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EMA perspectives on the regulatory contribution of Real-World Data (RWD)

CDDF Annual Conference 2024

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The views expressed in this presentation are personal

The needle is slowing moving

Navigating between

- Randomized controlled trials (RCTs) are irreplaceable
- Real-world data (RWD) can be helpful, sufficient even in some situations
- RWD are the only "real" data (RCTs are artificial)

Towards a balanced position

- Like all data there are limitations, these can be minimised but likely not reduced completely
- Most of the time, evidence better than no evidence; make the best of totality of data sources and use different approaches

Obviously there are many challenges…

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Operational

linked to feasibility, governance and sustainability issues → complicate access and routine use of multiple national data sources with different legal and ethical requirements for sharing data

Technological:

different terminologies, case definitions, data formats, coding systems, quality and content

Methodological:

original purpose of data collection may not be for research → possible missing data different biases/confounders → barrier to acceptability on reliability and validity of RWD

PERSPECTIVES

Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe

Alison Cave[1,*], Xavier Kurz[1] and Peter Arlett[1]

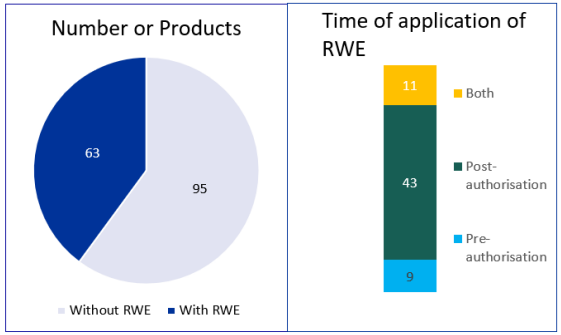
Real-world data (RWD) offers the possibility to derive novel insights on the use and performance of medicines in everyday clinical use, complementing rather than competing with evidence from randomized control trials. While Europe is rich in healthcare data, its heterogeneous nature brings operational, technical, and methodological challenges. We present a number of potential solutions to address the full spectrum of regulatory use cases and emphasize the importance of early planning of data collection.

https://doi.org/10.1002/cpt.1426

RWE in marketing authorisation applications submitted in 2018/2019

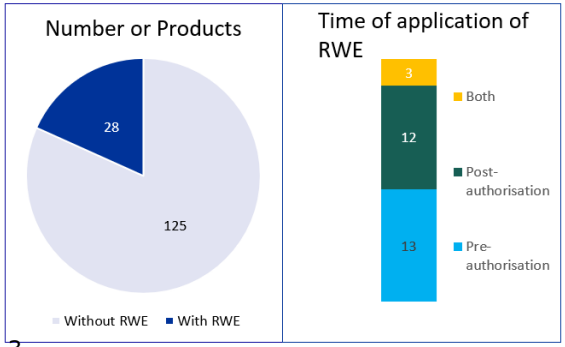
EMA descriptive study Part I: *Flynn R. et al. (2021), Marketing Authorization Applications Made to the European Medicines Agency in 2018–2019: What was the Contribution of Real-World Evidence?. Clin. Pharmacol. Therapeutics*

Initial MA Applications (n=158)



- **40%** (63/158) iMAA included RWD
- Mainly **post**-authorisation

Extensions of indications (n=153)



- **18%** (28/153) EoI included RWD
- Both **pre and post**-authorisation

- Majority of products: **Antineoplastic** and **Immunosuppressants** (35% iMAA and 42% EoI)
- Main RWD sources: **Registries, Hospital data**

Study Part II : Qualitative assessment of the impact of RWE on medicines' regulatory decision-making

Contribution of RWE in EMA's decision making (Study Part II)

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Clinical Pharmacology & Therapeutics

Article | Open Access

Contribution of Real-World Evidence in European Medicines Agency's Regulatory Decision Making

Elisabeth Bakker, Kelly Plueschke, Carla J. Jonker, Xavier Kurz, Viktoriia Starokozhko, Peter G. M. Mol

First published: 17 October 2022 | https://doi.org/10.1002/cpt.2766

Results

RWE to support claims on **efficacy**:

- ✓ **51% MAAs** (32 of 63) / **50% EoIs** (14 of 28)
- ✓ Generated **pre-approval : 50% MAAs** (16/32) / **71% EoIs** (10/14)
- ✓ Supporting CHMP decision making in **25% MAAs** (4/16) / **50% EoIs** (5/10) (authorized)

Conclusion

- **RWE can contribute to medicines BR decision-making**: well-recognised for safety monitoring/disease epidemiology, demonstration of efficacy remains challenging
- RWE part of the overall evidence package → difficult to isolate its impact on CHMP decisions
- **Case-by-case analysis** to ensure it is fit-for-purpose in the specific setting
- Awareness of **RWD opportunities and limitations** is key → **Early dialogue** with regulators

Initial Marketing Authorisation Applications

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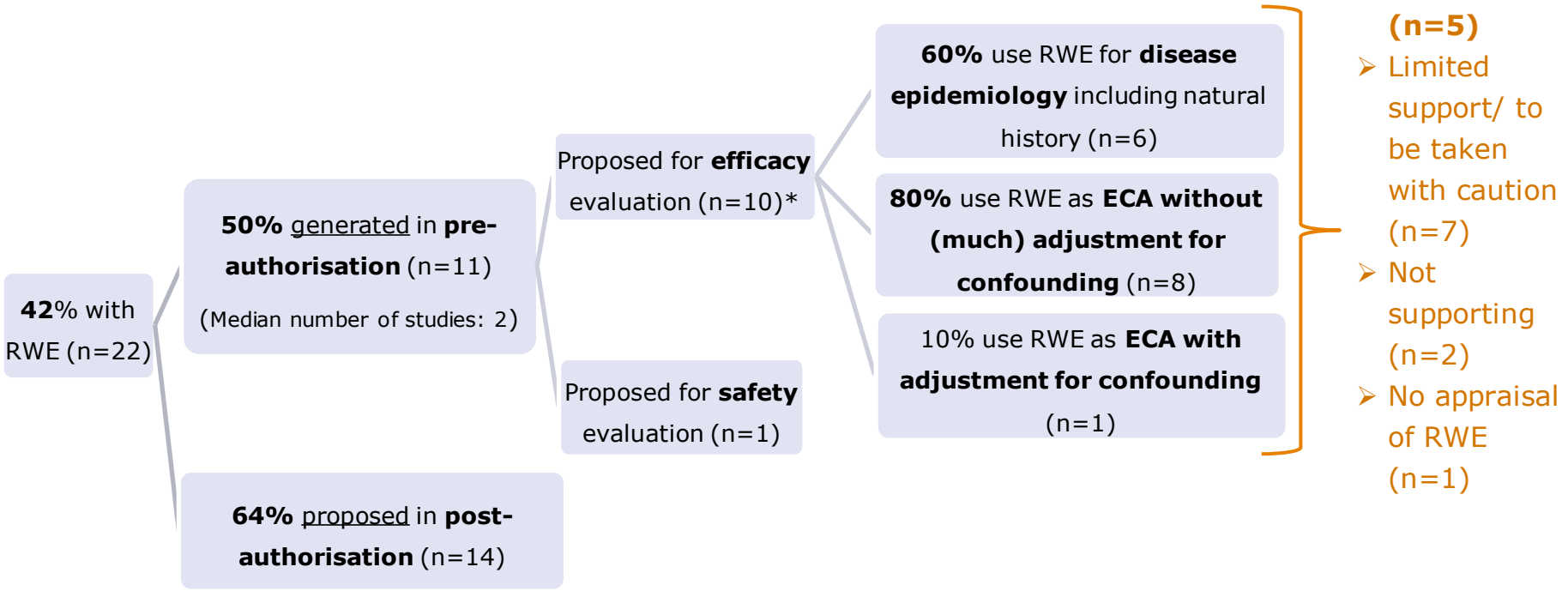
N=221 applications (2020-2023); Review of a random sample n=52 applications



P. Verpillat, ISPOR 2023

* 50% for Orphan Drugs

IQVIA "external control" study in collaboration with EMA

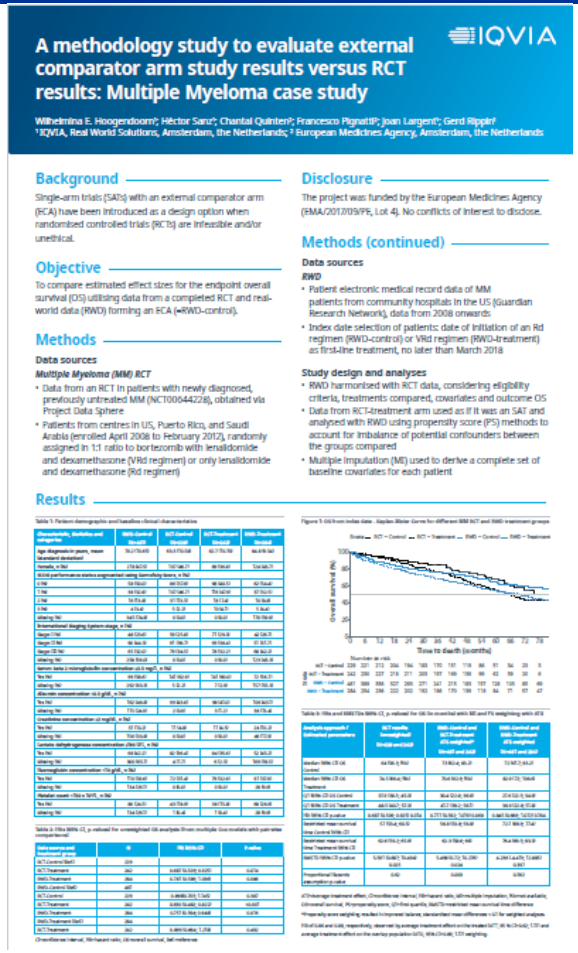
Objective

- Emulate RCT for single-arm trial with external RWD control, and compare estimated effect sizes for overall survival (OS) using completed RCT

Learnings

- In one out of 2 cases, RWD was effectively used as an external control to replicate conclusions for OS compared to the RCT
- **Missing data**, need for imputation (untestable assumptions), were the key challenges

W. Hoogendoorn et al. (ISPE 2022)



A methodology study to evaluate external comparator arm study results versus RCT results: Multiple Myeloma case study

IQVIA

Wilhelmina E. Hoogendoorn[1]; Héctor Sanz[1]; Chantal Quinten[2]; Francesco Pignatti[2]; Joan Largent[1]; Gerd Rippin[2]
[1] IQVIA, Real World Solutions, Amsterdam, the Netherlands; [2] European Medicines Agency, Amsterdam, the Netherlands

Background

Single-arm trials (SATs) with an external comparator arm (ECA) have been introduced as a design option when randomised controlled trials (RCTs) are infeasible and/or unethical.

Objective

To compare estimated effect sizes for the endpoint overall survival (OS) utilising data from a completed RCT and real-world data (RWD) forming an ECA (=RWD-control).

Methods

Data sources

Multiple Myeloma (MM) RCT

- Data from an RCT in patients with newly diagnosed, previously untreated MM (NCT00644228), obtained via Project Data Sphere
- Patients from centres in US, Puerto Rico, and Saudi Arabia (enrolled April 2008 to February 2012), randomly assigned in 1:1 ratio to bortezomib with lenalidomide and dexamethasone (VRd regimen) or only lenalidomide and dexamethasone (Rd regimen)

Disclosure

The project was funded by the European Medicines Agency (EMA/2017/09/PE, Lot 4). No conflicts of interest to disclose.

Methods (continued)

Data sources

RWD

- Patient electronic medical record data of MM patients from community hospitals in the US (Guardian Research Network), data from 2008 onwards
- Index date selection of patients: date of initiation of an Rd regimen (RWD-control) or VRd regimen (RWD-treatment) as first-line treatment, no later than March 2018

Study design and analyses

- RWD harmonised with RCT data, considering eligibility criteria, treatments compared, covariates and outcome OS
- Data from RCT-treatment arm used as if it was an SAT and analysed with RWD using propensity score (PS) methods to account for imbalance of potential confounders between the groups compared
- Multiple Imputation (MI) used to derive a complete set of baseline covariates for each patient

Results

RWD cannot fully replace phase II/III trial control patients when important covariates are missing

Real-world Data As Supplementary Controls For The Prospective Randomized Hovon-103 Trial In Intensively Treated Elderly Acute Myeloid Leukemia Patients

Hermans et al. (2023, Hemasphere. P565)

*H*ow does outcome of RWD patients compare to Outcome of trial control patients?

- randomized phase II HOVON-103 (H103) trial for elderly, intensively treated AML patients with the outcome of similarly treated elderly AML patients registered by the Netherlands Cancer Registry (NCR)

II/III trial control patients.

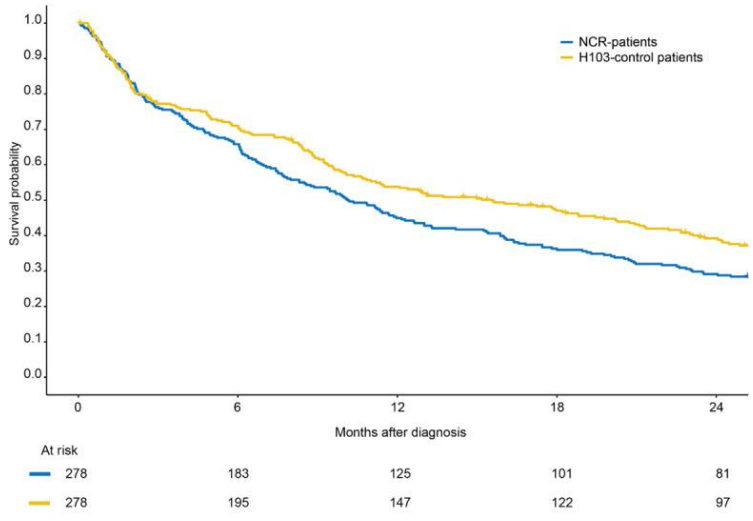


Figure 1. Overall survival for NCR-patients vs. H103-controls after 1:1 NN propensity score matching. NCR-patients were compared to H103-controls using a propensity score model informed by age, modified ELN2017 risk classification, and white blood cell count at diagnosis. Patient data were matched using 1:1 NN matching without replacement and overall survival was estimated using Kaplan-Meier analysis. Abbreviations: ELN: European LeukemiaNet; H103: HOVON-103 trial; NCR: Netherlands Cancer Registry; NN: Nearest Neighbor

Big Data Steering Group workplan 2022-2025 - LINK

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EU's current framework to unlock value, enable use of RWD and facilitate integration into regulatory decision-making

DARWIN EU	Gradual increase of **studies** and **data partners** **RWE pilots** in health crisis, HTA and Payers EMA committees phased **routine access to RWE**	Implement **use of CT Raw and CMC data** Enhance **EudraVigilance** safety data analysis Reflect on **AI use** and develop **guidance** **Knowledge sharing platform** on advance analytics **Network computing capability** to analyse data	**EU CAPABILITY TO ANALYSE**
DATA QUALITY AND REPRESENTATIVINESS	**Data quality framework** roll-out **Good practices** on regulatory data science, management and software Strengthen **data qualification** Activity links to **EHDS**	Consolidate **Methodology Working Party** **Data and methods** guidance **roadmap** **EU Specialist Expert Communities**: AI and RWE Launch **Cluster of Excellence for Clinical Trials**	**DELIVERY OF EXPERT ADVICE**
DATA DISCOVERABILITY	Publish **real-world data and studies catalogues** Explore **patient experience** data analysis **Clinical trials protocol** analytics Review utility of **eHealth data** and **social media**	Review **BDSG mandate** Strengthen engagement of **ethics expertise** Roll out of **data protection training** Support **TEHDAS & EHDS**, assess impact of EHDS Support **Pharma Strategy**	**GOVERNANCE FRAMEWORK**
EU NETWORK SKILLS	**Deliver training to regulators** on biostatistics, pharmacoepidemiology and data science Review **adequacy** of curricula Explore training **needs** for **patients, HCPs & academics**	Continue **RWE framework** collaboration Build on **ICMRA recommendations** Implement **data standardisation strategy** Clinical trial protocol **conceptual model** - ICH M11	**INTERNATIONAL INITIATIVES**
EU NETWORK PROCESSES	Publish **portfolio of RWE use cases** Harmonise **RWE terminology** EU network **RWE processes overview** **Report of RWE** in regulatory decision-making	Annual **multi-stakeholder** platform meetings Biannual **industry** meetings **Workshops** on DARWIN EU and RWE benefits Network **change management**	**STAKEHOLDER ENGAGEMENT**

Update on current initiatives and guidance

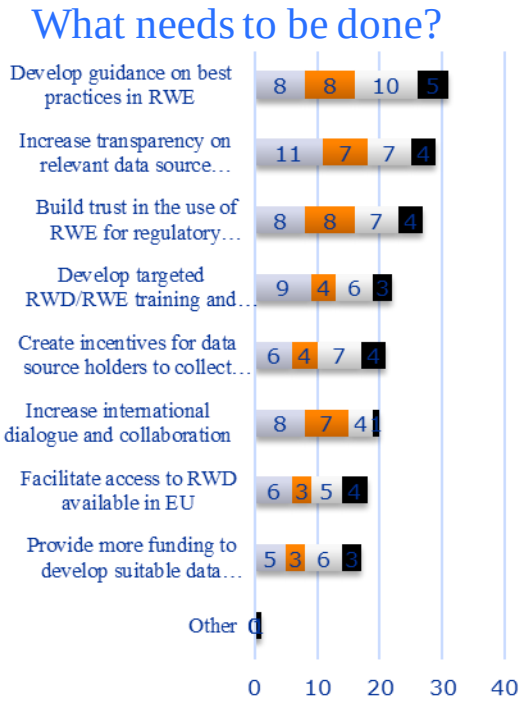
EMA multistakeholder workshop on RWD (2023): post workshop report (europa.eu)

- Survey on EMA guideline on registry-based studies : Lack of harmonisation, lack of interoperability, policies on data access and data sharing (K. Plueske)

EMA/TEHDAS data quality frameworks:

- data-quality-framework-eu-medicines-regulation_en.pdf (europa.eu)
- tehdas-recommendations-on-a-data-quality-framework.pdf

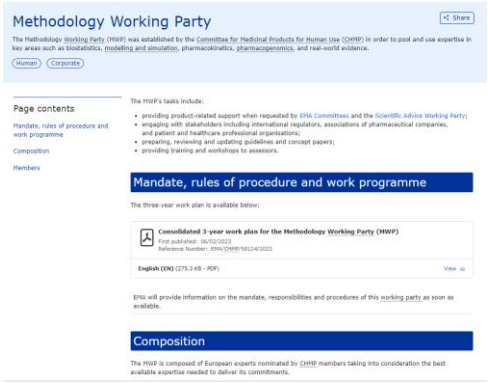
Good Practice Guide for the use of the Metadata Catalogue of Real-World Data Sources: real-world-metadata-good-practice-guide-for-public-consultation (europa.eu)



Survey of workshop participants. S. Prilla (2023)

Upcoming guidance

- EMA Methodology Working Party (MWP) (europa.eu)
  - Concept paper on the **use of RWE for regulatory decision** making.
  - Roadmap for development or RWE guidance
- ICH Reflection Paper on Harmonisation of **RWE Terminology** available for public consultation (LINK).
- ICH M14 on the Use of **RWD for safety** assessment (LINK)



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