Received: 13 May 2024 | Revised: 24 June 2024 | Accepted: 10 July 2024

DOI: 10.1111/cts.13903

ARTICLE

Real-world evidence to support regulatory submissions: A landscape review and assessment of use cases

Golnoosh Alipour-Haris[1,2] | **Xinyue Liu**[2] | **Virginia Acha**[2] | **Almut G. Winterstein**[1] | **Mehmet Burcu**[2]

[1]University of Florida, Gainesville, Florida, USA

[2]Merck & Co., Inc., Rahway, New Jersey, USA

Correspondence
Mehmet Burcu, Merck & Co., Inc., Rahway, New Jersey, USA.
Email: mehmet.burcu@merck.com

Abstract

Real-world evidence (RWE) has an increasing role in preapproval settings to support the approval of new medicines and indications. The main objectives of this study were to identify and characterize regulatory use cases that utilized RWE and other related observational approaches through targeted review of publications and regulatory review documents. After screening and inclusion/exclusion, the review characterized 85 regulatory applications with RWE. A total of 31 were in oncology and 54 were in non-oncology therapeutic areas. Most were for indications in adults only ($N=42$, 49.4%), while 13 were in pediatrics only (15.3%), and 30 were in both (35.3%). In terms of regulatory context, 59 cases (69.4%) were for an original marketing application, 24 (28.2%) were for label expansion, and 2 (2.4%) were for label modification. Most also received special regulatory designations (e.g., orphan indication, breakthrough therapy, fast track, conditional, and accelerated approvals). There were 42 cases that utilized RWE to support single-arm trials. External data to support single-arm trials were utilized in various ways across use cases, including direct matching, benchmarking, natural history studies as well as literature or previous trials. A variety of data sources were utilized, including electronic health records, claims, registries, site-based charts. Endpoints in oncology use cases commonly included overall survival, progression-free survival. In 13 use cases, RWE was not considered supportive/definitive in regulatory decision-making due to design issues (e.g., small sample size, selection bias, missing data). Overall, RWE is utilized in regulatory approval processes for new indications/label expansion across various therapeutic areas with wide range of approaches. Multifaceted cross-sector efforts are needed to further improve the quality and utility of RWE in regulatory decision-making.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

In addition to postmarketing studies to better understand the safety of medical products in the real-world setting for approved indications, RWE has an increasing role in supporting indication/label expansion or dose modification for

medical products that have already been approved. Additionally, RWE can also potentially play a role in preapproval settings to support the approval of new medicines and indications.

WHAT QUESTION DID THIS STUDY ADDRESS?

The study reviewed and characterized current uses of RWE and other related observational approaches in preapproval regulatory submissions overall and by the type of clinical trial design they supported. The study also assesses study design characteristics and limitations to inform on the current landscape and guide future methodological developments to address gaps and limitations.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This review highlights the utilization of various RWE designs and other related observational approaches in regulatory applications for new indications and label expansions across multiple therapeutic areas. While nearly half of identified RWE use cases involved an external control arm approach, the review also demonstrated a variety of other approaches including supplementing RCTs and providing primary evidence in lieu of clinical trial data. The study also identifies key methodological challenges that affect the quality and reliability of RWE.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Multifaceted cross-sector efforts including collaborative pilots are needed to further improve the quality and utility of RWE in both pre- and postapproval settings, especially on emerging designs and approaches.

INTRODUCTION

Real-world evidence (RWE) has become increasingly important in contributing to our understanding of the safety and effectiveness of medical products. RWE is defined as clinical evidence derived from the analysis of real-world data (RWD), which refers to data collected from routine clinical practice or other non-research settings.[1] While randomized clinical trials (RCTs) are considered the gold standard in producing evidence for clinical efficacy and safety of new treatments, RWE is increasingly recognized as an alternative in situations where RCTs are not always feasible (e.g., due to ethical concerns). In addition, even when randomization is feasible, traditional RCT studies may not fill all the evidentiary gaps in safety and effectiveness of medical products.[2,3]

In December 2016, the 21st Century Cures Act by the U.S. Congress required the US Food and Drug Administration (FDA) to develop a framework and guidance for using RWE to support regulatory decision-making for medical products.[4] Regulatory agencies such as European Medicines Agency (EMA) and others have also increasingly considered the use of RWE to support regulatory decision-making in both pre and postapproval settings.[5,6]

In addition to postmarketing studies to better understand the safety of medical products in the real-world setting for approved indications, RWE has an increasing role in supporting indication/label expansion or dose modification for medical products that have already been approved.[7] Additionally, RWE can also play a role in preapproval settings to support the approval of new medicines and indications.[7] For example, FDA has considered RWE as historical control to support several approval decisions in single-arm clinical trials in rare diseases with small patient populations or in disease settings with high unmet need.[7] However, several challenges are associated with using RWE in regulatory decision-making, including data quality concerns and biases inherent within observational study designs.[8]

Over the past few years, several reviews or assessments have been published on the regulatory use of RWE derived from RWD in preapproval settings. Some are restricted to specific therapeutic areas, some are just narrative reviews, and others do not present all important parameters in a comprehensive manner such as name/origin of data source, endpoint definition, and related algorithms utilized. There is a need for a comprehensive review and synthesis of published materials on RWE use cases that supported regulatory decisions in the preapproval setting. This study aims to provide a review of peer-reviewed scientific/medical publications and complementary FDA and EMA regulatory documents, providing a detailed assessment of RWE use cases and their

characteristics that were used in regulatory applications in the preapproval settings for new medicines or new indications of already marketed medicines. The objectives of this review are to characterize current uses of RWD/E in preapproval regulatory submissions (including external controls and other designs) overall and by type of clinical trial design they supported (e.g., single-arm trials, RCTs); and to assess their study design characteristics and limitations to inform on the current landscape and guide future methodological developments to address gaps and limitations.

METHODS

Search strategy and data sources

The research strategy was conducted in two stages: The first stage involved a systematic review of the published literature to identify RWE use cases and related product/indication information. The second stage included a targeted review of regulatory documents to gather additional information (not captured in the initial stage) regarding these use cases. More information on each stage of search strategy and data extraction are detailed below.

Stage 1—Targeted review of published literature: A comprehensive search was conducted using PubMed, Embase, and Web of Science databases between January 1, 2016, and June 30, 2022. The search query included relevant keywords related to real-world evidence (RWE) and regulatory approvals. Articles were selected for inclusion if they contained at least one keyword referring to real-world evidence ("Real world data," "Real-world data," "RWD," "Real world evidence," "Real-world evidence," "RWE") and at least one keyword relating to regulatory approvals ("Regulatory decision-making," "Regulatory decisions," "regulatory approval," "regulatory application," "Regulatory submission," "Regulatory License," "License application," "marketing authorization," "extension of indication," "label expansion," "label extension"). The search strategy was tailored to identify papers that specifically described RWE use cases in regulatory applications, rather than primary research studies.

Publications before January 1, 2016, and methodologic publications or commentaries without any product review or evidence related to the utilization of RWE for regulatory purposes were excluded. Two reviewers independently screened abstracts and full texts to identify relevant publications with RWE use cases utilized in regulatory applications. After the completion of screening, RWE use cases were identified from these publications and pre-specified data elements were extracted from these selected papers relating to these RWE use cases, such as product information, regulatory designation, and RWE information. Gray literature published by relevant data/technology companies (e.g., AETION, NY, United States,[9] newsletters) and organizations such as European Federation of Pharmaceutical Industries and Associations (EFPIA[10]) and Biotechnology Innovation Organization (BIO)[11] were also reviewed to identify other use cases not captured by the initial literature review. Any discrepancies between reviewers were resolved through discussion.

Stage 2—Targeted review of gray literature/regulatory documents: After identifying use cases in the systematic targeted review of published literature (in stage 1), we reviewed FDA and EMA publicly available regulatory documents associated with the medical products' approval applications and extracted additional details for these use cases. However, when there was no mention of any RWE-related information in the regulatory documents, these cases were excluded from the analyses (due to a lack of clarity on the utility of RWE in regulatory evaluation and decision-making). For product reviews associated with the US FDA, we utilized the Drugs@FDA[12] database which included detailed information on product labels, approval letters, reviews, and other details. Specifically, we used publicly available information in the drug approval packages through multi-discipline review/summary, clinical, non-clinical documents, medical reviews, and statistical reviews. For product reviews associated with EMA, the European public assessment reports[13] were utilized as they provided detailed information about drugs that have been evaluated by the EMA's Committee for Medicinal Products for Human Use (CHMP) and Committee for Medicinal Products for Veterinary Use (CVMP).

In summary, after employing the two-tiered search/review strategy described above, we extracted the following data elements for each identified RWE use case: therapeutic area, age group (e.g., pediatrics, adults), application information (e.g., orphan indication, accelerated approval, breakthrough therapy approval, fasttrack approval, conditional approval), regulatory use type and purpose (including original marketing application approval, label expansion, label modification), clinical trial data/design information, pivotal evidence trial phase, the nature of effectiveness or safety data from RWD, rationale for RWD use, RWE approach, RWE design, and sources of RWD. In addition to these elements, we also extracted any comments from regulatory review documents on the pitfalls of the RWE use cases that were limited in providing support for regulatory decision-making.

RESULTS

Data collection

We identified 2108 publications through our initial search. As detailed in the PRISMA flow diagram (Figure S1), after applying inclusion and exclusion criteria through title and abstract screening, we were left with 104 publications for full-text review. Of these, 84 were excluded because they were either methodological in nature, had only been published in abstract form, or did not include any regulatory facing RWE use cases. From the gray literature review, we identified an additional 8 publications, bringing the total number to 28 (Figure S1 and Table S1).[5,14–40] During the data extraction stage, we identified 129 use cases from these publications and an additional 17 cases from other gray literature resources. After further evaluation, 53 use cases were excluded because they were not to support preapproval regulatory decision-making (e.g., mostly to support postapproval regulatory requirements) in a postmarketing setting. Of the remaining 93 use cases, 14 were also excluded because they had not been mentioned in publicly available regulatory documents. After applying inclusion and exclusion criteria, a total of 85 use cases were included in the analysis (Figure S2).

Overall characteristics of RWE use cases

Table 1 provides a summary of detailed characteristics of the 85 use cases that utilized RWE or related observational approaches in preapproval regulatory settings. The use cases were submitted to FDA ($N=69$) or the EMA ($N=28$). They were distributed across various therapeutic areas, with oncology accounting for 36.5% ($n=31$) and non-oncology for the remaining 63.5% ($n=54$). The use cases varied in terms of age group, with 15.3% ($n=13$) exclusively involving pediatrics, 48.2% ($n=41$) focused on adults, and 36.5% ($n=31$) including both adults and pediatrics.

In terms of application information, a substantial number of cases were associated with special designations such as orphan drug indication, accelerated approval, breakthrough therapy approval, fasttrack approval, and conditional approval, predominantly for the FDA cases. The regulatory use type and purpose were primarily for approval of original marketing applications (69.4%, $n=59$), followed by label expansion (28.2%, $n=24$), and label modification (2.4%, $n=2$).

The use cases varied in terms of clinical trial data and design information, with the majority being single-arm trials (49.4%, $n=42$). The use of RWD for effectiveness or safety was also diverse, with efficacy/effectiveness data collection being the most common (57.6%, $n=49$).

TABLE 1 Characteristics of use cases that utilized real-world evidence or related observational approaches in preapproval regulatory settings.

	All $N=85$	FDA $N=69$	EMA $N=28$
Therapeutic area			
Oncology	31 (36.5%)	28 (40.6%)	8 (28.6%)
Non-oncology	54 (63.5%)	41 (59.4%)	20 (71.4%)
Age group			
Pediatrics	13 (15.3%)	11 (15.9%)	5 (17.9%)
Adults	41 (48.2%)	35 (50.7%)	12 (42.9%)
Adults and pediatrics	31 (36.5%)	23 (33.3%)	11 (39.3%)
Application information[a]			
Orphan indication	–	51 (73.9%)	21 (75.0%)
Accelerated approval	–	30 (43.5%)	–
Breakthrough therapy approval	–	24 (34.8%)	–
Fast track approval	–	30 (43.5%)	–
Conditional approval	–	26 (37.7%)	7 (25.0%)
Regulatory use type and purpose			
Original marketing application approval	59 (69.4%)	51 (73.9%)	18 (64.3%)
Label expansion	24 (28.2%)	16 (23.2%)	10 (35.7%)
Label modification	2 (2.4%)	2 (2.9%)	–
Clinical trial data/design information[b]			
Randomized clinical trial (double-blind)	17 (20.0%)	13 (18.8%)	4 (14.3%)
Randomized clinical trial (open-label)	7 (8.2%)	7 (10.1%)	–
Single-arm trial	42 (49.4%)	33 (47.8%)	18 (64.3%)
Compassionate use/ expanded access	5 (5.9%)	5 (7.2%)	–
None	13 (15.3%)	10 (14.5%)	6 (21.4%)
Effectiveness or safety from RWD			
Efficacy/effectiveness data collection	49 (57.6%)	42 (60.9%)	14 (50.0%)
Safety data collection	12 (14.1%)	12 (17.4%)	1 (3.6%)
Safety and efficacy/ effectiveness data collection	24 (28.2%)	15 (21.7%)	13 (46.4%)
Rationale for RWD use			
Provide primary evidence (without trial data/ expanded access program)	17 (20.0%)	14 (20.3%)	6 (21.4%)
Support single-arm trial(s)	42 (49.4%)	34 (49.3%)	17 (60.7%)
Provide supplementary data to RCT(s)	26 (30.6%)	21 (30.4%)	5 (17.9%)
RWE approach[a]			
External RWD controls (direct matching)	30 (35.3%)	23 (33.3%)	14 (50.0%)
External RWD controls (benchmark/natural history)	7 (8.2%)	5 (7.2%)	2 (7.1%)

TABLE 1 (Continued)

	All $N=85$	FDA $N=69$	EMA $N=28$
External controls (literature/prior trials)	12 (14.1%)	11 (15.9%)	4 (14.3%)
Expanded access program	4 (4.7%)	4 (5.8%)	–
Approaches to support RCTs (observational studies, literature review, etc.)	21 (24.7%)	17 (24.6%)	5 (17.9%)
Primary evidence without trial data	14 (16.5%)	11 (15.9%)	6 (21.4%)
Randomized trial with pragmatic elements	1 (1.2%)	1 (1.4%)	–
RWE design[a]			
Retrospective RWD cohort	53 (62.4%)	43 (62.3%)	21 (75.0%)
Prospective RWD cohort	1 (1.2%)	1 (1.4%)	–
Hybrid RWD cohort (prospective + petrospective)	7 (8.2%)	5 (7.2%)	2 (7.1%)
Prospective trial with RWD elements	4 (4.7%)	4 (5.8%)	–
Other (Literature review, prior trials, etc.)	21 (24.7%)	16 (23.2%)	6 (21.4%)
Sources of RWD[a]			
Electronic health records (EHRs)	16 (18.8%)	12 (17.4%)	8 (28.6%)
Claims	2 (2.4%)	2 (2.9%)	–
Registries	22 (25.9%)	15 (21.7%)	12 (42.9%)
Prior clinical trials	11 (12.9%)	6 (8.7%)	5 (17.9%)
Literature	25 (29.4%)	19 (27.5%)	10 (35.7%)
Site-based chart data	16 (18.8%)	15 (21.7%)	2 (7.1%)
Postmarketing safety data	6 (7.1%)	6 (8.7%)	–
RWE use cases deemed not supportive	13 (15.3%)	9 (13.0%)	4 (14.3%)

[a]Not mutually exclusive, some use cases can belong to more than one category.

[b]There was a use case with a pragmatic clinical trial design not included in any of the other categories under the section on "clinical trial data/design information."

The rationale for RWD use included providing primary evidence, supporting single-arm trials, and providing supplementary data to RCTs. The RWE approaches and design varied, with the most common being retrospective cohort (62.4%, $n=53$). The sources of RWD were diverse and included electronic health records (EHRs), claims, registries, prior clinical trials, literature, site-based chart data, and postmarketing safety data. Upon reviewing the use cases, 13 (15.3%) were explicitly categorized as not supportive of the regulatory application (as per methodological concerns specified in the regulatory review documents). These particular use cases are further detailed in the section "RWE Use Cases Deemed Not Supportive," which outlines instances where the RWE was inadequate for securing a favorable regulatory decision.

Support of single-arm trials

Out of the 42 cases of RWE specifically supporting *single-arm trials*, 45% ($n=19$) were in oncology. Specific details for each use case to support single-arm trials are documented in Table 2. Most cases (90%, $n=38$) were submitted for original marketing application approval, with the remaining supported label expansion. External controls were utilized in various ways across the studies. Direct matching of external RWD controls was the method of choice. However, for 17% ($n=7$), these controls were applied via benchmarking or natural history studies using external RWD. Additionally, some studies employed literature or previous trials as external controls. It is noteworthy that these categories are not mutually exclusive. Most of the RWE cases, or 88% ($n=37$), were retrospective cohort studies. For example, the allogeneic T cells (Zalmoxis) obtained original marketing application approval and the RWE approach used for this product involved external RWD controls through direct matching, sourced from registries. Similarly, other products like lepirudin (Refludan) used external controls through direct matching, and EHRs as sources of RWD. Across use cases, the primary endpoints encompassed a range of measures, including overall survival, overall response rate, complete response, best response, progression-free survival, and duration of response.

Support of RCTs

Out of 26 cases that used RWE and related observational approaches as supplementary information to data from randomized clinical trials (RCTs), 31% ($n=8$) were in the field of oncology (Table S2). Of these cases, 53.8% ($n=14$) were original marketing applications, while the remaining 46.2% ($n=12$) were for supporting label expansion. The use of RWE or other related observational approaches was to establish efficacy data at 42.3% ($n=11$), safety data collection at 30.7% ($n=8$), and both at 27% ($n=7$).

For example, a combination of avelumab and axitinib was approved, where additional observational data was collected to provide supplementary data for comparison with monotherapy approaches. In the case of lutetium Lu 177 dotatate (Lutathera), an expanded access program at Erasmus Medical Center provided supplementary safety and effectiveness data, while the primary evidence came from an RCT.

TABLE 2 Real-world evidence (RWE) and other observational approaches are used to support single-arm trials.

Regulatory information	Effectiveness or safety from RWD/observational approach	RWE/observational study approach approach	RWE design	Sources of RWD	RW primary endpoint(s):
Product: Allogeneic T cells (Zalmoxis), MolMed SpA, 2016 Therapeutic area: Oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: EMA	Efficacy/effectiveness data collection	External RWD controls (direct matching)	Retrospective RWD cohort	Registries	Overall survival (OS), leukemia-free survival (LFS), Non-relapse mortality (NRM), and relapse incidence (RI)
Product: Avapritinib (Ayvakit), Blueprint Medicines, 2020 Therapeutic area: Oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA	Efficacy/effectiveness data collection	External RWD controls (benchmark/natural history)	Retrospective RWD cohort	Site-based chart data	Best response, duration of response (DOR), and progression-free survival (PFS)
Product: Avelumab (Bavencio), EMD Serono, 2017 Therapeutic area: Oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA/EMA	Efficacy/effectiveness data collection	External RWD controls (benchmark/natural history)	Retrospective RWD cohort	Electronic health records (EHRs)	Overall response rate (ORR)
Product: Axicabtagene Ciloleuce (Yescarta), Kite Pharma, FDA 2017, EMA 2018 Therapeutic area: Oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: EMA	Efficacy/effectiveness data collection	External RWD controls (direct matching)	Retrospective RWD cohort	Prior clinical trials, Electronic health records (EHRs)	Overall response rate (ORR), complete response (CR), Overall survival (OS)
Product: Belantamab mafodotin (Blenrep), GlaxoSmithKline, 2020 Therapeutic area: Oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA	Efficacy/effectiveness data collection	External controls (literature/prior trials)	Retrospective RWD cohort	Literature	Overall response rate (ORR)
Product: Blinatumomab (Blincyto), Amgen, FDA 2014, EMA 2015 Therapeutic area: Oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA/EMA	Efficacy/effectiveness data collection	External RWD controls (direct matching)	Retrospective RWD cohort	Electronic health records (EHRs)	Complete response (CR) + complete response with partial hematologic recovery (CRh)

TABLE 2 (Continued)

Regulatory information	Effectiveness or safety from RWD/observational approach	RWE/observational study approach approach	RWE design	Sources of RWD	RW primary endpoint(s):
Product: Capmatinib (Tabrecta), Novartis, 2020 Therapeutic area: Oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA	Efficacy/effectiveness data collection	External RWD controls (benchmark/natural history)	Retrospective RWD cohort	Site-based chart data	Overall response rate (ORR)
Product: Entrectinib (Rozlytrek), Genetech, 2019 Therapeutic area: Oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA	Efficacy/effectiveness data collection	External RWD controls (direct matching)	Retrospective RWD cohort	Electronic health records (EHRs)	Time to disease progression (TTD)
Product: Erdafitinib (Balversa), Janssen, 2019 Therapeutic area: Oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA	Efficacy/effectiveness data collection	External RWD controls (direct matching)	Retrospective RWD cohort	Electronic health records (EHRs)	Overall survival (OS), real-world tumor response (rwTR), real-world disease control rate (rwDCR)
Product: Fam-trastuzumab deruxtecan-nxki (Enhertu), Daiichi Sankyo, FDA 2019 EMA 2021 Therapeutic area: Oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA/EMA	Efficacy/effectiveness data collection	External RWD controls (direct matching)/ External controls (literature/prior trials)	Retrospective RWD cohort	Electronic health records (EHRs), Literature	Progression-free survival (PFS), Overall response rate (ORR)
Product: Idecabtagene vicleucel (Abecma), Celgene, 2021 Therapeutic area: Oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA/EMA	Safety and Efficacy/effectiveness data collection	External RWD controls (direct matching)/external controls (literature/prior trials)	Retrospective RWD cohort	Registries, Site-based chart data, Literature	Overall response rate (ORR)
Product: Sotarasib (Lumakras), Amgen, 2021 Therapeutic area: Oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA	Efficacy/effectiveness data collection	External RWD controls (direct matching)/ External controls (literature/prior trials)	Retrospective RWD cohort	Electronic health records (EHRs), Registries, Literature	Progression-free survival (PFS), Overall survival (OS)
Product: Tafasitamab (Monjuvi), MorphoSys AG, 2020 Therapeutic area: Oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA	Efficacy/effectiveness data collection	External RWD controls (benchmark/natural history)	Retrospective RWD cohort	Electronic health records (EHRs)	Overall response rate (ORR)

(Continues)

TABLE 2 (Continued)

Regulatory information	Effectiveness or safety from RWD/observational approach	RWE/observational study approach approach	RWE design	Sources of RWD	RW primary endpoint(s):
Product: Tazemetostat (Tazverik), Epizyme, 2020 Therapeutic area: Oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA	Efficacy/effectiveness data collection	External RWD controls (direct matching)	Hybrid RWD cohort (prospective + retrospective)	Site-based chart data	Real-world overall response rate (rwORR)
Product: Tazemetostat (Tazverik), Epizyme, 2020 Therapeutic area: Oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA	Efficacy/effectiveness data collection	External RWD controls (benchmark/natural history)	Retrospective RWD cohort	Electronic health records (EHRs)	Overall response rate (ORR), progression-free survival (PFS), overall survival (OS)
Product: Tisagenlecleucel (Kymriah), Novartis, FDA 2017 EMA 2018 Therapeutic area: Oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: EMA	Safety and efficacy/effectiveness data collection	External RWD controls (direct matching)/ External controls (literature/prior trials)	Retrospective RWD cohort	Prior clinical trials, Electronic health records (EHRs), Registries	Response rate, historical context, overall survival (OS), objective response (OR), complete response (CR)
Product: Uridine triacetate (Vistogard), Wellstat Therapeutics, 2015 Therapeutic area: Oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA	Safety and efficacy/effectiveness data collection	External controls (literature/ prior trials)	Other (literature review, prior trials, etc.): Retrospective literature review (historical case reports)	Literature	Survival rate
Product: Selinexor (Xpovio), Karyopharm Therapeutics, 2019 Therapeutic area: Oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA	Efficacy/effectiveness data collection	External RWD controls (direct matching)	Retrospective RWD cohort	Electronic health records (EHRs)	Overall survival (OS)
Product: Blinatumomab (Blincyto), Amgen, FDA 2018 Therapeutic area: Oncology Regulatory use type and purpose: Label expansion Regulatory Agency: FDA	Efficacy/effectiveness data collection	External RWD controls (direct matching)	Retrospective RWD cohort	Registries	Hematologic relapse-free survival (HRFS)
Product: Avapritinib (Ayvakit), Blueprint Medicines, 2022 Therapeutic area: Non-oncology Regulatory use type and purpose: Label expansion Regulatory Agency: EMA	Efficacy/effectiveness data collection	External RWD controls (direct matching)	Retrospective RWD cohort	Site-based chart data	Overall survival (OS)

TABLE 2 (Continued)

Regulatory information	Effectiveness or safety from RWD/observational approach	RWE/observational study approach approach	RWE design	Sources of RWD	RW primary endpoint(s):
Product: Uridine triacetate (Xuriden), Wellstat Therapeutics, 2015 Therapeutic area: Non-Oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA	Efficacy/effectiveness data collection	External controls (literature/prior trials)	Other (literature review, prior trials, etc.): Case studies of 18 patients	Literature	Hematologic parameter improvement
Product: Alglucosidase alfa (Myozyme), Genzyme, 2006 Therapeutic area: Non-oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA/EMA	Efficacy/effectiveness data collection	External RWD controls (direct matching)	Retrospective RWD cohort	Site-based chart data	Survival
Product: Antithrombin (recombinant), ATryn, 2009 Therapeutic area: Non-oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA	Efficacy/effectiveness data collection	External RWD controls (direct matching)	Prospective RWD cohort	Site-based chart data	Thromboembolic event incidence
Product: Asfotase alfa (Strensiq), Alexion Pharmaceuticals, 2015 Therapeutic area: Non-oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA	Efficacy/effectiveness data collection	External RWD controls (direct matching)	Retrospective RWD cohort	Electronic health records (EHRs)	Overall survival (OS)
Product: Cerliponase alfa (Brineura), BioMarin Pharmaceutical, 2017 Therapeutic area: Non-oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA/EMA	Efficacy/effectiveness data collection	External RWD controls (direct matching)	Retrospective RWD cohort	Registries, Other (Research database)	CLN2 Clinical Rating Scale motor domain changes
Product: Cholic acid (Cholbam), Asklepion Pharmaceuticals, 2015 Therapeutic area: Non-oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA	Safety and efficacy/effectiveness data collection	External controls (literature/prior trials)	Other (literature review, prior trials, etc.): Literature review	Literature	Growth, survival, cholestatic marker reduction

(Continues)

TABLE 2 (Continued)

Regulatory information	Effectiveness or safety from RWD/observational approach	RWE/observational study approach approach	RWE design	Sources of RWD	RW primary endpoint(s):
Product: Defibrotide sodium (Defitelio), Jazz Pharmaceuticals, 2016 Therapeutic area: Non-oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA	Efficacy/effectiveness data collection	External RWD controls (direct matching)	Retrospective RWD cohort	Site-based chart data, Registries	Hematopoietic stem cell transplantation (HSCT) 100-day survival rate
Product: Eteplirsen (Exondys), Sarepta, 2016 Therapeutic area: Non-oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA	Efficacy/effectiveness data collection	External RWD controls (direct matching)	Retrospective RWD cohort	Registries	6-Minute Walk Test (6MWT) change
Product: Fish oil triglycerides injectable emulsion (Omegaven), Fresenius Kabi, 2019 Therapeutic area: Non-oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA	Safety and Efficacy/effectiveness data collection	External RWD controls (direct matching)	Retrospective RWD cohort	Site-based chart data	Age-adjusted body weight change
Product: Hepatitis B immune globulin intravenous (Human) (HepaGam B), Cangene Corp, 2012 Therapeutic area: Non-oncology Regulatory use type and purpose: Label expansion Regulatory Agency: FDA	Efficacy/effectiveness data collection	External RWD controls (direct matching)	Retrospective RWD cohort	Site-based chart data	Hepatitis B Virus (HBV) recurrence proportion
I Product: vacaftor (Kalydeco), Vertex, 2020 Therapeutic area: Non-oncology Regulatory use type and purpose: Label expansion Regulatory Agency: EMA	Efficacy/effectiveness data collection	External RWD controls (direct matching)	Retrospective RWD cohort	Registries	Lung function improvement
Product: Lepirudin (Refludan), Hoechst Marion Roussel, 1998 FDA, 1997 EMA Therapeutic area: Non-oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA/EMA	Efficacy/effectiveness data collection	External RWD controls (direct matching)	Retrospective RWD cohort	Registries	Death rates, limb amputations, new Thromboembolic Complications (TEC), bleeding rate
Product: Nifurtimox (Lampit), Bayer, 2020 Therapeutic area: Non-oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA	Efficacy/effectiveness data collection	External controls (literature/ prior trials)	Retrospective RWD cohort	Literature, Prior clinical trials	Seroconversion-based cure rates

TABLE 2 (Continued)

Regulatory information	Effectiveness or safety from RWD/observational approach	RWE/observational study approach approach	RWE design	Sources of RWD	RW primary endpoint(s):
Product: Nusinersen (Spinraza), Biogen, 2016 FDA, 2017 EMA Therapeutic area: Non-oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA/EMA	Safety and Efficacy/effectiveness data collection	External controls (literature/prior trials)	Retrospective RWD cohort	Literature	Motor milestone improvement
Product: Onasemnogene abeparvovec-xioi (Zolgensma), AveXis EU, 2019 FDA, EMA 2020 Therapeutic area: Non-oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA/EMA	Safety and Efficacy/effectiveness data collection	External RWD controls (direct matching)	Retrospective RWD cohort	Registries, Other (Research database)	Survival rate, motor function, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) scores
Product: Pretomanid (Dovprela), TB Alliance 2019 Therapeutic area: Non-oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA	Efficacy/effectiveness data collection	External RWD controls (direct matching)	Other (literature review, prior trials, etc.): Literature review	Registries, Literature	Success rate
Product: Risdiplam (Evrysdi), Genentech, 2020 Therapeutic area: Non-oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA	Efficacy/effectiveness data collection	External controls (literature/prior trials)	Retrospective RWD cohort	Literature	Type 1 spinal muscular atrophy (SMA) unsupported sitting demonstration
Product: Selumetinib (Koselugo), AstraZeneca, 2020 Therapeutic area: Non-oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA	Efficacy/effectiveness data collection	External RWD controls (benchmark/natural history)	Retrospective RWD cohort	Prospective data collection	Observed response rate
Product: Strimvelis, GlaxoSmithKline, 2016 Therapeutic area: Non-oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: EMA	Safety and Efficacy/effectiveness data collection	External RWD controls (direct matching)	Retrospective RWD cohort	Registries	3-year post-gene therapy survival

(Continues)

TABLE 2 (Continued)

Regulatory information	Effectiveness or safety from RWD/observational approach	RWE/observational study approach approach	RWE design	Sources of RWD	RW primary endpoint(s):
Product: Triheptanoin (Dojolvi), Ultragenyx Pharmaceuticals Inc, 2020 Therapeutic area: Non-oncology Regulatory use type and purpose: Original marketing application approval Regulatory Agency: FDA	Efficacy/effectiveness data collection	External RWD controls (direct matching)	Retrospective RWD cohort	Other (Research database)	Annualized major cardiovascular event (MCE) rate
Product: Catridecacog (NovoThirteen), Novo Nordisk, 2020 Therapeutic area: Non-oncology Regulatory use type and purpose: Label expansion Regulatory Agency: EMA	Safety and Efficacy/effectiveness data collection	External RWD controls (benchmark/natural history)	Retrospective RWD cohort	Registries	Adverse drug reaction (ADR) incidence
Product: Emicizumab (Hemlibra), Roche, 2019 Therapeutic area: Non-oncology Regulatory use type and purpose: Label expansion Regulatory Agency: EMA	Safety and efficacy/effectiveness data collection	External RWD controls (direct matching)	Retrospective RWD cohort	Electronic health records (EHRs), Registries	Bleed number and type

Provide primary evidence with RWE

RWE and other related observational approaches were used as the primary evidence in 53.6% ($n=17$) of use cases in the regulatory evaluations. Out of these, 23.5% ($n=4$) were in the field of oncology. Among the 17 cases, 53% ($n=9$) involved original marketing applications, while the remaining 35% ($n=6$) supported label expansions, and 12% ($n=2$) supported label modifications.

In 76.5% ($n=13$), RWE or observational approach served as primary evidence without conducting new clinical trials. These cases utilized published data from patients treated with the product from a different pharmaceutical manufacturer, foreign postmarketing data, or retrospective RWD cohorts in label expansion or modification. Additionally, data from expanded access programs were used in three cases. In one case, (3.6%), RWE was integrated as part of a randomized trial with pragmatic elements.

For example, Cetuximab (Erbitux) use case utilized RWE for a label modification, relying on retrospective RWD collected from electronic health records. Similarly, etravirine (Intelence) use case utilized RWE from registries for label expansion, focused on studying birth defects as the primary outcome. Another example is paliperidone palmitate (Invega Sustenna), which employed a prospective trial with RWD/pragmatic elements for a label expansion, with treatment failure as the primary outcome (Table S2).

RWE use cases deemed not supportive

Our study described 13 cases with insufficient support from submitted RWE due to various limitations as specified in regulatory review documents (Table 3). Major common themes of limitations included small sample size, selection bias, missing data, misclassifications, and confounding. In addition, certain studies provided inadequate information about data quality, endpoint assessment validity, and design choices in their protocols. Others had limitations in matching closely to trial populations, such as inclusion/exclusion criteria, complicating the determination of whether observed differences in clinical outcomes resulted from baseline imbalances in study populations. Some studies failed to report essential design elements, including study period and inclusion/exclusion criteria, raising concerns about generalizability, potential selection bias, and confounding bias.

For example, entrectinib (Rozlytrek) and erdafitinib (Balversa) use cases used EHR data to support single-arm trials but encountered small sample sizes, selection bias, missing data, and misclassifications. Polatuzumab vedotin-piiq (Polivy) and ivacaftor/tezacaftor/elexacaftor

TABLE 3 Real-world evidence use cases with specified methodological concerns during regulatory review.

Application information	Specified limitations	Selected reviewer comments directly from regulatory documents (Notes)
Product: Entrectinib (Rozlytrek), Genentech, 2019 Indication: Adult patients with metastatic non-small cell lung cancer (NSCLC) Regulatory Agency: FDA Regulatory Use Type: Original marketing application approval Purpose for RWD Use: Support single-arm trial(s) Sources of RWD: Electronic health records (EHRs)	• Small sample, • Selection bias • Missing data, • Posthoc analysis • Generalizability concern	• "DEPI concluded that the crizotinib arm (RWD control) is unlikely to be generalizable to the entire population of patients with ROS1-positive NSCLC" • "Differentially implemented study eligibility criteria, resultant differences in baseline criteria, and limitations in statistical modeling due to low sample size make it difficult to determine what proportion of the observed differences in rates of clinical outcomes are due to imbalances in study populations at baseline (i.e., selection bias) vs. differential treatment effects of the study drugs (including RWD control.)"[57]
Product: Erdafitinib (Balversa), Janssen, 2019 Indication: Adult patients with urothelial carcinoma Regulatory Agency: FDA Regulatory Use Type: Original marketing application approval Purpose for RWD Use: Support single-arm trial(s) Sources of RWD: Electronic health records (EHRs)	• Small sample • Selection bias • Misclassification • Missing data	• "Given the inherent subjectivity and variable application of real-world radiologic assessment, the FDA sent an IR to obtain patient-level clinical and radiologic response narratives. The FDA review of data submitted in response revealed that two of the SD (stable disease) patients originally classified as having a Real-World Best Tumor Response (rwBTR) of SD had incomplete restaging to support an assessment of SD at any point."[43]
Product: Polatuzumab vedotin-piiq (Polivy), Genentech, 2019 Indication: In combination with bendamustine and a rituximab product for the treatment of adult patients with relapsed or refractory DLBCL Regulatory Agency: FDA Regulatory Use Type: Original marketing application approval Purpose for RWD Use: Provide supplementary data to RCT(s): contextualization Sources of RWD: Literature	• Selection bias • Inadequate protocol • Mismatched population	• "In the control arm, the ORR of 25% is approximately half that described in the literature on BR (bendamustine + rituximab) in rel/ref DLBCL"[44]
Product: Selinexor (Xpovio), Karyopharm Therapeutics, 2019 Indication: Adults with relapsed or refractory multiple myeloma Regulatory Agency: FDA Regulatory Use Type: Original marketing application approval Purpose for RWD Use: Support single-arm trial(s) Sources of RWD: Electronic health records (EHRs)	• Small sample • Immortal time bias • Selection bias • Misclassification • Confounding • Missing data	• "Differences in selection criteria between the study arms systematically ensure that the STORM cohort will have longer expected OS compared with FHAD (RWD) cohort." • "Systematic differences in how the index date was defined may have resulted in biased results."[42]
Product: Ivacaftor/tezacaftor/elexacaftor (Kaftrio), Vertex, 2019 Indication: Treatment in CF patients aged 12 and above Regulatory Agency: EMA Regulatory Use Type: Original marketing application approval Purpose for RWD Use: Provide supplementary data to RCT(s): To confirm efficacy in specific subpopulations Sources of RWD: Registries	• Selection bias, • Misclassification • Confounding • Missing data	• "Bearing in mind the limitations and questions arising from the registry data, the magnitude of the additional response from treatment with VX445/TEZ/IVA over prior CFTR therapies is limited." • "It is however agreed that effect size estimates in these real-world analyses are not directly comparable to results from a clinical study in which data are collected in a controlled setting."[58]
Product: Methotrexate (Nordimet), Nordic Group B.V., 2019 Indication: Treatment of mild to moderate Crohn's disease either alone or in combination with corticosteroids in patients refractory or intolerant to thiopurines Regulatory Agency: EMA Regulatory Use Type: Label expansion Purpose for RWD Use: Provide supplementary data to RCT(s): Showing efficacy for methotrexate in Crohn's Disease Sources of RWD: Literature, Prior clinical trials	• Selection bias • Small sample	• "Patients included in these main studies do not represent the proposed population to be included in the indication, that is, mild to moderate Crohn's disease either alone or in combination with corticosteroids in patients refractory or intolerant to thiopurines." • "Based on such heterogeneous data, no conclusions can be drawn for dosage, route of administration, and CD Assessment report in the pediatric population. Consequently, the CHMP concluded that the use of Nordimet for treatment of CD in the pediatric population is not recommended."[59]

(Continues)

TABLE 3 (Continued)

Application information	Specified limitations	Selected reviewer comments directly from regulatory documents (Notes)
Product: Emicizumab (Hemlibra), Roche, 2019 Indication: Routine prophylaxis of bleeding episodes in adults and children with hemophilia A with or without factor VIII inhibitors Regulatory Agency: EMA Regulatory Use Type: Label expansion Purpose for RWD Use: Support single-arm trial(s) Sources of RWD: Electronic health records (EHRs), Registries	• Unfair interpatient comparison	• "A comparison of real-world experience vs. experience in clinical studies is not considered a 'fair comparison' upon which to make clinical/scientific judgment"[60]
Product: Tazemetostat (Tazverik), Epizyme, 2020 Indication: Adults and pediatric patients ages 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection Regulatory Agency: FDA Regulatory Use Type: Original marketing application approval Purpose for RWD Use: Support single-arm trial(s) Sources of RWD: Site-based chart data	• Selection bias • Inadequate protocol • Mismatched population	• "An observational study whose intent is to serve as a historical control for single-arm data should be designed such that the patient populations to be compared in the analyses are as similar as possible." • "The protocol should justify choosing different eligibility criteria and give a rationale for why the resulting populations may be assumed to be similar in spite of differences retained" • "The historical study does not specify any methods to evaluate potential confounding variables in the resulting data set."[61]
Product: Tazemetostat (Tazverik), Epizyme, 2020 Indication: Adult patients with relapsed or refractory follicular lymphoma Regulatory Agency: FDA Regulatory Use Type: Original marketing application approval Purpose for RWD Use: Support single-arm trial(s) Sources of RWD: Electronic health records (EHRs)	• Missingness • Generalizability • Misclassification • Selection bias • Confounding	• "The study did not report how the patients' EZH2 (RWD) mutation status, anticancer treatment patterns, tumor responses, disease progress, and vital status were determined and whether they were validated. Potential misclassification may be introduced" • "All outcome analyses were conducted as crude analyses without accounting for potential confounding factors or effect modifiers, thus the internal validity of the study results is questionable" • "Some key design elements such as study period and inclusion and exclusion criteria, were not reported in the study, which raised the concerns about generalizability, potential selection bias and confounding bias"[62]
Product: Triheptanoin (Dojolvi), Ultragenyx Pharmaceuticals Inc, 2020 Indication: Source of calories and fatty acids for the treatment of pediatric and adult patients with molecularly confirmed long-chain fatty acid oxidation disorders (LCFAOD) Regulatory Agency: FDA Regulatory Use Type: Original marketing application approval Purpose for RWD Use: Support single-arm trial(s) Sources of RWD: Other (Research database)	• Selection bias • Missing data • Vague event definitions	• "FDA does not find it acceptable to rely on the open-label, single-arm design chosen for study UX007-CL201 when designs providing more scientific certainty are potentially feasible."[63]
Product: Viltolarsen (Viltepso), NS Pharma, 2020 Indication: Duchenne muscular dystrophy (DMD) Regulatory Agency: FDA Regulatory Use Type: Original marketing application approval Purpose for RWD Use: Provide supplementary data to RCT(s): to compare change from baseline in Time Function Tests, 6MWD and NSAA compared with CINRG Natural history subjects (no placebo arm in clinical trial) Sources of RWD: Site-based chart data	• Imprecise matching • Selection bias	• "The applicant's argument lends no credence in establishing clinical benefit with such comparison, given the imprecision of population matching due to lack of control of all known and unknown biases and selection bias of the retrospectively collected natural history control population."[64]

TABLE 3 (Continued)

Application information	Specified limitations	Selected reviewer comments directly from regulatory documents (Notes)
Product: Fam-trastuzumab deruxtecan-nxki (Enhertu), Daiichi Sankyo, FDA 2019 EMA 2021 Indication: Unresectable or metastatic HER2-positive breast cancer (HER2+) Regulatory Agency: FDA; EMA Regulatory Use Type: Original marketing application approval Purpose for RWD Use: Support single-arm trial(s) Sources of RWD: Electronic health records (EHRs), Literature	• Selection bias • Uncontrolled confounders	• "Patients in the control (RWD) and experimental could differ in important prognostic factors despite matching, this is considered data of an exploratory nature." • "For the Unicancer study, selection was based on a postbaseline variable (tumor scan) which may introduce selection bias." • "A full comparison of baseline characteristics between patients in U201 and the Unicancer matched cohort could not be provided."[65]
Product: Idecabtagene vicleucel (Abecma), Celgene, 2021 Indication: Relapsed or refractory multiple myeloma after at least 4 prior lines of therapy Regulatory Agency: FDA; EMA Regulatory Use Type: Original marketing application approval Purpose for RWD Use: Support single-arm trial(s) Sources of RWD: Electronic health records (EHRs), Literature	• Selection bias • Follow-up & endpoint differences	• "There was a significant amount of missing data for baseline prognostic features such as ECOG performance status, revised ISS, cytogenetics, and LDH in the eligible RRMM (RWD) cohort which required imputation." • "The results of NDS-MM-003 (RWD) are based on data that is collected and merged from multiple sources such as registries, clinical trial sites, and external research databases. Differences in follow-up and response assessment of subjects from these different sources may impact the interpretability of the study results."[66]

(Trikafta) use cases leveraged literature and registries for supplementary RCT data, facing challenges with selection bias, data quality, and endpoint validity. Selinexor (Xpovio) use case, supported by EHR data, faced issues associated with small sample sizes, multiple biases such as immortal bias, and misclassification bias. Methotrexate (Rheumatrex) use case, using literature and previous clinical trials, faced sample size constraints and selection bias. Emicizumab (Hemlibra) and tazemetostat (Tazverik) use cases utilized EHR and registries for single-arm trials, dealing with issues in interpatient comparisons, data quality, and potential other biases. Triheptanoin (Dojolvi) use case, using a research database, was subject to several limitation including selection bias, missing data, and unclear event definitions. Viltolarsen (Viltepso) use case, employing site-based chart data for supplementary RCT data, faced population matching and selection bias challenges. Fam-trastuzumab deruxtecan-nxki (Enhertu) and idecabtagene vicleucel (Abecma) use cases used EHR and literature and also faced challanges with selection bias, confounding, and differences in endpoint assessment (Table 3).

DISCUSSION

In this targeted review, we identified use cases that utilized RWE and other related observational approaches in the context of preapproval regulatory decision-making. Through a comprehensive literature search and screening process, we characterized relevant use cases identified from 2016 to 2022. These use cases were primarily utilized to support regulatory submissions for original marketing application approval, label expansion, and label modification. The findings illustrated a broad distribution of RWE application across different therapeutic areas, with a significant representation in oncology, involving both pediatrics and adult cases. Over the past few years, the use of real-world external controls in interpretation of results from single-arm trials has gained prominence in supporting regulatory decisions. This was evident in our review as well, where nearly half of identified use cases involved an external control arm approach. However, the review also demonstrated a variety of other approaches including supplementing RCTs and providing primary evidence in lieu of clinical trial data. Moreover, these use cases included both retrospective and prospective designs, and the data sources encompassed a wide range of options, including EHRs, claims, registries, and literature.

Our study findings complement prior reports showing the increasing utility of RWE and other related approaches in regulatory submissions and decision making. For example, recent reviews showed a growing proportion of approvals by the FDA that incorporated RWE in assessment, with evidence on safety or effectiveness influencing final decisions. In addition, another review also concluded that there is an increasing use of RWE to support the evaluation of marketing authorization applications and extensions of indications submitted to the EMA.[41]

While there is now a wide range of RWE applications/designs in preapproval regulatory settings, the study findings also underscore that there are methodological issues associated with RWE designs in certain use cases (e.g.,

selection bias, misclassification, and data omissions), as highlighted in regulatory review documents. For instance, when RWD is used to create external control arms, some use cases lacked critical inclusion and exclusion criteria from the corresponding single-arm trial that are often not recorded or are subject to a large degree of missingness in routine healthcare data sources. For example, in one use case (Selinexor), the RWD external control arm used in support of single-arm control trial lacked critical life expectancy data (life expectancy for at least <4 months) required by the clinical trial's exclusion criteria. This oversight led to regulatory criticism as described in the regulatory review package.[42] Similarly, the use of RWE in the Erdafitinib trial encountered issues with data misclassification and missing information, prompting the FDA to require more detailed patient data.[43] Further, in the Polatuzumab vedotin-piiq (Polivy) study, discrepancies between real-world response rates and those reported in the literature indicated significant selection bias and population mismatches.[44] These methodological challenges in RWE studies highlight the urgent need for methodological enhancements and frameworks, that are designed to strengthen the reliability and applicability of RWD/E in regulatory decisions.[45]

The US FDA activities on RWE (e.g., RWE framework, workshops, and guidance documents), as a result of the 21st Century Cures Act,[4] are intended to accelerate medical product development utilizing fit-for-purpose innovative designs. There are multifaceted cross-sector initiatives and methodology development efforts to facilitate and improve methodological issues and gaps in RWD/E for regulatory decision-making purposes. These include and are not limited to data quality assessments (e.g., cross-sector collaborative efforts by Duke Margolis Institute for Health Policy), feasibility assessment frameworks, methods on missing data and unmeasured confounding, and sensitivity analyses including quantitative bias analyses.[7,46,47]

There is also a growing trend toward leveraging artificial intelligence (AI) and machine learning (ML) tools, including ML extraction techniques, and improving biases related to missing data. An example application (within the context of Oncology disease areas) is the emulation of the Eastern Cooperative Oncology Group (ECOG) performance status (PS) through EHRs. By utilizing detailed patient demographic, treatment, and clinical data, it can be feasible to enhance the accuracy of ECOG PS predictions.[48] As our review demonstrated, there are also emerging hybrid RCT designs supported by RWD/E. By augmenting clinical trial control data with external datasets, such hybrid trial designs potentially offer adaptability to a wider range of patient populations and treatments. However, data quality and standardization efforts are imperative to ensure consistent and reliable data capture across different settings, especially in multisource design settings.[3,49,50] A pertinent case study of a hybrid study design is for MDNA55, an interleukin-4 (IL-4)-guided toxin developed for recurrent glioblastoma (rGBM). The sponsor utilized an innovative open-label hybrid control design for its phase III registration trial targeting rGBM patients without 1DH1/1DH2 gene mutations. Highlighting the promise of these emerging designs, the FDA has indicated its willingness to consider interim analysis if certain criteria are met.[51]

In terms of endpoints, our study revealed that the RWE use cases more often utilized “hard endpoints” such as overall survival endpoint in oncology cases. Renowned organizations, like Friends of Cancer Research and the Duke-Margolis Center for Health Policy, are emphasizing the importance of validation and development of diverse endpoints to gain a comprehensive understanding of treatment effects.[52] For example, within Oncology, there is a growing number of initiatives to explore and assess the utility and validity of non-overall survival (non-OS) endpoints (e.g., real-world progression-free survival, time to next treatment).

Overall, efforts on improving the quality and validity of RWD and real-world endpoints are positive steps in support of advancing trials with innovative designs, for example, hybrid clinical trial designs and trials with patient-generated health data. Collaborations across sectors and disciplines are essential to enhance RWD quality and to ensure that RWE studies meet strict regulatory standards.[53–55] In addition to data quality, transparent discussions with health authority agencies on study proposals and feasibility assessments/data quality checks are also very critical in the regulatory acceptability of RWE study findings.[56]

Limitations

In our study, we focused solely on preapproval setting applications of RWE and related observational approaches, but it is important to acknowledge the emerging applications of the utility of RWD/RWE in other settings. For example, the FDA has recently released guidance on diversity and inclusion, highlighting the necessity to build diverse trials. Although this is a positive development, it is important to recognize that patient diversity is infinite, and RCTs alone may not always be best suited to answer research questions in all subgroups or heterogeneity of treatment effects.[50] A new FDA guidance document published recently on “Post marketing Approaches to Obtain Data on Populations Underrepresented in Clinical Trials for Drugs and Biological Products” discusses several non-RCT options, including single-arm trials, RWE,

and pooled studies, among others.[49] This indicates opportunities for the utility of RWE in the postmarketing setting beyond Post-Authorization Safety Studies (PASS)/Post-Authorization Efficacy Studies (PAES) to support evidence generation in populations underrepresented in clinical trials for drugs and biological products.

Moreover, it is important to note that the total number of use cases identified does not necessarily represent the entirety of use cases employed in regulatory decisions with RWE. This review primarily synthesized information in a structured manner from previously published reviews and other publications. Thus, our findings are primarily dependent on the availability and accessibility of these resources. Consequently, some use cases may not have been mentioned in the literature we reviewed or may be used in practice but not formally documented. While this study provides a comprehensive overview of documented use cases, it may not capture the full scope of RWE use in regulatory decisions.

CONCLUSION

This review highlights the utilization of various RWE approaches and designs in regulatory application for new indications and label expansions across multiple therapeutic areas. While nearly half of identified use cases involved an external control arm approach, the review also demonstrated a variety of other approaches including supplementing RCTs and providing primary evidence in lieu of clinical trial data. Multifaceted cross-sector efforts including collaborative pilots are needed to further improve the quality and utility of RWE in both pre and postapproval settings, especially on emerging designs and approaches.

AUTHOR CONTRIBUTIONS

GAH and MB wrote the manuscript; GAH, XL, and MB designed the research; GAH, XL, and MB performed the research; GAH, XL, VA, AGW, and MB analyzed the data.

FUNDING INFORMATION

No specific grant funding was provided for this project. GAH, XL, VA, and MB are salaried employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. AGW reports grant/contract from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, consulting fees from Arbor Pharmaceuticals, Novo Nordisk, Ipsen Pharmaceuticals, Genentech, Inc., and payment or honoraria from Bayer AG.

CONFLICT OF INTEREST STATEMENT

GAH, XL, VA, and MB are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. XL, VA, and MB own stock in Merck & Co., Inc., Rahway, NJ, United States. AGW reports grant/contract from Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, consulting fees from Arbor Pharmaceuticals, Novo Nordisk, Ipsen Pharmaceuticals, Genentech, Inc., and payment or honoraria from Bayer AG. The views and opinions expressed in this article may not necessarily represent the views and opinions of a public or private entity (e.g., agency, government, university, institution, or company).

REFERENCES

1. Bothwell LE, Greene JA, Podolsky SH, Jones DS. Assessing the gold standard–lessons from the history of RCTs. *N Engl J Med*. 2016;374(22):2175-2181. doi:10.1056/NEJMms1604593
2. Basch E, Schrag D. The evolving uses of "real-world" data. *JAMA*. 2019;321(14):1359-1360. doi:10.1001/jama.2019.4064
3. Burcu M, Dreyer NA, Franklin JM, et al. Real-world evidence to support regulatory decision-making for medicines: considerations for external control arms. *Pharmacoepidemiol Drug Saf*. 2020;29(10):1228-1235. doi:10.1002/pds.4975
4. An act to accelerate the discovery, development, and delivery of 21st century cures, and for other purposes. Published online December 13, 2016. Accessed March 23, 2023. https://www.govinfo.gov/app/details/PLAW-114publ255
5. Bakker E, Plueschke K, Jonker CJ, Kurz X, Starokozhko V, Mol PGM. Contribution of real-world evidence in European medicines Agency's regulatory decision making. *Clin Pharmacol Therapeut*. 2023;113(1):135-151. doi:10.1002/cpt.2766
6. Burns L, Roux NL, Kalesnik-Orszulak R, et al. Real-world evidence for regulatory decision-making: guidance from around the world. *Clin Ther*. 2022;44(3):420-437. doi:10.1016/j.clinthera.2022.01.012
7. Berger M, Daniel G, Frank K, et al. A framework for regulatory use of real-world evidence. White Paper Prepared by the Duke Margolis Center for Health Policy. 2017;6.
8. Rudrapatna VA, Butte AJ. Opportunities and challenges in using real-world data for health care. *J Clin Invest*. 2020;130(2):565-574. doi:10.1172/JCI129197
9. FDA Decision Alerts | What is FDA Approved. Aetion. Accessed May 15, 2023. https://aetion.com/resources/fda-decision-alerts/
10. EFPIA Homepage. Accessed May 15, 2023. https://www.efpia.eu/
11. Biotechnology Innovation Organization (BIO). Accessed May 15, 2023. https://www.bio.org/
12. Drugs@FDA: FDA-Approved Drugs. Accessed May 15, 2023. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm
13. European Medicines Agency (EMA). European public assessment reports: background and context. Published September 27, 2018. Accessed May 15, 2023. https://www.ema.europa.eu/en/medicines/what-we-publish-when/european-public-assessment-reports-background-context
14. Park MS. Regulatory innovation for expansion of indications and pediatric drug development. *Transl Clin Pharmacol*. 2018;26(4):155-159. doi:10.12793/tcp.2018.26.4.155
15. Cave A, Kurz X, Arlett P. Real-world data for regulatory decision making: challenges and possible solutions for Europe. *Clin Pharmacol Ther*. 2019;106(1):36-39. doi:10.1002/cpt.1426

16. Davi R, Mahendraratnam N, Chatterjee A, Dawson CJ, Sherman R. Informing single-arm clinical trials with external controls. *Nat Rev Drug Discov*. 2020;19(12):821-822. doi:10.1038/d41573-020-00146-5
17. Purpura CA, Garry EM, Honig N, Case A, Rassen JA. The role of real-world evidence in FDA-approved new drug and biologics license applications. *Clin Pharmacol Therapeut*. 2022;111(1):135-144. doi:10.1002/cpt.2474
18. Jandhyala R. The effect of adding real-world evidence to regulatory submissions on the breadth of population indicated for rare disease medicine treatment by the European medicines agency. *J of Pharm Policy and Pract*. 2022;15(1):36. doi:10.1186/s40545-022-00433-z
19. Izem R, Buenconsejo J, Davi R, Luan JJ, Tracy L, Gamalo M. Real-world data as external controls: practical experience from notable marketing applications of new therapies. *Ther Innov Regul Sci*. 2022;56(5):704-716. doi:10.1007/s43441-022-00413-0
20. Jaksa A, Louder A, Maksymiuk C, et al. A comparison of 7 oncology external control arm Case studies: critiques from regulatory and health technology assessment agencies. *Value Health*. 2022;25(12):1967-1976. doi:10.1016/j.jval.2022.05.016
21. Mishra-Kalyani PS, Amiri Kordestani L, Rivera DR, et al. External control arms in oncology: current use and future directions. *Ann Oncol*. 2022;33(4):376-383. doi:10.1016/j.annonc.2021.12.015
22. Derman BA, Belli AJ, Battiwalla M, et al. Reality check: real-world evidence to support therapeutic development in hematologic malignancies. *Blood Rev*. 2022;53:100913. doi:10.1016/j.blre.2021.100913
23. Arondekar B, Duh MS, Bhak RH, et al. Real-world evidence in support of oncology product registration: a systematic review of new drug application and biologics license application approvals from 2015–2020. *Clin Cancer Res*. 2022;28(1):27-35. doi:10.1158/1078-0432.CCR-21-2639
24. Costa E, Girotti S, Pauro F, Leufkens HGM, Cipolli M. The impact of FDA and EMA regulatory decision-making process on the access to CFTR modulators for the treatment of cystic fibrosis. *Orphanet J Rare Dis*. 2022;17(1):188. doi:10.1186/s13023-022-02350-5
25. Eskola SM, Leufkens HGM, Bate A, De Bruin ML, Gardarsdottir H. Use of real-world data and evidence in drug development of medicinal products centrally authorized in Europe in 2018–2019. *Clin Pharmacol Therapeut*. 2022;111(1):310-320. doi:10.1002/cpt.2462
26. Girman CJ, Ritchey ME, McNeill AM, Sundell KA, Meyer RJ. Demonstrating that real world evidence is fit-for-purpose to support labeling: parallels to patient reported outcomes in the pursuit of labeling claims. *Ther Innov Regul Sci*. 2021;55(3):561-567. doi:10.1007/s43441-020-00252-x
27. De S, Larson L, Kelly K, Hanson B, Mack CD. Leveraging real-world evidence: a paradigm shift in regulation. *J Orthop Trauma*. 2021;35:S13-S16. doi:10.1097/BOT.0000000000002039
28. Franklin JM, Liaw KL, Iyasu S, Critchlow CW, Dreyer NA. Real-world evidence to support regulatory decision making: new or expanded medical product indications. *Pharmacoepidemiol Drug Saf*. 2021;30(6):685-693. doi:10.1002/pds.5222
29. Gross AM. Using real world data to support regulatory approval of drugs in rare diseases: a review of opportunities, limitations & a case example. *Curr Probl Cancer*. 2021;45(4):100769. doi:10.1016/j.currproblcancer.2021.100769
30. Schmidli H, Häring DA, Thomas M, Cassidy A, Weber S, Bretz F. Beyond randomized clinical trials: use of external controls. *Clin Pharmacol Ther*. 2020;107:806-816. doi:10.1002/cpt.1723
31. Seeger JD, Davis KJ, Iannacone MR, et al. Methods for external control groups for single arm trials or long-term uncontrolled extensions to randomized clinical trials. *Pharmacoepidemiol Drug Saf*. 2020;29:1382-1392. doi:10.1002/pds.5141
32. Jaksa A, Vondeling G, Martin L, Draganigos A, Louder A, Rosenlund M. ON3 comparison of external control arm (ECA) critiques in regulatory and health technology assessment (HTA) oncology submissions. *Value Health*. 2020;23:S408. doi:10.1016/j.jval.2020.08.063
33. Raphael MJ, Gyawali B, Booth CM. Real-world evidence and regulatory drug approval. *Nat Rev Clin Oncol*. 2020;17(5):271-272. doi:10.1038/s41571-020-0345-7
34. Seifu Y, Gamalo-Siebers M, Barthel FMS, et al. Real-world evidence utilization in clinical development reflected by US product labeling: statistical review. *Ther Innov Regul Sci*. 2020;54(6):1436-1443. doi:10.1007/s43441-020-00170-y
35. Baumfeld Andre E, Reynolds R, Caubel P, Azoulay L, Dreyer NA. Trial designs using real-world data: the changing landscape of the regulatory approval process. *Pharmacoepidemiol Drug Saf*. 2020;29:1201-1212. doi:10.1002/pds.4932
36. Wu J, Wang C, Toh S, Pisa FE, Bauer L. Use of real-world evidence in regulatory decisions for rare diseases in the United States—current status and future directions. *Pharmacoepidemiol Drug Saf*. 2020;29:1213-1218. doi:10.1002/pds.4962
37. Feinberg BA, Gajra A, Zettler ME, Phillips TD, Phillips EG, Kish JK. Use of real-world evidence to support FDA approval of oncology drugs. *Value Health*. 2020;23(10):1358-1365. doi:10.1016/j.jval.2020.06.006
38. Goring S, Taylor A, Müller K, et al. Characteristics of non-randomised studies using comparisons with external controls submitted for regulatory approval in the USA and Europe: a systematic review. *BMJ Open*. 2019;9(2):e024895. doi:10.1136/bmjopen-2018-024895
39. Morant AV, Jagalski V, Vestergaard HT. Characteristics of single pivotal trials supporting regulatory approvals of novel non-orphan, non-oncology drugs in the European Union and United States from 2012 to 2016. *Clin Transl Sci*. 2019;12:361-370. doi:10.1111/cts.12617
40. Hampson G, Towse A, Dreitlein WB, Henshall C, Pearson SD. Real-world evidence for coverage decisions: opportunities and challenges. *Journal of Comparative Effectiveness Research*. 2018;7(12):1133-1143. doi:10.2217/cer-2018-0066
41. U.S. Food and Drug Administration. Use of real-world evidence to support regulatory decision-making for medical devices. Published August 27, 2019. Accessed March 23, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices
42. Xpovio (selinexor). NDA/BLA multi-disciplinary review and evaluation. Published online 2019. Accessed April 15, 2024. Accessed September 5, 2023. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212306Orig1s000MultidisciplineR.pdf
43. Balversa (erdafitinib). Other review(s). Published online April 11, 2019. Accessed April 15, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212018Orig1s000OtherR.pdf

44. Polivy (polatuzumab vedotin-piiq). Clinical review. Published online 2019. Accessed April 15, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212306Orig1s000MultidisciplineR.pdf
45. Acha V, Barefoot B, Garcia AJ, et al. Principles for good practice in the conduct of non-interventional studies: the view of industry researchers. *Ther Innov Regul Sci*. 2023;57(6):1199-1208. doi:10.1007/s43441-023-00544-y
46. Gray CM, Grimson F, Layton D, Pocock S, Kim J. A framework for methodological choice and evidence assessment for studies using external comparators from real-world data. *Drug Saf*. 2020;43(7):623-633. doi:10.1007/s40264-020-00944-1
47. Thorlund K, Duffield S, Popat S, et al. Quantitative bias analysis for external control arms using real-world data in clinical trials: a primer for clinical researchers. *J Comp Eff Res*. 2024;13(3):e230147. doi:10.57264/cer-2023-0147
48. Sadetsky N, Chuo CY, Davidoff AJ. Development and evaluation of a proxy for baseline ECOG PS in advanced non-small cell lung cancer, bladder cancer, and melanoma: an electronic health record study. *Pharmacoepidemiol Drug Saf*. 2021;30(9):1233-1241. doi:10.1002/pds.5309
49. Food and Drug Administration. Postmarketing approaches to obtain data on populations underrepresented in clinical trials for drugs and biological products. Published August 10, 2023. Accessed August 29, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postmarketing-approaches-obtain-data-populations-underrepresented-clinical-trials-drugs-and
50. Segal JB, Varadhan R, Groenwold RHH, et al. Assessing heterogeneity of treatment effect in real-world data. *Ann Intern Med*. 2023;176(4):536-544. doi:10.7326/M22-1510
51. Corp MT. Medicenna Provides MDNA55 rGBM clinical program update following positive end of phase 2 meeting with the U.S. Food and Drug Administration (FDA). *GlobeNewswire News Room*. Published October 15, 2020. Accessed August 29, 2023. https://www.globenewswire.com/news-release/2020/10/15/2109598/0/en/Medicenna-Provides-MDNA55-rGBM-Clinical-Program-Update-Following-Positive-End-of-Phase-2-Meeting-with-the-U-S-Food-and-Drug-Administration-FDA.html
52. Mercon K, Mahendraratnam N, Eckert J. *A Roadmap for Developing Study Endpoints in Real-World Settings*. Margolis Center for Health Policy; 2020.
53. Food and Drug Administration. Considerations for the use of real-world data and real-world evidence to support regulatory decision-making for drug and biological products. 2021 Accessed August 29, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-real-world-data-and-real-world-evidence-support-regulatory-decision-making-drug
54. Food and Drug Administration. Real-World Data: assessing electronic health records and medical claims data to support regulatory decision-making for drug and biological products. 2021 Accessed August 29, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory
55. Food and Drug Administration. Data standards for drug and biological product submissions containing real-world data. 2021 Accessed August 29, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/data-standards-drug-and-biological-product-submissions-containing-real-world-data
56. Wang SV, Schneeweiss S. Data checks before registering study protocols for health care database analyses. *JAMA*. 2024;331(17):1445-1446. doi:10.1001/jama.2024.2988
57. Rozlytrek (entrectinib). Other review(s). Accessed April 16, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212725Orig1s000,%20212726Orig1s000OtherR.pdf
58. Kaftrio epar public assessment report. Accessed April 16, 2024. https://www.ema.europa.eu/en/documents/assessment-report/kaftrio-epar-public-assessment-report_en.pdf
59. Nordimet epar assessment eport ariation. Accessed April 16, 2024. https://www.ema.europa.eu/en/documents/variation-report/nordimet-h-c-3983-ii-0016-epar-assessment-report-variation_en.pdf
60. Hemlibra epar assessment report variation. Accessed April 16, 2024. https://www.ema.europa.eu/en/documents/variation-report/hemlibra-h-c-4406-ii-0002-epar-assessment-report-variation_en.pdf
61. Tazverik (Tazemetostat). Multi-discipline review. 2018 Accessed April 16, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/211723Orig1s000MultidisciplineR.pdf
62. Tazverik (Tazemetostat). Other review(s). Accessed April 16, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213400Orig1s000OtherR.pdf
63. Dojolvi (Triheptanoin). Integrated review. Accessed April 16, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/213687Orig1s000IntegratedR.pdf
64. Viltepso (Viltolarsen). Clinical review. Accessed April 16, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/212154Orig1s000MedR.pdf
65. Enhertu epar public assessment report. Accessed April 16, 2024. https://www.ema.europa.eu/en/documents/assessment-report/enhertu-epar-public-assessment-report_en.pdf
66. Abecma (Idecabtagene vicleucel). Clinical review. Accessed April 16, 2024. https://www.fda.gov/media/147740/download

SUPPORTING INFORMATION

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

How to cite this article: Alipour-Haris G, Liu X, Acha V, Winterstein AG, Burcu M. Real-world evidence to support regulatory submissions: A landscape review and assessment of use cases. *Clin Transl Sci*. 2024;17:e13903. doi:10.1111/cts.13903