HPR170

Real-World Data for External Controls: Insights from EMA Regulatory Submissions

Jun Chen Collet, Jean-Paul Collet, Walid Shouman, Mir Sohail Fazeli
Evidinno Outcomes Research Inc. Vancouver, BC, Canada

Background

- External controls (ECs) derived from real-world data (RWD) are increasingly used to augment analyses of outcomes from single-arm trials submitted to the European Medicines Agency (EMA), providing a practical alternative when randomized control arms are not feasible.
- RWD-derived ECs improve the interpretability of treatment effects by supplying comparative evidence from registries, electronic health records, and other data sources.
- The EMA's recent methodological initiatives[1, 2] indicate growing regulatory openness toward these designs.
- However, variations in study methods and data sources continue to limit consistent regulatory acceptance across submissions.[3]
- Understanding EMA precedents and reviewer feedback is essential to guide evidence planning and ensure that RWD-derived EC generate credible, fit-for-purpose evidence for regulatory decision-making.

Objective

- To examine how RWD has been used to establish EC in EMA regulatory submissions, including:
  - The frequency, context, and therapeutic areas where RWD-derived ECs were applied.
  - The types of data sources and analytical methods used to construct external comparators.
  - EMA reviewers' feedback and regulatory outcomes associated with these submissions.
  - Methodological learnings to guide future use of RWD in developing ECs.

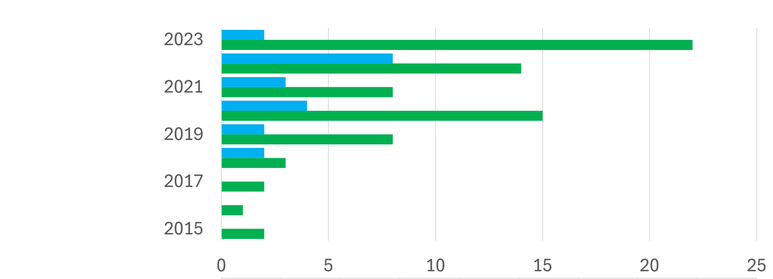
Methods

- **Data sources**: Publicly available European Public Assessment Reports from the EMA website.
- **Selection**: A targeted review of 75 EMA submissions (2015-2023) incorporating RWD was conducted to determine whether RWD was used to develop EC supporting efficacy or comparative effectiveness assessments.
- **Extraction domains**:
  - Product type and indication
  - Regulatory pathway
  - Study design and data source (registry, EHR, chart review, literature synthesis)
  - Regulatory feedback and outcome.
- **Analysis & Synthesis**: Narrative summary and descriptive analysis grouped by therapeutic area and regulatory outcome, with reviewer feedback analyzed to identify key methodological themes influencing regulatory acceptance.

Results

- Among 75 EMA submissions incorporating RWD, 21 were identified as using RWD-derived ECs. (**Figure 1**)

Figure 1. Use of RWD for EC in EMA Submissions



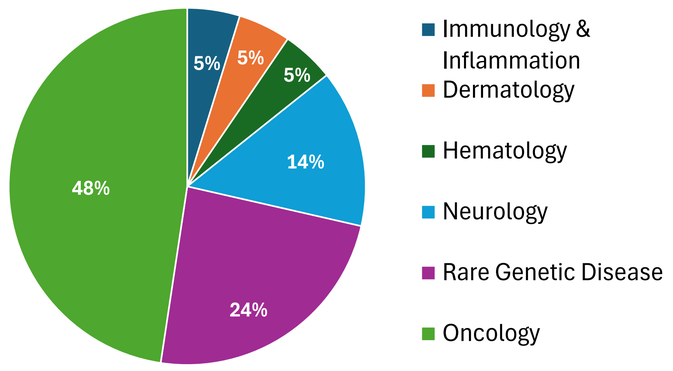
	2015	2016	2017	2018	2019	2020	2021	2022	2023
RWD used to develop EC	0	0	0	2	2	4	3	8	2
Submissions with RWD	2	1	2	3	8	15	8	14	22

Results (Continued)

Therapeutic Area

- Oncology (n = 10, 48%) and rare genetic diseases (n = 5, 24%) accounted for most EMA submissions with RWD-derived ECs, reflecting areas with important unmet therapeutic needs. (**Figure 2**)

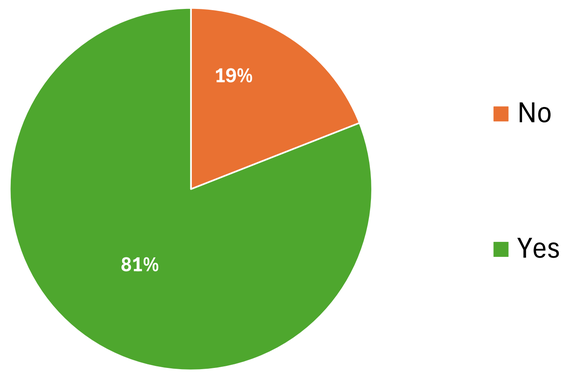
Figure 2: RWD-ECs by therapeutic area (N = 21)



Submission Type

- Among 21 EMA submissions using RWD to form EC, 81% (n = 17) had an orphan designation (**Figure 4**).

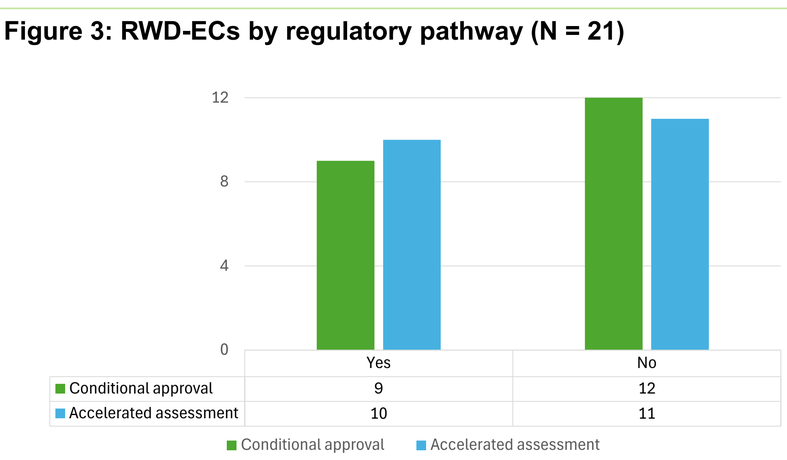
Figure 4: RWD-ECs with orphan designation (N = 21)



Regulatory Pathway

- Among 21 EMA submissions using RWD-derived ECs, 9 (43%) received conditional approval and 10 (48%) underwent accelerated assessment. (**Figure 3**)

Figure 3: RWD-ECs by regulatory pathway (N = 21)



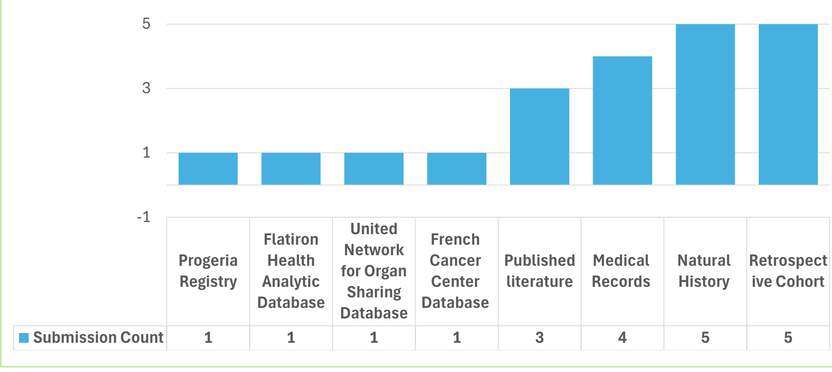
	Yes	No
Conditional approval	9	12
Accelerated assessment	10	11

Conditional approval Accelerated assessment

Data Sources

- Prospective cohort studies to determine the natural history of the condition (n = 5) and retrospective cohort studies (n = 5) were the most common RWD sources used to construct ECs. (**Figure 5**)

Figure 5: Data sources used for RWD-ECs (N = 21)



	Progeria Registry	Flatiron Health Analytic Database	United Network for Organ Sharing Database	French Cancer Center Database	Published literature	Medical Records	Natural History	Retrospective Cohort
Submission Count	1	1	1	1	3	4	5	5

Regulatory Outcomes

- EMA considered RWD-derived ECs supportive in 11 submissions (52%), of limited importance in 3 (14%), and inadequate in 7 (33%).
- EMA reviewers commonly raised concerns about selection bias and baseline uncertain comparability between trial arm and EC populations, residual or unmeasured confounding, and inconsistent outcome definitions across RWD sources.
- **Table 1** provides three examples of RWD-derived ECs with supportive, limited, and inadequate regulatory outcomes.

Table 1: Illustrative EMA case examples demonstrating different regulatory acceptance of RWD-derived ECs

Proprietary Name (Submission #)	Therapeutic Area	RWD Sources	EMA Feedback	Regulatory Outcome
Ebvallo EMA/858618/2022	Immunology & inflammation	Retrospective, observational real-world study	An external comparison using historical controls was conducted between Study ATA129-EBV-302 and the pivotal Study RS002 (2010–2018 cohort). After propensity score matching, tabelecleucel showed a notable overall survival benefit versus standard of care (unadjusted HR = 0.46; adjusted HR ≈ 0.34). Although subject to the inherent limitations of historical comparisons, the findings were considered supportive for contextualizing efficacy.	Supportive on efficacy/safety
Enhertu EMA/2446/2021	Oncology	Metastatic breast cancer database - French multicenter registry	Comparisons with the historical cohort were limited by differences in ORR and PFS definitions and timing, incomplete patient-level data, and uncertainties in population comparability and follow-up, resulting in insufficient evidence to consider the cohort supportive.	RWE cannot be considered supportive. The data is considered of an exploratory nature.
Zolgensma EMA/200482/2020	Rare genetic disease	Natural History Study	Due to limited follow-up and heterogeneity in natural history data, no definitive benefit could be concluded. Completion of Study CL-304 is required as a condition of the conditional marketing authorization, and the applicant committed to further characterize natural history using literature and RESTORE registry data.	Not adequate for decision making

Conclusions

- RWD-derived ECs are gaining prominence in EMA submissions, especially for rare diseases and high unmet need conditions.
- Their successful use depends on robust study designs that emulate target trials, endpoint alignment, and transparent documentation of data provenance, completeness, and analytical assumptions.
- As regulatory expectations evolve, proactive collaboration between sponsors, regulators, and data partners on methodological frameworks, bias mitigation, and validation of RWD sources will be crucial to ensure that the use of ECs provides credible and reproducible evidence to inform regulatory decision.

References

1. Agency EM. Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorization application: Considerations on evidence from single-arm trials. 2024
2. Liu J, Yao M, Wang M, et al. Design, Conduct, and Analysis of Externally Controlled Trials. JAMA Network Open. 2025;8(9):e2530277-e2530277.
3. FDA. Considerations for the Use of Real-World Data and Real-World Evidence to Support Regulatory Decision-Making for Drug and Biological Products - Guidance for Industry. In: CDER C, OCE, ed2023.

Acknowledgments

This study was conducted by Evidinno Outcomes Research Inc. JCC, JPC, WS and MSF report employment with Evidinno Outcomes Research Inc. Authors report no other conflict of interest.

EVIDINNO
EVIDENCE NAVIGATION & SYNTHESIS

Presented at ISPOR Europe 2025; November 9-12; Glasgow, Scotland, UK

Email: mfazeli@evidinno.com