or optimal dosing regimens are summarized in Table 1.
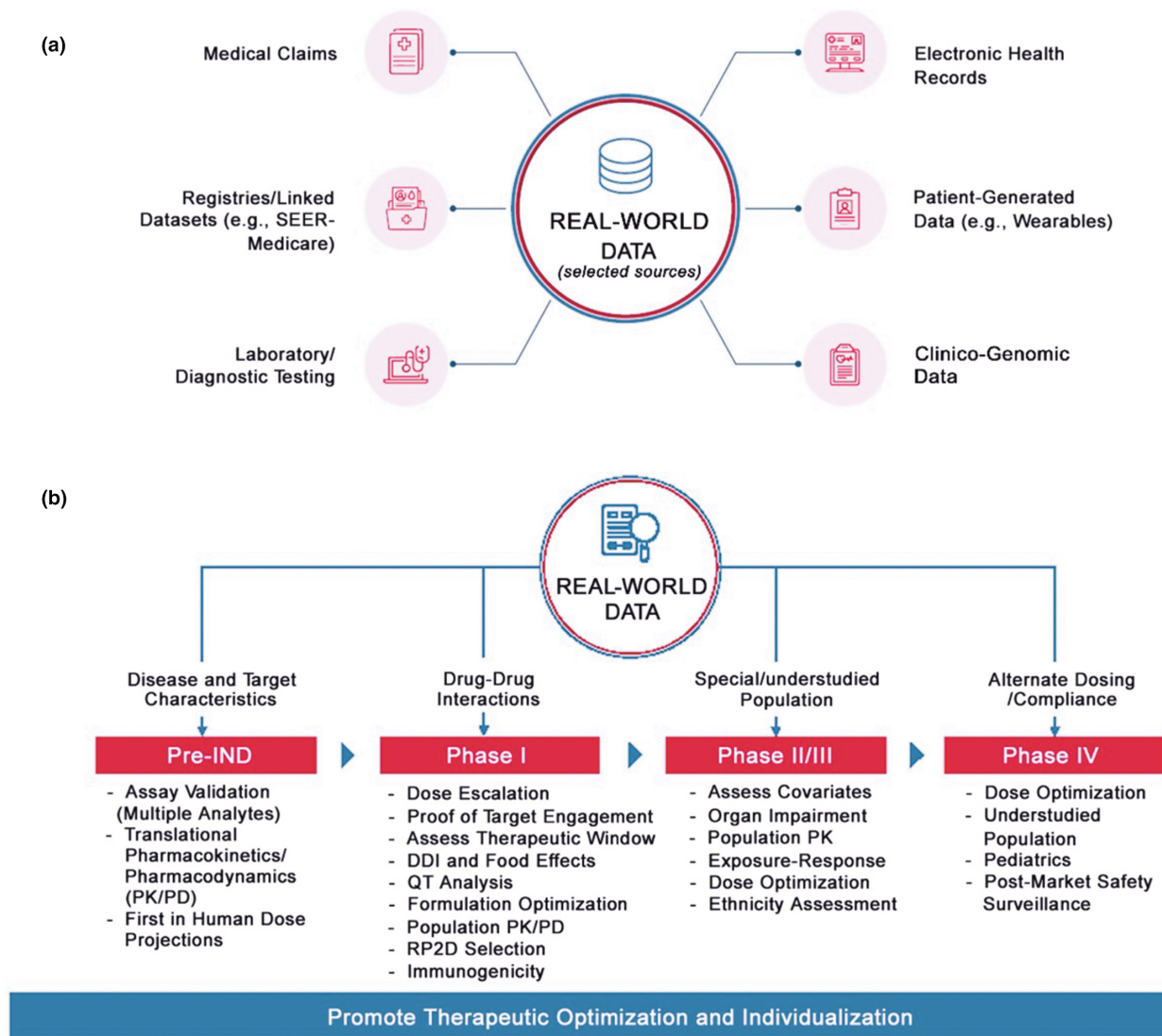
FIGURE 1 Real world data source and its contribution to clinical pharmacology characterization across the drug development process. (a) Selected real-world data (RWD) sources. RWD can come from a number of sources, such as electronic health records, medical insurance claims, patient-generated health data, medical product/device/disease registries, laboratory/diagnostic testing, clinicogenomic data and others. (b) An overview of critical clinical pharmacology questions at different stages of the drug development process highlighted opportunities for using RWD for functional characterization of disease, facilitating biomarker development, informing drug–drug interactions, and drug usage in special or understudied populations, as well as optimizing treatment and dosing regimens. DDI, drug–drug interaction; IND, investigational new drug; PD, pharmacodynamics; PK, pharmacokinetics; RP2D, recommended phase II dose; RWD, real-world data; SEER, surveillance, epidemiology, and end results.

In April 2021, the FDA approved an alternate biweekly (Q2W) dosing regimen for cetuximab (Erbitux) in addition to the previously approved once weekly (Q1W) dosing regimen.[8] Efficacy results from overall survival analyses using Flatiron Health RWD in patients with metastatic colorectal cancer, who received either the weekly or biweekly dosing regimens, supported the population PK model prediction of similar cetuximab exposures between two schedules. The approval was also supported by pooled efficacy analyses from the published literature. This alternate Q2W regimen allows physicians to provide patients with the same efficacious cetuximab treatment with less

frequent clinic visits. The approval was a testimony to the successful use of RWD to fill evidence gaps in the post-approval setting for regulatory decision making.

Dosing for select population subgroups may specifically benefit from evidence and insight generated through RWD analysis. Pediatric dosing has often been extrapolated from adults based on systemic exposure (PK) matching, largely due to challenges associated with performing clinical trials in children. With an increased use of EHR, data from the clinical practice setting provides an opportunity to guide pediatric dosing via PK/PD analysis. For example, in a pediatric population PK analysis for fentanyl,

TABLE 1 Selected examples of RWD to improve and optimize dosing regimens

Reference	Therapeutic product/disease area	Study objective(s)	Data source(s) (collection period, N)	Study highlight(s)
FDA website[8]	Cetuximab/cancer	Compare OS in patients with mCRC who received either the weekly or biweekly cetuximab regimens using RWD	Flatiron Health EHR data (Jan 2013–Dec 2019, $N = 1074$)	Consistent efficacy was observed between weekly and biweekly regimens and supported approval of cetuximab biweekly regimen in addition to the previously approved weekly dosing
Van Driest et al.[9]	Fentanyl/severe pain	Characterize PK of fentanyl in children using sparse remnant specimens and data collected during clinical care	EMR and VUMC Enterprise Data Warehouse (Jul 2012–May 2014, $N = 130$)	PK model-driven weight-adjusted per kg fentanyl dosing led to more consistent therapeutic fentanyl concentrations than fixed per kg dosing
Chanu et al.[10]	Methoxy polyethylene glycol-epoetin beta/anemia	Determine PK/PD properties of CERA in pediatric patients with anemia of CKD and support the design of a confirmatory pediatric trial	International Pediatric Dialysis Network registries (collection period not available, $N = 158$)	PK/PD relationship for CERA was similar in adult and pediatric patients, and model-based simulations confirmed by RWD support a similar s.c. starting dose in pediatrics to i.v. dose
Albiges et al.[19]	Cabozantinib/cancer	Evaluate treatment patterns and outcomes of cabozantinib in real-world patients with mRCC	French Early Access Program (Sep 2016–Feb 2018, $N = 410$)	Cabozantinib was effective in heavily pretreated patients with mRCC, and initiation at 60 mg/day was associated with improved outcomes
Raje et al.[20]	Carfilzomib/cancer	Evaluate OS and treatment progression in real-world MM patients treated with carfilzomib combination optimized versus legacy doses	IQVIA EMR data (Jan 2013–Jul 2017, $N = 1469$)	The optimized Kd doses improved treatment outcomes in eligible patients with MM

Abbreviations: CERA, continuous erythropoietin receptor activator; CKD, chronic kidney disease; EHR, electronic healthy records; EMR, electronic medical records; FDA, US Food and Drug Administration; mCRC, metastatic colorectal cancer; MM, multiple myeloma; mRCC, metastatic renal cell carcinoma; OS, overall survival; PD, pharmacodynamic; PK, pharmacokinetic; RWD, real-world data; VUMC, Vanderbilt University Medical Center.

Van Driest et al. used RWD without any additional blood sampling in children after cardiac surgery to demonstrate that model-driven weight-adjusted per kg fentanyl dosing led to more consistent therapeutic concentrations than standard fixed per kg weight dosing.[9] Model-predicted fentanyl concentrations during standard fixed weight-based dosing were not consistently within the therapeutic concentration range for pediatric patients of different weights due to the nonlinear relationship of fentanyl PKs with weight. Therefore, further weight adjustment on per kg dosing resulted in a higher proportion of simulated 6.4 and 20 kg patients within the targeted drug therapeutic range and led to more consistent fentanyl concentrations in the therapeutic range across the size spectrum. This work shows the value of using remnant clinical specimens and EHR data.

In another example, a pediatric study for continuous erythropoietin receptor activators (CERA) in patients with anemia of chronic kidney disease, RWD on CERA doses and hemoglobin levels obtained from the International Pediatric Dialysis Network registries was leveraged to validate PK/PD model simulations and supported a subcutaneous starting dose in pediatric patients similar to the intravenous dose.[10] A model-based approach confirmed by RWD helped to optimize a pediatric drug development plan approved by health authorities, with reduced drug exposure and treatment burden for children. RWE has become increasingly accepted to inform optimal dosing regimens for clinical practice, and, in some cases, to provide complementary evidence to support regulatory decisions.

Facilitate pharmacogenomic biomarker development

Clinical pharmacology plays an essential role in therapeutic individualization by incorporating individual heterogeneity in intrinsic (e.g., genes and organ function) and extrinsic (e.g., food and concomitant medication) factors on the trajectory of response to medications. Information on pharmacogenomic biomarkers is regularly incorporated in FDA product-approved labeling to guide precise dosing, reduce adverse events, and maximize benefit to patients.[11] The availability of large clinical and genomic biomarker data from real-world patients provides a unique opportunity to understand drug efficacy and safety beyond the clinical trial population and to better inform treatment decisions in routine care. Selected literature examples on the use of RWD to support pharmacogenomic biomarker identification are summarized in Table 2.

Large scale real-world longitudinal patient-level data, including baseline demographic, clinical, and laboratory characteristics, is now routinely used to identify prognostic markers associated with disease outcomes and/or biomarkers that are predictive of response to specific drugs.[12] This has significantly enhanced the exploration of novel drug targets and strategies to develop combination therapeutics, especially in the field of oncology. Simultaneously, lower costs of genomic sequencing and the increasing linkage of genomic data to patient EHR records have led to the development of clinicogenomic databases that can provide a better understanding of patient response, disease heterogeneity, and mechanisms of resistance to specific therapies. This practice is highlighted in the search for the association of patient characteristics and tumor genomics with clinical outcomes for non-small cell lung cancer (NSCLC).[13] As an example, a Flatiron Health Analytic Database of patients with NSCLC who underwent comprehensive genomic profiling was linked to de-identified EHR data. Close to 400 genes were included along with tumor mutation burden (TMB) stratification, and PD-L1 expression. The results demonstrated the power of TMB as a predictor of cancer immunotherapy response and confirmed that combining the real-world dataset, clinical outcomes, and genomic profiling can enable novel biomarker discovery and identify potential treatment responders to help guide clinical practice and the design of future trials.[13] Similarly, another example includes the use of geographically diverse clinicogenomic databases to identify a small cohort of real-world patients with neurotrophic tropomyosin receptor kinase (*NTRK*)-mutant tumors, complementing traditional clinical trial evidence for this rare population and improving generalizability of trial results.[14]

Overall, the integration of patients' genomic and molecular profiles with RWD has focused on identifying population subgroups likely to demonstrate maximum effectiveness in trials or likely to experience adverse events, which translates into more evidence-based clinical decisions. Its influence on regulatory decisions remains to be seen, however, the future impact on informing clinical trial design and precision medicine cannot be ignored.

Informed drug use in understudied or excluded populations

Another dimension of RWE's value to clinical pharmacology is better defining dose/dosing regimen in historically under-represented groups, whether due to disease rarity, trial eligibility criteria, or conservation for the vulnerable populations (e.g., children, pregnant women, the elderly, and those with organ dysfunction). Numerous efforts have been made in clinical pharmacology to help understand the effect of gender, body size metrics, and pathophysiological characteristics (e.g., body size, CYP450 ontogeny,

TABLE 2 Selected examples of RWD to facilitate pharmacogenomic biomarker development

Reference	Therapeutic product/ disease area	Study objective(s)	Data source(s) (collection period, N)	Study highlight(s)
Julian et al.[12]	PD1/PD-L1 inhibitors/ cancer	Develop a prognostic model for OS using baseline demographic and clinical factors from real-world patients with NSCLC receiving PD1/PD-L1 inhibitors as 2L treatment	Flatiron Health EHR (Jan 2011– Feb 2020, N = 4049)	The top risk-increasing prognostic factors for OS were abnormally low ALB and chloride, ECOG PS ≥2, and abnormally high ALP and WBC. The top risk-decreasing prognostic factors were positive PD-L1, longer time from advanced diagnosis to start of 1L therapy, and higher SBP
Singal et al.[13]	PD1/PD-L1 inhibitors/ cancer	Assess the association of patient characteristics and tumor genomics with clinical outcomes among patients with NSCLC using a real-world clinicogenomic dataset	Flatiron Health EHR linked with FM genomic data (Jan 2011–Jan 2018, N = 4064)	For NSCLC patients with a driver mutation, improved OS was observed among those treated with versus not treated with targeted therapies. For NSCLC patients who received anti-PD-1/PD-L1 therapies, TMB ≥20 was significantly associated with improved OS, longer DOT, and increased clinical benefit rate (fraction of patients with SD, PR, and CR) than TMB <20
Miksad et al.[14]	Larotrectinib/cancer	Enable the identification of real-world patients with NTRK-mutant tumors, a rare population, from a geographically diverse clinicogenomic dataset	Flatiron Health EHR linked with genomic data (collection period and N not available)	Small-cohort RWE expanded the evidence base for the rare population and improved generalizability of trial results
Kavathi et al.[21]	Omalizumab/asthma	Evaluate the association of biomarkers with omalizumab treatment outcomes in real-world patients with allergic asthma	Allergy Partners Network EMR (Jan 2017–Jun 2018, N = 473)	Real-world patients with allergic asthma could benefit from omalizumab regardless of pretreatment biomarker levels
Jukić et al.[22]	Escitalopram/depression	Determine the effect of CYP2C19 genotype on escitalopram exposure and therapeutic failure in a large real-world clinical setting	Hospital therapeutic drug monitoring database (collection period not available, N = 2087)	The CYP2C19 genotype had a substantial impact on exposure and therapeutic failure of escitalopram. The results support the potential clinical utility of CYP2C19 genotyping for individualization of escitalopram therapy

Abbreviations: 1L, first line; ALB, albumin; 2L, PD-1 second line programmed cell death protein 1; ALP, alkaline phosphatase; CIT, cancer immunotherapy; CR, complete response; DOT, duration of therapy; ECOG PS, Eastern Cooperative Oncology Group performance status; EHR, electronic health record; EMR, electronic medical records; FM, Foundation Medicine; NCCN, national comprehensive cancer network; NSCLC, non-small cell lung cancer; NTRK, neurotrophic tropomyosin receptor kinase; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PR, partial response; RWD, real-world data; RWE, real-world evidence; SBP, systolic blood pressure; SD, stable disease; TMB, tumor mutation burden, defined as the number of mutations per megabase (mutations/Mb); TRK, neurotrophic tropomyosin receptor kinase; WBC, white blood cells.

enzyme activity and maturation function, organ impairment, etc.) on treatment selection and dosing. Dosing recommendations for patients who were not studied in clinical trials are often derived based on extrapolation, where uncertainty remains in clinical care about whether dose adjustment or additional management strategy is required. RWD collected from such individuals during clinical practice can improve patient management and inform benefit/risk assessment as well as dosing, compliance, and adherence in these subpopulations. Examples of studies from the literature based on RWD to inform the usage of drug in such subgroups are summarized in Table 3.

The rarity of men diagnosed with breast cancer presents as a challenge for conducting timely and adequately powered randomized clinical trials (RCTs). Although guidelines recommend treating men with metastatic breast cancer (mBC) similarly to postmenopausal women, there are limited data on the effectiveness and safety of palbociclib in men. Three independent real-world studies were conducted to assess palbociclib treatment in men with mBC.[15] The first one leveraged commercially available pharmacy and medical claims data to describe real-world treatment patterns and duration. The second approach retrospectively analyzed demographically and geographically diverse EHR-derived data to understand real-world response. Furthermore, the global safety dataset was searched for any adverse events reported in this setting. Overall, RWD contributed to the totality of evidence and supported an expansion of the palbociclib US label to include men with mBC. Considering the challenges of conducting RCTs in some disease settings or subpopulations, RWD highlights a potential new pathway to expand the body of evidence for regulatory decision making and improve patient access to effective therapies in real-world settings.

The need to understand dose compliance and treatment outcomes also expands to patients with organ dysfunction/impairment, and clinical pharmacology is likewise tasked with identifying how disposition of drugs is altered by modified intrinsic factors. For example, varying degrees of renal or hepatic impairment is often an exclusion criterion in clinical trials. However, safety and efficacy data in patients with some degree of organ impairment can often help determine if dose adjustments and/or contraindications are warranted in lieu of dedicated organ impairment clinical pharmacology studies. RWD can also be leveraged to streamline the eligibility criteria of clinical trials and inform dosing for dedicated organ impairment studies if needed. In an RWD retrospective analysis of the efficacy and safety of sorafenib in patients with advanced renal cell carcinoma with renal impairment, patients were divided into two groups by an estimated glomerular filtration rate cutoff of $45\,\text{ml/min/1.73}\,\text{m}^2$ and propensity scores matching was conducted to adjust for key demographic factors that could affect the prognosis.[16] The results confirmed similar efficacy and safety for patients regardless of renal function and thus warranted a continuation of treatment without adjustment and eliminated the need to conduct a clinical trial in this subset of the population.

DISCUSSION

Although the momentum to leverage RWE to inform drug development decisions is undeniable, its evidentiary value and the place in regulatory decision making remains an area of active research. It is important to appreciate that RWE can provide important complementary evidence for current drug development processes including RCTs and fill the gaps in knowledge.[17] More recently, to encourage and guide the use of RWD for regulatory submissions, the FDA issued a series draft guidance on data standards and considerations for the use of RWD/RWE in regulatory submissions.[3] The European Medicines Agency also outlined the vision for use of RWE in EU medicines regulation.[4]

However, issues related to data availability, data quality (e.g., accuracy, completeness, and traceability), lack of standardization in data from different sources (e.g., EHRs, claims, and registries), inherent biases, and lack of best practices in methodology or analysis when interrogating RWE are challenges that can often limit the ability to fully leverage such data for decision making. There are also limitations in RWD that are specific to answering clinical pharmacology related research questions. Often special or understudied patient populations with organ impairment (e.g., hepatic or renal impairment) are defined by biomarkers in different laboratory measures. Most RWD sources have limited (e.g., EHRs) or no data (e.g., administrative claims) on laboratory parameters. This can significantly reduce the patient pool for studying special populations and can introduce unknown biases due to missing or incomplete data. Similarly, it is difficult to obtain all important pregnancy and pregnancy-related information (e.g., exact gestational age) from most RWD sources. Information on race and ethnicity could be incomplete or missing, making it difficult to study racial or ethnic subgroups. Complete data on administered doses, number of prescription days, or the quantity of drugs dispensed are extremely important for dosing or dose adjustment studies or drug–drug interaction studies. Most RWD sources have varying degrees of data availability for these parameters, especially regarding the number of prescriptions days or quantity actually dispensed. In many cases, statistical imputations or data driven algorithms are used to derive relevant clinical information but validation of

TABLE 3 Selected examples of RWD to inform drug use in the understudied subgroups

Reference	Therapeutic product/disease area	Study objective(s)	Data source(s) (collection period, N)	Study highlight(s)
Kraus et al.[15]	Palbociclib/cancer	Evaluate the benefits and risks of palbociclib plus ET in men with mBC using RWD, given the challenges of conducting randomized clinical trials in this setting	Pharmacy and medical claims coupled with EHR and global safety dataset (Feb 2015–Apr 2017, $N = 1139$)	RWD indicated that men with mBC benefit from palbociclib plus ET, with a safety profile consistent with previous observations in women. Together with other evidence, RWD supported US approval of an expansion of palbociclib indication to include men with mBC
Tatsugami et al.[16]	Sorafenib/cancer	Evaluate the efficacy and safety of sorafenib for advanced RCC in real-world patients with renal impairment	Postmarketing surveillance study in Japan (Feb 2018–Mar 2021, $N = 2943$)	Sorafenib in patients with an eGFR of <45 and ≥45 ml/min/1.73 m^2 showed similar safety and efficacy, supporting the use of sorafenib without dose adjustment for patients with renal impairment
Gerhart et al.[23]	Enoxaparin/thrombosis	Evaluate differences in enoxaparin dosing and disposition in children with obesity using RWD	Pediatric Trials Network data repository (Jan 2013–Jun 2017, $N = 596$)	Obesity is a significant predictor of anti-Xa concentration in children based on extensive RWD. Using fat-free mass instead of total body weight under recommended weight-based dosing resulted in more comparable exposure across age and obesity groups
Wu et al.[24]	Azlocillin/sepsis	Assess the population PK of azlocillin in neonates with EOS using RWD and make dose recommendations based on PK/PD model	Monocenter prospective study from a neonatal ICU in China (Jun 2018–Sep 2018, $N = 95$)	A new model-based dosing regimen of azlocillin developed using RWD provided a safe and tolerable treatment with high target attainment in neonates with EOS
Assie et al.[25]	Nivolumab/cancer	Evaluate long-term outcomes of nivolumab treatment in real-world NSCLC patients and potentially vulnerable subgroups: elderly (≥80 years), renal impairment, and patients with brain metastases	Hospital discharge dataset of the French National Health Data System (Jan 2015–Dec 2018, $N = 10,452$)	OS in a real-world setting was consistent with that observed in clinical trials. Survival rates were comparable in the three special populations of interest and the overall population

Abbreviations: DAAs, direct acting antivirals; eGFR, estimated glomerular filtration rate; EHR, electronic health record, EOS, early-onset sepsis; ET, endocrine therapy; ICU, intensive care unit; mBC, metastatic breast cancer; NSCLC, non-small cell lung cancer; OS, overall survival; PK/PD, pharmacokinetic and pharmacodynamic; RCC, renal cell carcinoma; RWD, real world data; Xa, activated factor X.

such algorithms is often incomplete or resource intensive and rather relied upon expert opinions and accuracy of external data driven assumptions. EHR datasets can also have limited longitudinal patient data needed for long follow-up studies. Smaller sample sizes for patients with genomic information, lack of standardization of data across assays or platforms, and relatively high price points for clinicogenomic data sources are some challenges for widespread use of pharmacogenomic studies for patient selection, disease heterogeneity, efficacy, or toxicity indicators. There are many ongoing efforts to mitigate some of these issues: common data models are being used to ensure interoperability between data sources, digital tokenization can link multiple data sources of different types (claims data with EHR data) providing a more complete and more longitudinal picture of patient journeys, availability of genomic data has also been increasing exponentially. RWD sources usually include a wide array of clinical and demographic data on millions of patients that allows the flexibility of stratifying patients, exploring research questions, and confirming pre-established hypotheses. The promise it holds for use in clinical pharmacology is abundant and yet vastly untapped.

In this paper, we provided some key examples in the literature of RWE to guide clinical decisions on dosing expansion and treatment for certain subgroups of patients, however, further research is still required to harness its potential in areas such as dose predictions for drugs with similar mechanism of actions, food effect, formulation optimization, dose adherence, compliance, and more. In one particular area, off-label use of drugs in neonates is more common than an exception due to insufficient new drug development in this high-risk population. However, there is an urgency to generate the evidence to support safety, efficacy, and dosage in the neonatal population. Innovative methodologies, increased needs for better health care, data-sharing collaboration, and recent regulatory use cases provide the opportunity to accelerate quality RWD collection to support drug development for this underserved population. The availability of new treatment modalities and epidemiological changes make the periodic reassessment of prognostic factors using RWE of great relevance to guide clinical practice and the design of future trials.

The development and availability of mRNA vaccines for coronavirus disease 2019 (COVID-19) would not have been possible without the insights gathered from RWE where, among others, a Centers for Disease Control and Prevention (CDC)-led study confirmed a COVID-19 risk reduction of over 90% after second dose of mRNA vaccines among healthcare personnel, first responders, and other essential workers supporting a full FDA approval of mRNA vaccines.[18] The pandemic accelerated the expansion of RWE by uncovering much of its untapped potential in an unprecedented situation where expedited rollouts were vital to the public health, but now it is time to apply those learnings to other unmet areas. However, the lessons learned on the challenges of utilizing RWD during the pandemic, for example, incomplete patient care information, missing data or clinical outcomes, and lack of validation or standardization, should also be considered carefully to mitigate these issues. The growing landscape of RWD provides an opportune moment to embrace RWE and leverage its full potential for clinical pharmacology strategies. This will allow clinical pharmacologists to further advance scientific innovation and promote optimization and individualization for current and future generations of drug therapies.

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CONFLICT OF INTEREST

X.Z., S.I., M.D., and S.G. are employees of Gilead Sciences, Inc. and hold stock in the company. I.L.V. declared no competing interest in this work.

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