




REVIEW

Trial designs using real-world data: The changing landscape of the regulatory approval process

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Abstract

Purpose: There is a need to develop hybrid trial methodology combining the best parts of traditional randomized controlled trials (RCTs) and observational study designs to produce real-world evidence (RWE) that provides adequate scientific evidence for regulatory decision-making.

Methods: This review explores how hybrid study designs that include features of RCTs and studies with real-world data (RWD) can combine the advantages of both to generate RWE that is fit for regulatory purposes.

Results: Some hybrid designs include randomization and use pragmatic outcomes; other designs use single-arm trial data supplemented with external comparators derived from RWD or leverage novel data collection approaches to capture long-term outcomes in a real-world setting. Some of these approaches have already been successfully used in regulatory decisions, raising the possibility that studies using RWD could increasingly be used to augment or replace traditional RCTs for the demonstration of drug effectiveness in certain contexts. These changes come against a background of long reliance on RCTs for regulatory decision-making, which are labor-intensive, costly, and produce data that can have limited applicability in real-world clinical practice.

Conclusions: While RWE from observational studies is well accepted for satisfying postapproval safety monitoring requirements, it has not commonly been used to demonstrate drug effectiveness for regulatory purposes. However, this position is changing as regulatory opinions, guidance frameworks, and RWD methodologies are evolving, with growing recognition of the value of using RWE that is acceptable for regulatory decision-making.

KEYWORDS

external control, long-term follow-up study leveraging RWD, pharmacoepidemiology, pragmatic trial, real-world data (RWD), real-world evidence (RWE)

Robert Reynolds, Affiliation at the time this manuscript was developed

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1 | INTRODUCTION

Randomized controlled trials (RCTs) have been considered the gold standard to demonstrate efficacy since the 1960s.^{1,2} While current routes to market for investigational drugs typically require at least two pivotal RCTs, these are time-consuming, costly, and produce evidence that can have limited applicability in real-world clinical practice. There is, therefore, a move towards investigating innovative ways to improve the efficiency of clinical research.^{3,4}

The controlled nature of an RCT offers advantages in evidence generation as there are standard methods to reduce bias (like randomization and blinding), and they have comprehensive measurement of outcomes to demonstrate efficacy against both active and placebo controls.⁵ However, RCTs do not accurately reflect real-world circumstances under which patients are treated; thus, there is often a need for observational studies to support additional evidence generation, particularly around questions of safety.

Real-world data (RWD) forms the basis for real-world evidence (RWE) and can be extracted from a broad range of sources such as patient registries, health care databases, claims databases, patient networks, social media, and patient-generated data from wearables.⁶⁻⁹ The definitions of RWD and RWE are relatively consistent between key regulatory agencies (see Table 1).^{7,8,10} While RWE from observational studies is well accepted for post-approval safety monitoring and to answer pharmaco-economic questions^{3,11,12} its contribution to regulatory decisions around effectiveness has been more limited. Indeed, evidence quality can be compromised by confounding by indication or a general lack of rigorous collection standards.⁵ There is, therefore, a need for the development of novel trial methodologies that can take the best parts of traditional RCT and observational study designs to produce RWE that provides adequate scientific evidence for regulatory decision-making. It has already been recognised by health authorities that there is a wide spectrum of potential uses of RWD/RWE in clinical studies, some of which preserve key features such as randomization.¹³

2 | REGULATORS ARE WILLING TO EMBRACE NEW APPROACHES TO RWE

While acceptance of the role RWE could play in regulatory decision-making is not universal, opinions within regulatory agencies

are evolving, and there is a growing acknowledgement that the current drug approval process no longer fully meets current health care needs.¹⁴ For example, Dr Janet Woodcock, Director of the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research, has acknowledged that the current drug approval system is “broken” and expressed the agency's commitment to find new ways to collect and utilize patient data to improve the process.¹⁴ Dr Woodcock has said, “FDA will work with its stakeholders to understand how RWE can best be used to increase the efficiency of clinical research and answer questions that may not have been answered in the trials that led to the drug approval, for example how a drug works in populations that weren't studied prior to approval.”¹⁴

The use of RWE to support effectiveness decisions has been used in rare diseases, as highlighted by the examples of BAVENCIO and BLINCYTO (Case study boxes 1 and 2), both of which received accelerated approval using data from external, historical controls.^{15,16} The case of BLINCYTO is of particular interest, as it was subsequently approved as a treatment for minimal residual disease in patients with acute lymphoblastic leukemia.¹⁷ This approval was based on the results of a single-arm trial supported by RWE providing benchmarking information and was the first example of the FDA approving a drug for minimal residual disease.¹⁸ A randomized clinical trial incorporating pragmatic design elements was also recently used to support a label extension for a drug treating a more common condition, schizophrenia, as demonstrated by the example of INVEGA/SUSTENNA (Case study box 3).¹⁹⁻²¹ This demonstrates the willingness of regulatory authorities to consider RWE for regulatory decision-making when there is an unmet medical need.²²

Regulators (including the FDA and European Medicines Agency [EMA]), data science companies (eg, Flatiron Health, New York, NY, USA, and IQVIA, Research Triangle Park, NC), and pharmaceutical companies are actively evaluating ways to embrace RWE to optimize the drug development cycle.²³ While the FDA and EMA are often seen to be at the forefront of these changes, other agencies are also leading the way in producing their own guidance, sharing different perspectives and approaches based on their specific needs and region characteristics.

The Japanese Pharmaceuticals and Medical Devices Agency (PMDA) has recently updated its regulations and published guidelines to encourage the use of RWD to satisfy post-safety requirements and has shown a willingness to expand its application to regulatory

TABLE 1 Definitions of RWD and RWE from some key international regulatory authorities

	RWD	RWE
FDA (United States) ⁸	“Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources”	“Clinical evidence about the usage and potential benefits or risks of a medical product derived from analysis of RWD”
EMA (Europe) ⁷	“Health care related data that is collected outside of randomized clinical trials”	“Evidence coming from registries, electronic health records, and insurance data”
PMDA (Japan) ¹⁰	“Data that is electronically generated and stored by medical institutions”	<i>No official definition has been issued at this time</i>

Abbreviations: EMA, European Medicines Agency; FDA, United States Food and Drug Administration; PMDA, Pharmaceuticals and Medical Devices Agency; RWD, real world data; RWE, real-world evidence.

Case study box 1.

BAVENCIO (avelumab) Developed by Merck KGaA in alliance with Pfizer and Eli Lilly

- Received accelerated approval by the FDA (2017) for the treatment of metastatic Merkel cell carcinoma and urothelial carcinoma.
- Received conditional approval by the EMA (2017) for the treatment of Merkel cell carcinoma.
- These approvals were based on findings from a single-arm, open-label, Phase II study, JAVELIN Merkel 200 (<https://clinicaltrials.gov/ct2/show/NCT02155647>). Historical controls that met the enrollment criteria were identified using McKesson's iKnowMed electronic healthcare records and a German patient registry, and were used as a benchmark to characterize the natural history of the disease.¹⁵

Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Administration.

Case study box 2.

BLINCYTO (blinatumomab) Developed by Amgen

- Received accelerated approval by the FDA (2014) and EMA (2015) for the treatment of relapsed/refractory Philadelphia chromosome-negative acute lymphoblastic leukemia based on a single-arm, open-label, phase 2 study.^{16,99}
- Historical controls who received standard of care were used to show effectiveness based on weighted analysis of patient-level data from medical chart reviews.¹⁰⁰
- Full approval was subsequently granted (2017 FDA; 2018 EMA) based on confirmatory phase 3 data.¹⁰¹

Abbreviations: EMA, European Medicines Agency; FDA, United States Food and Drug Administration.

Case Study Box 3.

INVEGA SUSTENNA (paliperidone palmitate) Developed by Janssen

- Data were added to the previously approved FDA label (January 2018) for this long-acting form of INVEGA, indicated for the treatment of schizophrenia, on the basis of a randomized, open-label, pragmatic clinical trial.¹⁹⁻²¹
- This trial was conducted in real world clinical practice and included flexible treatment interventions, active comparators, and relaxed exclusion criteria to include higher-risk patients. It evaluated time to first treatment failure, defined in terms relevant to the clinician and the patient.
- The study included patients who had prior contact with the criminal justice system and was the first example of the use of RWE from a pragmatic trial in schizophrenia to support a regulatory decision, in this case, an expansion of the label.

Abbreviation: FDA, United States Food and Drug Administration.

assessments other than safety (see Table 2).³⁹ More active discussions in this area are expected, and the agency anticipates further international collaborations that utilize RWD for better regulation of drug life cycles.³⁸

Similarly, Health Canada has published guidance to optimize the use of RWE for regulatory decision-making,⁴⁰ and a draft guidance has been issued for comments by the National Medical Products Administration of China, which includes some use cases showing

how RWE has already been used for regulatory labelling.⁴¹ Indeed, Health Canada has begun to consider RWE as part of the totality of evidence to support its regulatory decisions, as illustrated by the fact that in April 2019 they approved an expansion of the existing approved pediatric indication for Pevnar 13 to include acute otitis media in children 6 weeks to 5 years of age using real-world data from the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey.^{42,43} Health Canada is also collaborating with Health Technology Assessment (HTA) partners to establish a joint document that aims to formalize and optimize the use of RWE throughout the drug life cycle.⁴⁴ Similarly, in Europe, the report of the HMA-EMA joint big data taskforce has also reinforced the need for collaboration across all stakeholders, from regulators to payers, HTA bodies, patients, academia, and industry to assess how RWE can contribute to effectiveness decisions.²⁵

3 | THE EMERGING RULES FOR RWE THAT IS FIT FOR REGULATORY PURPOSES

The 21st Century Cures Act and PDUFA VI requires the FDA to accelerate drug development and approval processes, and more specifically, to produce guidance on how to incorporate patient perspectives and innovative study designs, including RWE, into the drug development process.⁴⁵⁻⁴⁷ The recently published FDA

TABLE 2 Examples of recent regulator-supported initiatives that drive forward the application of RWE

	Details of the Initiative
Guidance to submit documents using real-world data and real world evidence to FDA for drugs and biologics (2019) ²⁴	This guidance is intended to encourage sponsors and applicants who are using RWD to generate RWE as part of a regulatory submission to FDA to provide information on their use of RWE in a simple, uniform format.
HMA/EMA Joint Task Force on Big Data (2019) ²⁵	This document provides recommendations for a path towards understanding the acceptability of RWE from “Big data” sources to support regulatory evaluation and monitoring.
Framework for FDA: Real-world evidence program (2018) ⁸	The FDA published a framework to help evaluate the potential use of RWE to support new indications for drugs already approved or to satisfy post-approval study requirements. This framework demonstrates a commitment to transforming the drug development cycle.
Guidance on the use of Electronic Health Records (FDA) (2018) ²⁶	The focus of this guidance is on data integrity. It emphasizes the need to cite the “data originator” and preserve the audit trail. It also reinforces that RWE may be used to inform approval of new indications for approved drugs and to satisfy post-approval study requirements.
Brigham and Women's Hospital/Harvard Medical School/Aetion study, RCT DUPLICATE (FDA funded) (Started end of 2017) ²⁷	This initiative explores whether results from 30 clinical trials (previously used for approval decisions and from multiple therapeutic areas) can be replicated with RWE. FDA also recently announced, the expansion of their demonstration project, using real-world evidence to predict the results of seven ongoing Phase IV trials. Along the same lines, another study (REPEAT; ENCePP registration number: EUPAS19636) is also underway independently of the FDA (https://www.repeatinitiative.org/).
MyStudies mobile App (FDA) (2018) ²⁸	This is a validated and publicly available software application (App) from the FDA, aiming to provide a template for the collection of RWD.
Complex Innovative Trial Designs Pilot Program (FDA) (Started 2018) ²⁹	This pilot program offers drug developers a chance to increase their interactions with the FDA to discuss and develop innovative trial designs and analysis plans. This could include the use of RWD to generate RWE.
Clinical Trials Transformation Initiative (FDA) (Started 2017) ³⁰	Established by the FDA and Duke University, this public-private collaboration aims to create and disseminate recommendations for improving clinical trials. Several of their initiatives encourage the increased use of RWD. This initiative is also responsible for the Sentinel IMPACT-Afib international, prospective, cluster-randomized pragmatic study, which is currently testing the effect of early educational intervention on real-world clinical practice. ^{31,32}
Patient registries initiative (EMA) (Started 2015) ³³	This project aims to facilitate the establishment and systematic approach to use of patient registries in order to collect high-quality data for regulatory decision-making.
Adaptive pathways (EMA) (2014-2016) ³⁴	This initiative aims to use current European regulatory framework to speed up patient access to medicines. It encouraged principles such as iterative development/approvals, RWD as a supplement to trial data, and early discussions with patients and health-technology-assessment bodies. In parallel, the Innovative Medicines Initiative (IMI) launched the ADAPT-SMART initiative (https://www.infographic.adaptsmart.eu/), which brought together stakeholders to develop better ways to achieve “adaptive pathways.”
IMI GetReal (EMA is a member) (2013-2016) ³⁵⁻³⁷	IMI is a partnership between the European Union and the European pharmaceutical industry that collaborates on a range of initiatives aimed to advance and accelerate patient access to medicines, particularly where there is unmet need. The GetReal project discussed, proposed, and created tools to support new robust methods of RWE synthesis for use throughout the drug lifecycle, including regulatory decision-making. Although the initial project has formally finished, their work continues through the IMI GetReal initiative launched in 2018.
Regulatory Update for Promoting RWD Utilization (PMDA) (Started 2017) ³⁸	To encourage RWD utilization, the ministerial ordinance (Good Post-Marketing Study Practice, or GPSP) was amended in October 2017 and implemented on April 1, 2018. MID-NET (Medical Information Database Network) was also formally launched on April 1, 2018, allowing certain stakeholders to utilize this database. The next five years will be an important period for considering and expanding the use of RWD to support regulatory processes.

Abbreviations: EMA, European Medicines Agency; FDA, United States Food and Drug Administration; IMI, Innovative Medicines Initiative; PMDA, Pharmaceuticals and Medical Devices Agency; RWD, real-world data; RWE, real world evidence.

framework for evaluation of how RWE can be incorporated into the regulatory approval process highlights the key topics for which full evaluation will be undertaken.⁸

There is a need to define the rules for RWE that is fit for regulatory purposes. However, while the development of innovative trial designs is being actively encouraged by the major regulatory agencies, particularly with the FDA's Complex Innovative Trial Designs Pilot Program and Clinical Trials Transformation Initiative and the EMA's adaptive pathways initiative, the required standards to produce RWE that is acceptable for regulatory decision-making have not yet been fully defined.^{29,30,34} Although regulators are open to proposals for studies with RWD and receiving RWE, the decision to pursue an innovative study design as part of a clinical development program and regulatory approval strategy is not straightforward, as the routes to obtaining pilot guidance are complex and the "rules" for acceptance of evidence in regulatory decision-making are not yet firmly defined. It is therefore essential to engage with regulatory authorities early to obtain alignment on objectives, inform the study design, and ensure the study design and data are acknowledged as "fit-for-purpose" before conducting a study that may not meet the regulatory goals.

To aid this process, several stakeholders have published frameworks and recommendations for the creation of RWE suitable for use in regulatory decisions. The Duke-Margolis Center for Health Policy, with support from the FDA, released a white paper on the regulatory use of RWE in 2017 following open consultation with academics, patients, and industry.⁴⁸ Emphasizing considerations for developing RWE that is fit for regulatory purposes, they identified several areas for practical improvement, including the need to ensure that the appropriate RWD sources are matched with appropriate study designs and data collection and handling methods to address the research question. They also encourage the formation of transparent collaborations and the sharing of datasets. Professional societies have also weighed in here too, with the International Society for Pharmacoeconomics and Outcomes Research and the International Society for Pharmacoepidemiology publishing recommendations for good procedural practices for RWE, aiming to build trust and expand its current use in health care decision-making.⁴⁹ Many of the recommendations made in these aforementioned publications have been formalized in the FDA framework document.⁸

An important part of planning innovative studies to produce RWE that provides adequate scientific evidence for regulatory decision-making is preparation of a thorough analytical plan at the outset of the study. This is already an integral part of most traditional pivotal and post-safety trials and should reasonably be extended to effectiveness studies that use RWD. Some also argue that pivotal and safety outcome RCTs and observational post authorization safety studies should be registered on appropriate repositories (eg, ClinicalTrials.gov or the EU PAS Register) prior to study initiation as a requirement of the regulatory process. Whether RWE studies will be required to be registered in such a way is a topic of ongoing debate, with opinion sharply divided. Registration by itself is no guarantee of study quality, and any benefit from registration would be heavily dependent on what

information would be required to be posted (eg, study protocols, methodological details, etc.). Further discussions between stakeholders will be required before a consensus develops.

In a separate framework on the regulatory use of RWE, Dreyer (2018) has discussed the requirement and transferability of key RCT study design elements to real-world studies. This builds on the current thinking around clinical outcomes from RWD analysis, suggesting that outcomes should be patient-centric and should be observable and relevant to daily clinical practice. Specific issues are addressed, such as blinding, which is routinely used in RCTs, but is often impractical to achieve under "real-world" circumstances, especially when comparing pharmacologic and nonpharmacologic treatments and when using a selection of "standard of care" comparators, which differ by locale, and while informative, would be impossible to blind. Furthermore, blinding might not be necessary for objective outcomes such as the results of a blood tests and imaging, for example, where in most cases, third-party raters, such as pathologists, are essentially blinded to treatment.⁵⁰ The importance of using data sources that are "fit for purpose" and the familiarity of researchers with potential sources of bias or error so that the most appropriate study methodology is employed is also emphasized. Analytical methods should be transparent, defined up front, and optimized to answer the research question.

Regulators and industry have acknowledged the value of scientifically rigorous and innovative study methodologies as the key route to achieving the standard of substantial evidence for RWE.^{8,48,51} As a means to achieve this, the FDA framework proposes that the following should be considered: (a) whether the RWD are fit for use; (b) whether the trial or study design used to generate RWE can provide adequate scientific evidence to answer or help answer the regulatory question; (c) whether the study conduct meets FDA regulatory requirements (eg, for study monitoring and data collection).⁸ It should be noted that strict applicability of these rules, particularly for monitoring, is rarely feasible for studies that rely on existing data, since the identities of patient and care providers are masked to protect privacy in most secondary data sources.

Similarly, the EMA in its recent report on the use of large datasets for RWE made several recommendations to improve the quality of RWE, including the need to define standard formats for documenting datasets, protocols, and tools used to ensure study reproducibility. In addition, it emphasizes the need to ensure that outcome measures from novel data sources such as wearables should be reflective of a defined clinical benefit.²⁵ If these considerations and recommendations are fully addressed by novel study methodologies, the quality of RWE will improve, and studies using RWD could increasingly be used in support of decisions about therapeutic effectiveness. The development of sufficiently robust RWE will ultimately depend on the ability of experts such as pharmacoepidemiologists, statisticians, data scientists, and academics to develop these new methodologies to optimize hybrid study designs, RWD collection and analysis in a way that is compliant with our current understanding of best practice for RWE generation, and open to regulatory scrutiny.⁸ Sponsors and data owners should proactively identify and develop standard

TABLE 3 Examples of FDA and EMA accelerated approvals, full approvals, and label expansions that used RWE to support regulatory decision-making in the past decade

Drug	Indication (Health Authority, Year)	RWE Use Examples
Lumizyme/Myozyme (alglucosidase alfa)	Pompe Disease (FDA, 2010)	The approval relied on a placebo-controlled trial, in late-onset Pompe disease, supported by clinical outcomes data in infantile-onset patients from the Pompe Registry, which was launched as a post-marketing commitment for the 2006 Myozyme approval in Europe. The registry data showed increased survival at 18 months in Lumizyme patients compared with age- and disease-matched historical controls. The Myozyme approval also relied on a comparison to a 61-patient historical control group. ⁵⁶
Carbaglu (carglumic acid) tablets	Hyperammonia caused by N-acetylglutamate (NAGS) deficiency (FDA, 2010)	The approval relied on a retrospective review of 23 NAGS deficiency patients who received Carbaglu for a median of approximately eight years, and on data from 3 patients with NAGS deficiency treated in a prospective trial. ⁵⁹
Voraxaze (glucarpidase)	Toxic plasma methotrexate concentrations in patients with delayed methotrexate clearance due to impaired renal function (FDA, 2012)	The chemotherapy toxicity reversal agent approval was supported by clinical evidence from 22 patients in two efficacy studies, including an open-label non-randomized compassionate use protocol. ^{56,60-62}
NovoSeven (Coagulation Factor VIIa)	Glanzmann's thrombasthenia with refractoriness to platelet transfusions (Treatment of bleeding episodes and the peri-operative management) (FDA, 2014)	The approval was based upon evidence collected from the global Glanzmann's Thrombasthenia Registry (218 patients with 1,073 bleeding and surgical events) and the Hemostasis & Thrombosis Research Society Registry (7 patients with 23 bleeding episodes). ⁶³
Blinicyto (blinatumomab)	Philadelphia chromosome-negative (Ph -) relapsed or refractory positive B-cell precursor acute lymphoblastic leukemia (ALL) (FDA 2014, EMA 2015)	The main study supporting this accelerated approval was a Phase 2, multicenter, open-label, single-arm trial that included a core study of 185 patients to assess the treatment efficacy and safety. The results of this study were compared to a retrospective pooled analysis of historical data on 1139 patients from 1990 to 2014 on hematological remission rates and survival among adult patients with relapsed/refractory ALL treated with standard of care therapy. This historical database was assembled by combining existing databases from the USA and European Union from 1139 patients that had similar characteristics to the patients in the main study with respect to previous treatment status. ^{16,64-66}
Cholbam (cholic acid)	Bile acid synthesis disorders (FDA, 2015)	The approval was based on a retrospectively devised case report form from chart review of patients in the open-label, single-arm expanded access protocol and a retrospective literature review to construct a historical control. ⁵⁶
Vistogard (Uridine triacetate)	Emergency treatment of certain types of chemotherapy overdose (FDA, 2015)	Vistogard was approved as an emergency treatment for patients who receive overdoses of two chemotherapy drugs or exhibit severe adverse reactions to the drugs following open-label safety and efficacy trials of 135 patients. The patient had either received overdoses of fluorouracil or capecitabine or presented with severe or life-threatening toxicities within four days following administration of either chemotherapy drug. The agency also utilized historical data, including its evaluation of 25 historical case reports of patients who received overdoses of the two chemotherapy agents and who did not receive Vistogard. ^{58,67}
ProVay Blue (methylene blue)	Acquired methemoglobinemia (FDA, 2016)	The ProVay Blue accelerated approval was based on retrospective case reports found in a multicenter chart review along with cases found in literature search. Like many of the orphan products approved with RWE, ProVay Blue used the 505(b)(2) NDA pathway, which allows for data not developed by the sponsor to be incorporated in the application. ^{56,68-71}
Zalmoxis (allogeneic T cells)	Hematopoietic stem cell transplantation with high-risk hematological malignancies (EMA, 2016)	For this approval, a control group was collected from the European transplant registry based on the same criteria used in the control group of an ongoing Phase III trial and a specific sets of matching parameters. ⁷²⁻⁷⁴
Exondys (eteplirsen)	Duchenne muscular dystrophy (FDA 2016)	The Accelerated approval was based on matching and comparison of eteplirsen arm with historic control arm from the Italian DMD Registry database. ⁷⁵
Kalydeco (ivacaftor)	10 cystic fibrosis (CF) mutations to 33 (FDA, 2017)	The label expansion was based on post-marketing registry data and mechanistic information from lab studies. ⁵⁶
Soliris (eculizumab)	Paroxysmal nocturnal hemoglobinuria where evidence of clinical benefit is demonstrated in patients with	Soliris was initially restricted to use in patients with a certain disease severity. The expanded indication was based on disease registry data to help demonstrate effectiveness. The registry was established at the time of authorization of Soliris

(Continues)

TABLE 3 (Continued)

Drug	Indication (Health Authority, Year)	RWE Use Examples
	haemolysis with clinical symptom(s) indicative of high disease activity, regardless of transfusion history (EMA, 2017)	with the twin aims of evaluating the safety of Soliris and also characterizing disease progression, clinical outcomes, morbidity, and mortality. The registry included data from both Soliris treated and untreated patients. ^{74,76,77}
Brineura (cerliponase alfa)	Batten disease (EMA and FDA 2017)	The FDA approved Brineura as a treatment for a form of Batten disease, following a single-arm study which used a natural history control. Brineura was the first FDA-approved treatment to slow loss of walking ability in patients with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2). The clinical trial establishing Brineura's efficacy was a non-randomized, single-arm dose escalation clinical study in 22 symptomatic pediatric patients. The control or comparator consisted of 42 untreated patients with CLN2 disease from a natural history cohort. ^{56,58,78-82}
Bavencio (avelumab)	Metastatic Merkel cell carcinoma (FDA and EMA 2017)	Accelerated approval based on a single-arm, open-label study compared with historical control from electronic health records. ^{15,83}
Yescarta (Axicabtagene Ciloleuce)	Diffuse large B-cell lymphoma (FDA 2017 and EMA 2018)	The full approval was granted for adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy based on the findings of the single-arm ZUMA-1 study which compared the treatment response with historical controls from scientific literature. ^{84,85}
Tepadina (thiotepa)	Reduce the risk of rejection in pediatric call 3 beta-thalassemia (FDA, 2017)	The label expansion was based on a retrospective study of pediatric patients with class 3 beta-thalassemia who underwent allogeneic hematopoietic stem cell transplantation.
Galafold (migalastat)	Fabry disease (FDA 2018 and EMA 2016)	This was an accelerated approval by the FDA. The data included new cardiac and renal data from clinical trials, data from long-term extension studies and real-world data from the commercial launch of migalastat in Europe, particularly on patients transitioning from existing enzyme replacement therapy. The sponsor also provided patient perspectives to FDA on the unmet need in Fabry and the lack of treatment options in the US. ⁸⁶⁻⁹⁰
Lutathera (lutetium Lu 177 dotatate)	Gastroentereopancreatic neuroendocrine tumors (FDA, 2018)	The FDA approved Lutathera, a radioactive drug for treatment of somastatin receptor-positive instances of a type of cancer that affects the pancreas or gastrointestinal tract known as gastroenteropancreatic neuroendocrine tumors (GEP-NETs), based in part on data generated through the expanded access program. Lutathera's approval was supported by two studies. One was a RCT with 229 patients. The second study was based on data from a single-arm, open-label study of 1,214 patients with somatostatin receptor-positive tumors, including GEP-NETS, who received Lutathera at a single site in the Netherlands. ^{58,62,91-93}
INVEGA SUSTENNA (paliperidone palmitate)	Treatment of schizophrenia in adults and treatment of schizoaffective disorder in adults as monotherapy and as an adjunct to mood stabilizers or antidepressants (FDA, 2018)	The label expansion for this long-acting form of INVEGA was based on the Paliperidone Palmitate Research In Demonstrating Effectiveness (PRIDE) study a prospective, open-label, randomized, 15-month pragmatic study comparing the long-acting form with oral antipsychotic medications in patients with schizophrenia who have a history of contact with the criminal justice system. ¹⁹⁻²¹
Omegaven (fish oil triglycerides)	Parenteral nutrition-associated cholestasis (PNAC) (FDA, 2019)	The approval was based on two single-arm trials, matched to historical control arm from hospital records. ^{94,95}
Blincyto (blinatumomab)	B-cell precursor acute lymphoblastic leukemia in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% (FDA 2018 and EMA 2019)	The label expansion was based on the results of a single-arm trial supported by RWE to include indication for patients with minimal residual disease in which cancer cells are present at a low level that cannot be detected microscopically. ^{17,18,22,96}
Ibrance (Palbociclib)	HR+, HER2- advanced/metastatic breast cancer (FDA, 2019)	The label was expanded to include treatment in males based on post-marketing reports and electronic health records as part of the totality of evidence. Real-world data from electronic health records showed encouraging response rates with Ibrance, a CDK4/6 inhibitor in combination with an aromatase inhibitor or fulvestrant in the male patient population. The safety profile of Ibrance in male patients was consistent with the tolerability in female patients who were treated with palbociclib, according to the data. ¹⁰²

Abbreviations: EMA, European Medicines Agency; FDA, United States Food and Drug Administration; RCT, randomized controlled trial.

operating procedures to be prepared for FDA audits and oversight by defining requirements for record retention, auditing, and patient privacy.

4 | MODERNIZING THE CLASSICAL RCT

Some specific hybrid study designs under consideration for regulatory decision-making by the FDA fall into three broad categories: (a) investigational new drug submissions for RCTs that use RWD to capture clinical outcomes or safety data, including pragmatic and large simple trials; (b) protocols for single-arm trials that use external controls; (c) clinical trials using RWE to fulfil a post-marketing requirement for further evaluation of safety or effectiveness to support a regulatory decision.²⁴

4.1 | Pragmatic and large simple trials

Pragmatic and large simple trials mirror many of the features of RCTs including randomization but are typically very large RCTs and enable a broader patient group to participate. These trials are increasingly being used to demonstrate effectiveness in a daily clinical practice setting and allow more clinically meaningful outcomes to be studied, creating readily transferable benefits for patients. This notion links in with the ever-developing narrative around patient-centric care and the increasing involvement of patients in the drug development process, aiming to increase the relevance of new therapeutic interventions to the patient experience.^{52,53} One of the first examples of a large simple trial was the Salk polio vaccine field trial of 1954, which led to regulatory approval of the vaccine and a nationwide public health response to eradicate polio.⁵⁴ More recently, the feasibility of pragmatic trials was also tested by the label expansion achieved for Janssen's INVEGA SUSTENNA (Case study 3) that was based on the findings of the Paliperidone Palmitate Research in Demonstrating Effectiveness (PRIDE) trial which was designed to include treatment randomization and pragmatic outcomes.¹⁹⁻²¹ The trial was uniquely designed to mirror the population of adults living with serious and poorly controlled schizophrenia that health care professionals commonly see in clinical practice.⁵⁵

4.2 | External controls

Non-randomized clinical trials involving comparison against external controls have already been used to demonstrate effectiveness in an ever-increasing number of cases, often relating to rare diseases. These types of designs are particularly useful where randomization may not be feasible or ethical, or where there are limited numbers of patients with a given condition.

Trials with external controls have also been the subject of recent innovation. In Table 3, we have compiled a list of examples where RWE has been used in the past decade to support regulatory decisions on effectiveness that have led to accelerated approval, full approval, or label expansion. The examples fall into three broad categories: (a)

approvals based on data from registry-like case series; (b) approvals where external control data have been obtained from registries, medical records, scientific literature, etc.; (c) approvals based on data from expanded access programs.

4.3 | Long-term follow-up studies using RWD

Many post-marketing requirement and commitment studies of safety rely on observational designs and methods. There are instances, however, where evidence about safety from RCTs is preferred or required due to feasibility (eg, level of measurement and/or monitoring). These studies often include a secondary aim of evaluating efficacy endpoints. While pragmatic approaches to randomized, comparative safety studies have been tested in the past,¹⁰³ the regulatory framework for RWE along with new technology and data have created new opportunities for conducting streamlined safety and efficacy studies. The capture of RWD using methodologies such as decentralization (eg, trained nurses), direct-to-patient approaches (eg, wearables, patient-reported outcomes), or databases (eg, registries, claims) could be leveraged to capture long-term outcomes, and may be considered another step towards the adoption of hybrid study designs to improve clinical efficiencies. These innovative approaches are also potentially useful when conducting long-term studies of pre-approval, investigational drugs, particularly when the safety and effectiveness outcomes of interest require longer follow-up durations.

While most traditional data processing and analysis tools applicable to RWD can be used to identify and reduce the impact of some of the limitations inherent in real-world studies, such as potential confounding factors, real-world datasets require development of new methodologies or applications to unlock their full potential.^{9,11,97} The growth of machine learning and the application of natural language processing to RWD will bring additional opportunities in the future, enabling even more meaningful outcomes to be elucidated from the wealth of available RWD.⁹ Machine learning techniques have already been used to enhance the prediction accuracy of algorithms to identify women with early and advanced stage breast cancer in a claims database using predictive modeling.⁹⁸

These examples demonstrate the potential that hybrid study methodologies offer by combining the best features of RCTs and studies with RWD, while negating some of the drawbacks. This approach could therefore potentially augment or even replace RCTs for regulatory decision-making in certain situations, and as researchers, clinicians, and regulators gain more experience with these types of study designs, they may become more accepted and applied more widely.

5 | CONCLUSIONS

RWE has typically been associated with lower-quality evidence than that from RCTs, but this opinion is changing as guidance frameworks and the study methodologies using RWD are evolving. The development and refinement of hybrid study designs consolidate the benefits

of RCTs and RWD while minimizing the limitations of both traditional study types. This has the potential to generate RWE that provides adequate scientific evidence for regulatory decision-making, a potential that is increasingly being realized, with a growing number of examples demonstrating how RWE can be used to support and drive decisions on effectiveness.

Further acceptance of RWE by regulators and other key stakeholders has the potential to make drug development more efficient and generate a paradigm shift in the drug approval process. Progress towards this goal can be aided by the early establishment of a cross-disciplinary team to provide expert judgment on the appropriate research question, study design, systematic evaluation of feasibility, pre-specification of the study protocol, and validation, where needed. Pharmacoepidemiologists can play an important role in supporting cross-functional teams in adapting to the changing landscape where RCTs are increasing reliance on RWD. While pharmacoepidemiologists have historically played a central role in the design and implementation of post-approval safety studies, they have the knowledge and skills to support colleagues in clinical development to implement these hybrid designs and leverage the recommendations of the RWE frameworks being developed. This is critical in ensuring wider acceptance of RWE for regulatory decision-making, given the complexity of some of these modern designs.

Trial designs using RWD represents a logical, much-needed step in the development and future-proofing of the regulatory approval system, but will require regulators, pharmaceutical companies, and RWE experts to collaborate early on to unlock the scientific potential of RWD through innovative study designs generating solid and dependable RWE, as well as to address privacy concerns that often accompany linking primary and secondary data.

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E.B.A. and P.C. are employees and shareholders of Pfizer, but the expressed views are their own. R.R. was an employee of Pfizer while this manuscript was in development. N.D. is an employee of IQVIA and is actively involved in the design and conduct of innovative RW studies, as described here; IQVIA contributed the external comparators used for the avelumab approval in the European Union.

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