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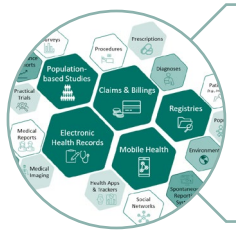
Anwendung von Beobachtungsdaten für die regulatorische Forschung

Julia Wicherski

IQWiG im Dialog 24.06.2025

Content



Observational data in regulatory decision-making

Real4Reg
Unlocking Real-World Data with AI

Regulatory research at BfArM
– an introduction into FQrisk & Real4Reg

Challenges and perspectives of observational data for regulatory research

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Observational data in regulatory decision-making

An overview of the current literature

„Real World Data“

“Routinely collected data relating to a patient's health status or the delivery of health care from a variety of sources other than traditional clinical trials.” *(European Medicines Agency [1])*

“Data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.” *(US Food and Drug Administration [2])*

“Data obtained outside the context of randomized controlled trials generated during routine clinical practice.” *(International Society of Pharmacoepidemiology [3])*

Figure 1. Data sources (Wicherski & Hänisch 2021)

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RWD around the product lifecycle

Discovery	Early Development	Full Development	Registration / Market Access	Lifecycle Management
Identify number of patients	Identify current treatment pathways affected by a new drug	Identify inclusion criteria to speed up RCTs recruitment by genetic and biomarker information	Assist health economic evaluation by comparing new vs. SOC	Reduce costs of follow-up trial to assess effectiveness
Identify SOC and assess adherence to clinical guidelines	Identify costs of unmet needs	Use of historical controls	Identify outcomes associated with SOC and compare these to new compound	Information on drug usage within target population
Identify number of patients with insufficiently controlled disease or inapproriate treatment	Refine selection criteria of cohorts to ensure trials better represent target population	Identify rates of adverse events expected during RCTs	Anticipate budget impact of new compound across patient segments	Assess outcomes of use (predicted benefits, adverse events as expected?)

Figure 2. Examples of using real-world data in the stages of the medicine lifecycle (modified figure based on Hennessy et al. [4])

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RWD sources in drug approval

European Medicines Agency, 2018-2019

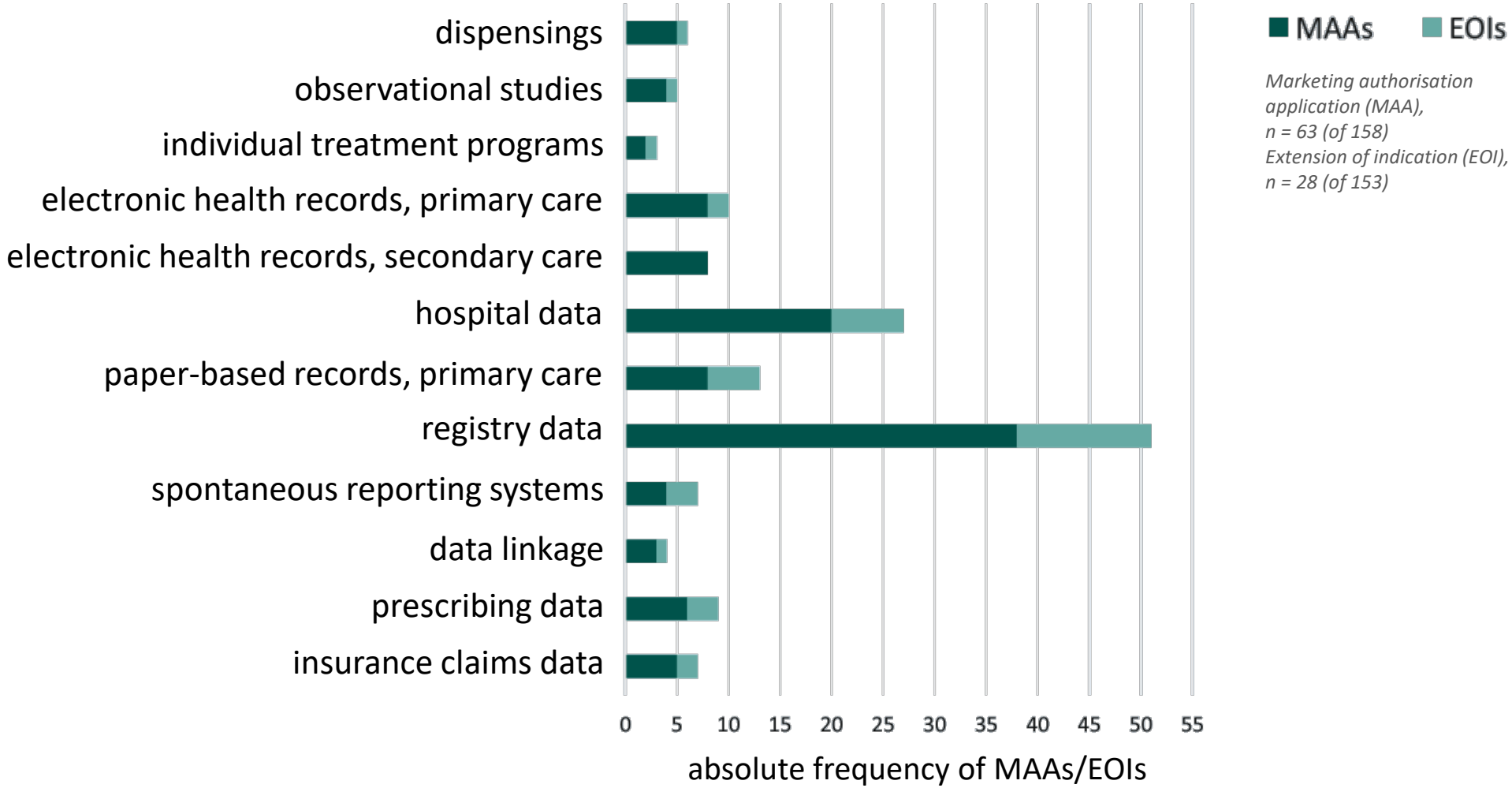

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Figure 3. Absolute frequency of RWD sources in drug approval, EMA 2018-2019, own illustration based on Flynn et al. [5]

RWD purpose of use in drug approval

European Medicines Agency, 2018-2019

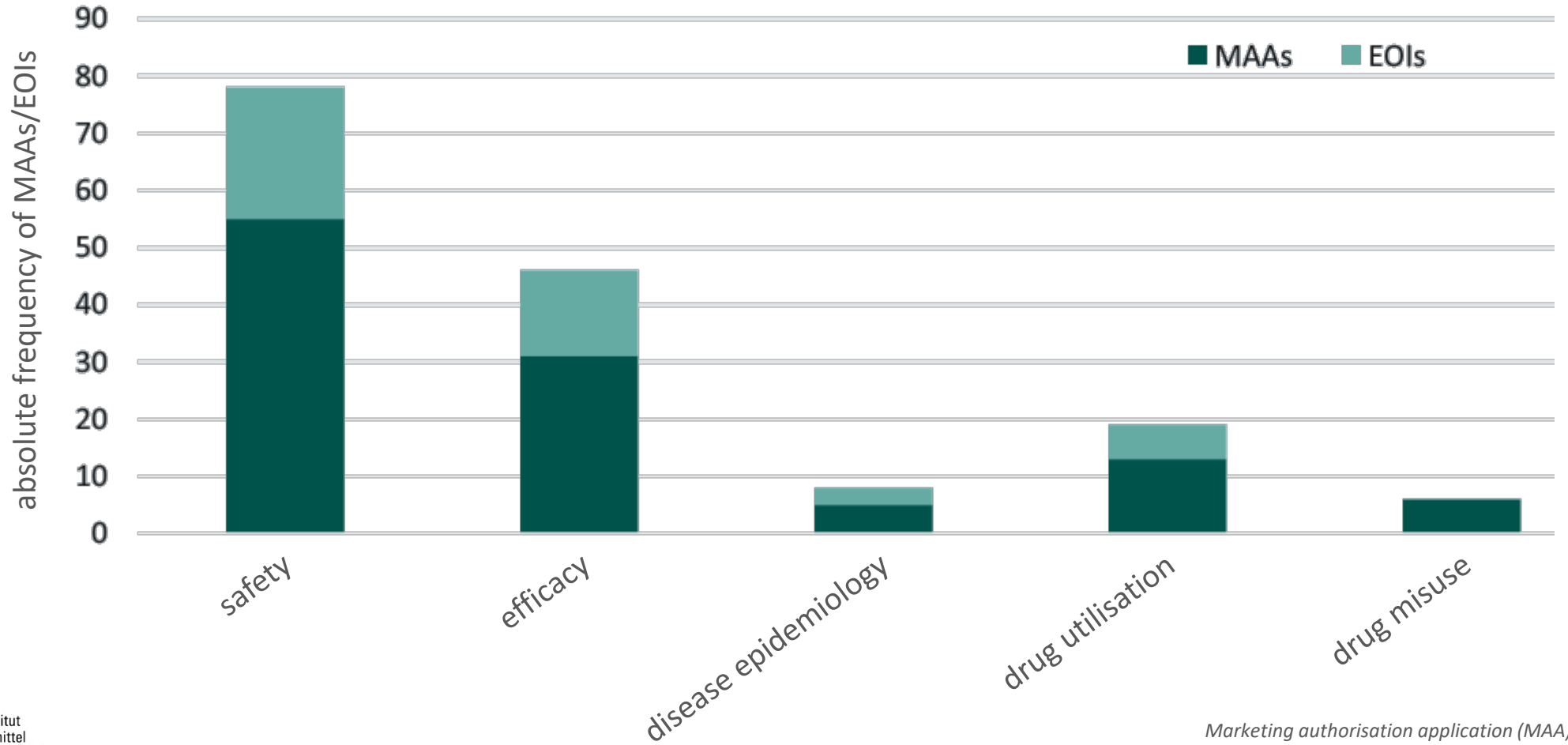

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Figure 4. Absolute frequency of RWD usage in drug approval, EMA 2018-2019, own illustration based on Flynn et al. [5]

Marketing authorisation application (MAA), n = 63 (of 158)
Extension of indication (EOI), n = 28 (of 153)

RWE consideration in regulatory decision-making

European Medicines Agency, 2018-2019

- RWD usage in MAAs/EOIs ≠ considered for decision-making [6]
- RWD is used and considered widely in post-authorisation to address safety and effectiveness [5-7]
- But are RWD considered for pre-authorisation decision-making processes?

Figure 5. Reviewed initial MAAs and EoIs and its contribution to regulatory decision-making, EMA 2018-2019, modified illustration based on Bakker et al. [6]

Regulatory research at BfArM

An introduction into FQrisk & Real4Reg

Research Devision at BfArM

- Lead: Prof. Dr. Britta Hänisch
- Research concentrates on important and contemporary questions with regard to the marketing authorisation, improving safety and assessing risks
- 5 interdisciplinary research groups

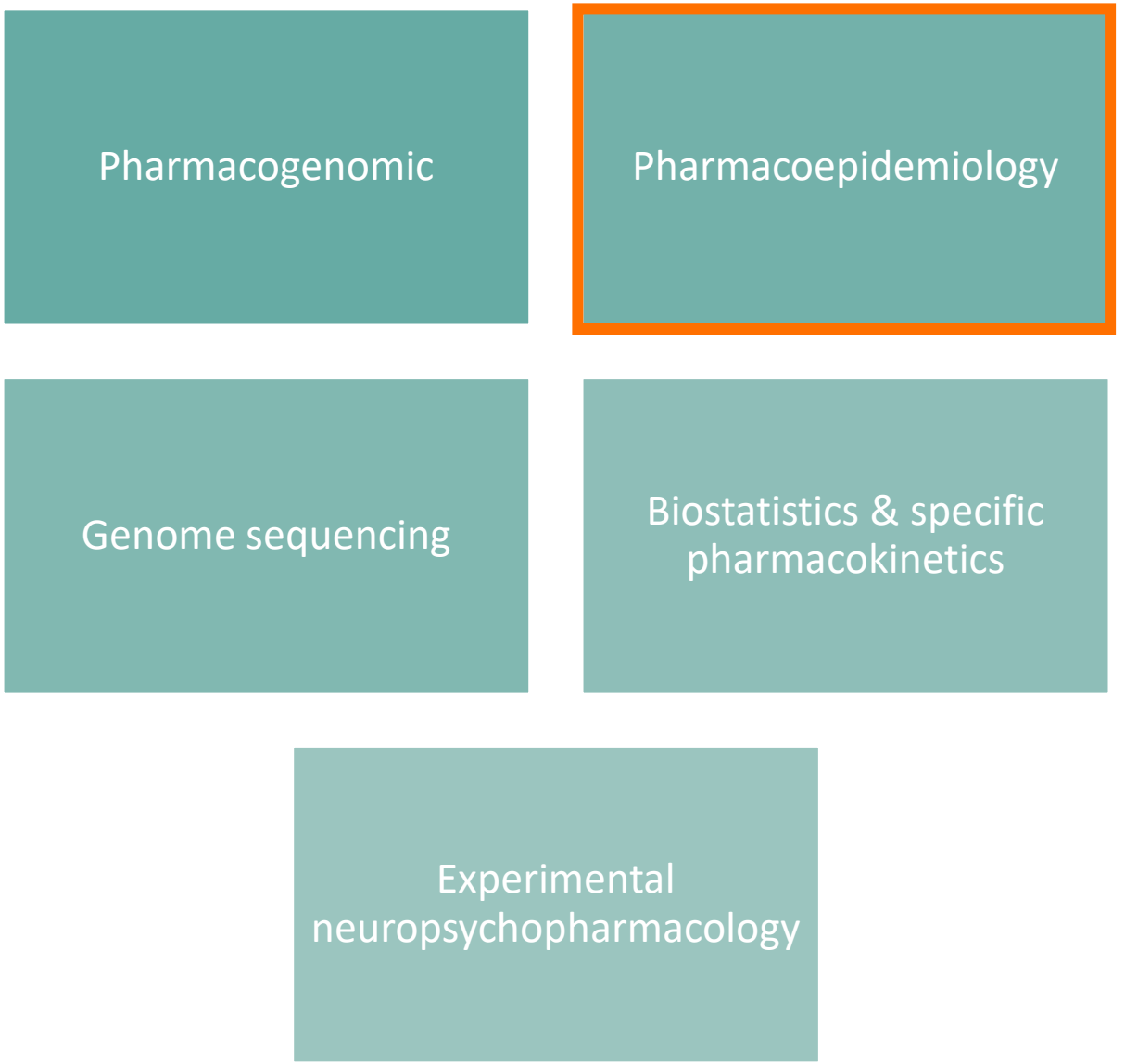

Figure 6. Research groups of the Research Devision at BfArM

FQrisk

Serious adverse drug reactions of fluoroquinolones – a pharmacoepidemiological secondary data analysis

German regulatory warnings on FQ-associated risks

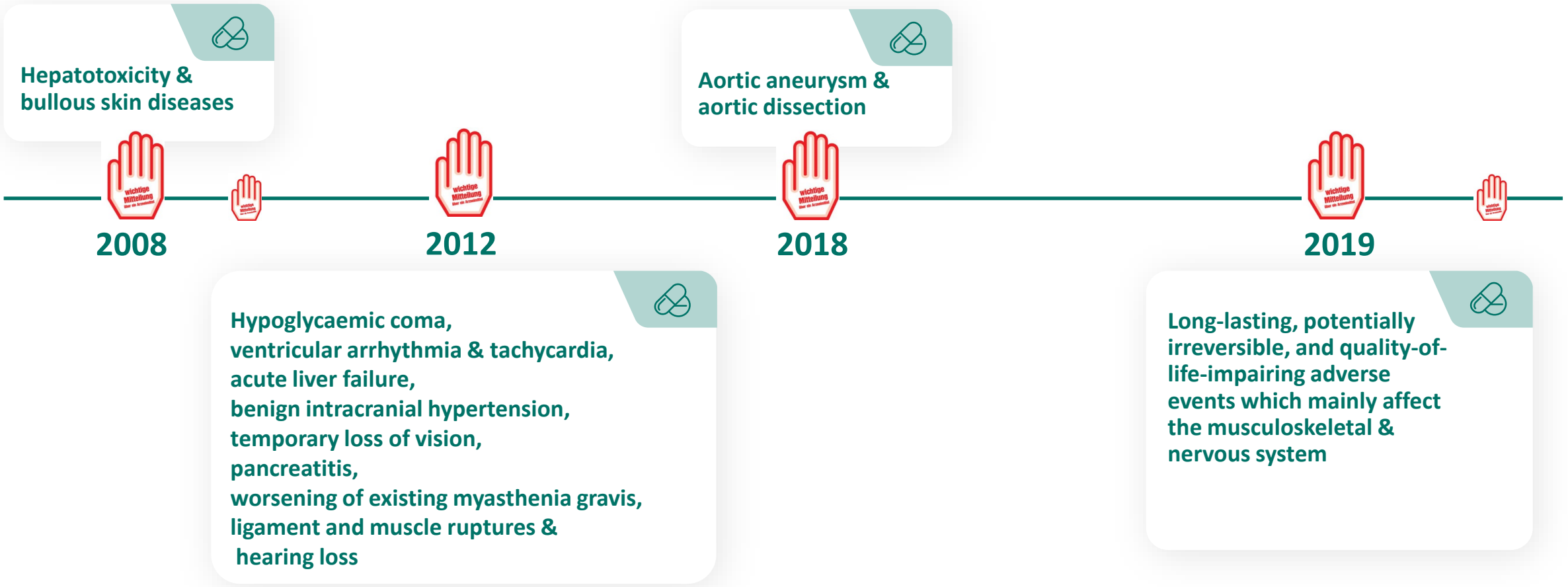

Figure 11. Dear Doctor Letters on Fluoroquinolones (own illustration, based on information retrieved from https://www.bfarm.de)

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FQrisk motivation

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 March 2019
EMA/175398/2019

Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics

(European Medicines Agency, EMA, 2019)

Follow-up time? Active comparators?
Differences in patient characteristics?
Incidence in Germany?

FQrisk aims to…

- Characterise real-world conditions of fluoroquinolone (FQ) prescribing
- Contribute to real-world evidence of FQ-associated adverse events
- Provide first insights into FQ safety in routine care in Germany

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Study design

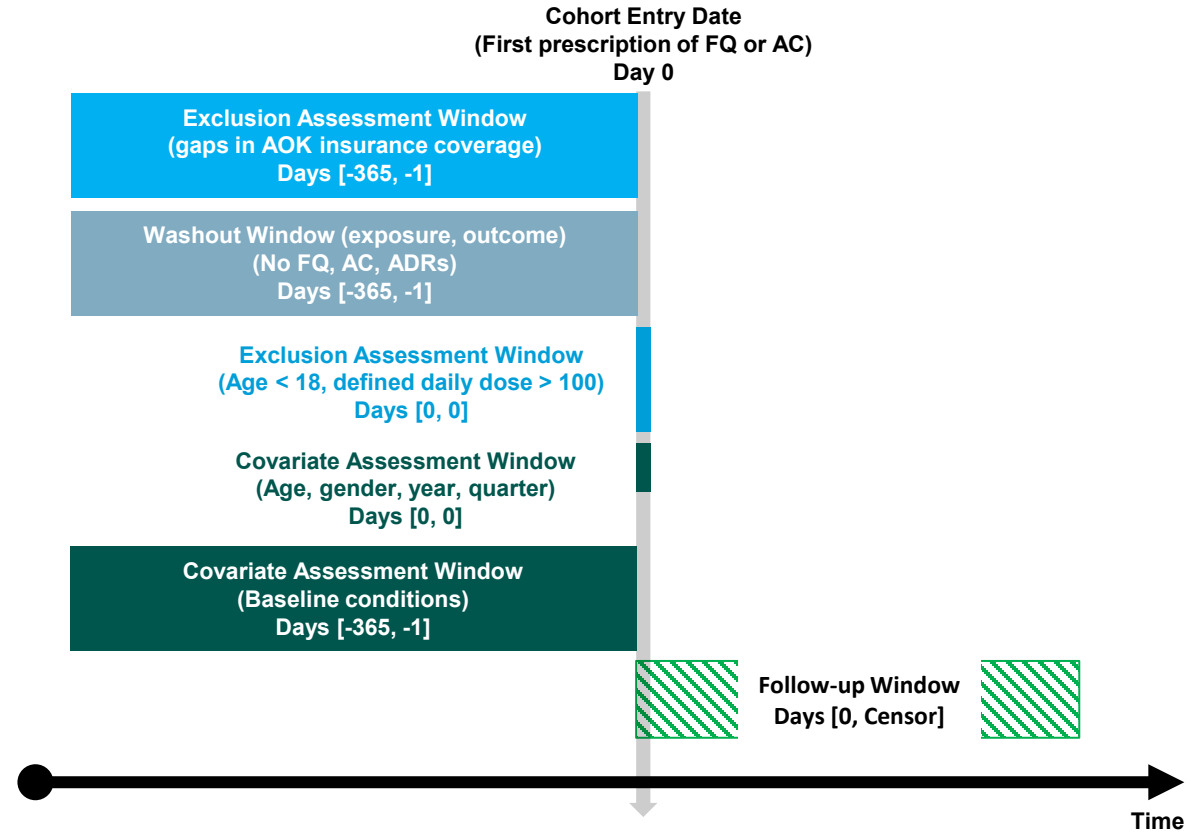

Figure 12. FQrisk study design diagram (template by Schneeweiss et al. [8])

- **FQ**: ciprofloxacin, levofloxacin, enoxacin, moxifloxacin, ofloxacin, norfloxacin
- **Active comparators (AC)**: amoxicillin, amoxicillin clavulanic acid, azithromycin, cefuroxime, cephalexin, clindamycin, sulfamethoxazole-trimethoprim, doxycycline

Observational data from nation-wide AOK-covered adults, insurance period: 01.01.2013-31.12.2019

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Antibiotic prescribing behaviour

- N = 20,114,846 index episodes (14,028,365 individuals)

- 28% beta-lactam antibiotics/ penicillines
- 18% other beta-lactam antibiotics
- 16% macrolides
- 15% FQ

- Ciprofloxacin was the 3rd common agent overall (10%)

- Proportion of FQ episodes increased, making them the most common antibiotic class in the group of ≥ 70-year-old women (22%)

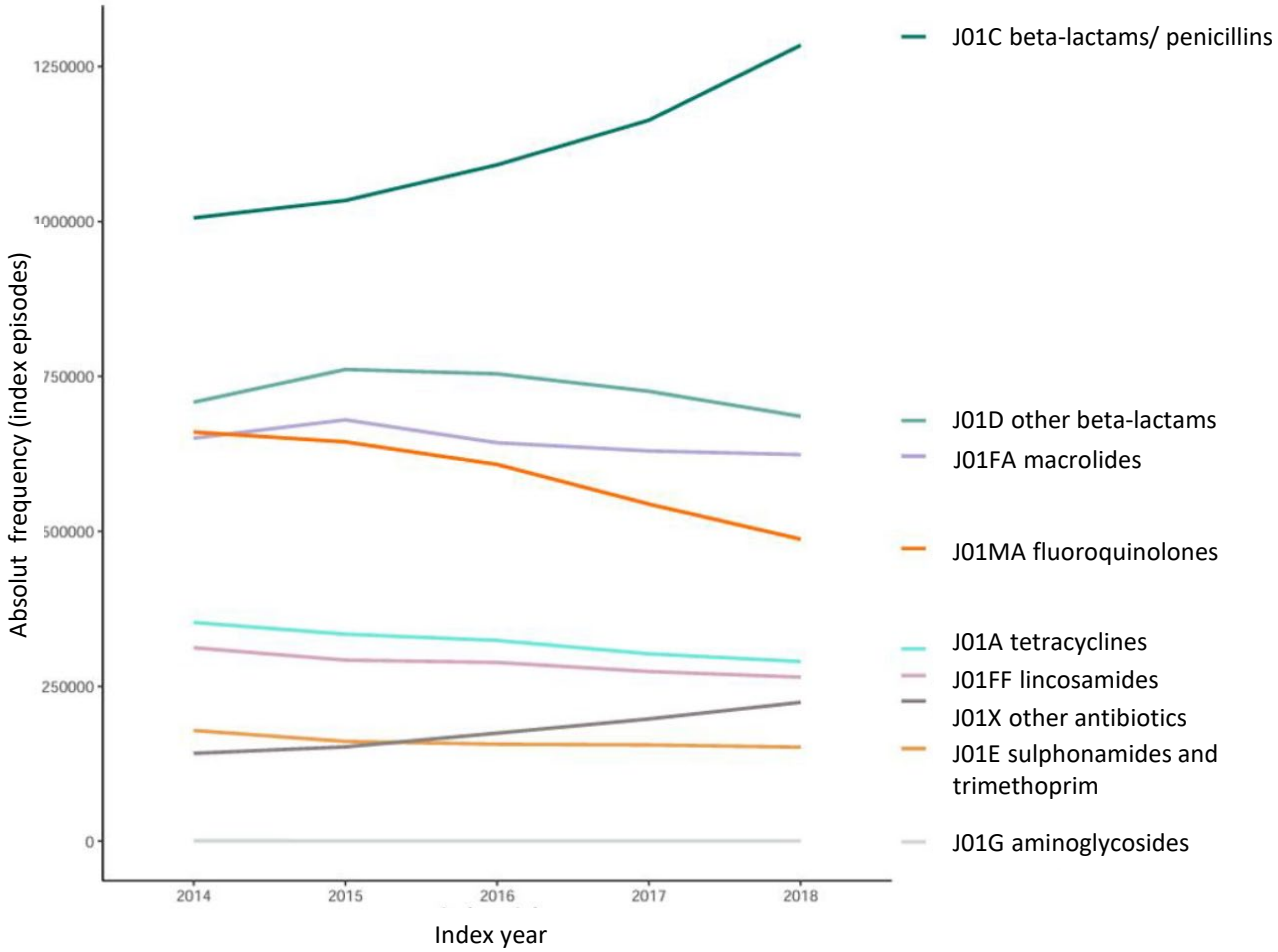

Figure 13. FQrisk index episodes by index year, 2014-2018 (source: Wicherski 2025)

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FQ-associated relative risks

Age and gender differences

Primary outcomes	aHR_{FQ} [95% CI]**					
	Women			Men		
	18-39 yrs	40-69 yrs	≥ 70 yrs	18-39 yrs	40-69 yrs	≥ 70 yrs
Aortic aneurysm/ dissection						
Cardiac arrhythmia						
Toxic liver diseases						
(Poly-)neuropathy/ other PNS-related diseases						
Drug-induced polyneuropathy						
Depression/ other affective disorders						
Mood-related symptoms						
Somnolence, sopor, coma						
Consciousness-related symptoms						
Musculotendinous injuries/ diseases						
Retinal detachment						
All-cause mortality						

*aHR_{FQ} [95% CI] colour code:

≤ 0,9 [< 1] | < 1,1 [> 1] | ≥ 1,1 [> 1] | ≥ 1,2 [> 1] | ≥ 1,3 [> 1] | ≥ 1,4 [> 1]

Figure 14. FQrisk results of PAMM regressions, age- and gender-disaggregation (source: Wicherski 2025)

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FQ-associated relative risks

Active comparator differences

Primary outcome	aHR_{FQ} [95% CI]** *active comparators (AC)*							
	AC 1	AC 2	AC 3	AC 4	AC 5	AC 6	AC 7	AC 8
Aortic aneurysm/ dissection								
Cardiac arrhythmia								
Toxic liver diseases								
(Poly-)neuropathy/ other PNS-related diseases								
Drug-induced polyneuropathy*								
Depression/ other affective disorders								
Mood-related symptoms								
Somnolence, sopor, coma								
Consciousness-related symptoms								
Musculotendinous injuries/diseases								
Retinal detachment								
All-cause mortality								

AC 1 = Amoxicillin
AC 2 = Amoxicillin clavulanic acid
AC 3 = Azithromycine
AC 4 = Cefalexine
AC 5 = Cefuroxime
AC 6 = Clindamycine
AC 7 = Cotrimoxazole
AC 8 = Doxycycline

*subset without cancer diagnoses at baseline

** aHR_{FQ} [95% CI] colour code:

≤ 0,9 [< 1] | < 1,1 [> 1] | ≥ 1,1 [> 1] | ≥ 1,2 [> 1] | ≥ 1,3 [> 1] | ≥ 1,4 [> 1]

Figure 15. FQrisk results of PAMM regressions, active comparator disaggregation (source: Wicherski 2025)

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Discussion

- This is the first study analyzing different active comparators together and disaggregated, and stratified for age-gender combinations
- Large study population (population-based & powerful), high completeness of data
- FQ are associated with an increased risk of serious adverse events
  - Especially during the first 60 days after exposure
  - Age & gender need to be considered when prescribing FQs
  - Selection of AC agent matters when interpreting FQs safety
- residual confounding / unmeasured variables (e.g., body weight), restricted measured exposure (i.e., dispensed ≠ administered with compliance), and non-random treatment allocation
- Future studies needed on young individuals and safety after authorization changes

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Real4Reg

Real4Reg

Unlocking Real-World Data with AI

Overview

Real4Reg

Unlocking Real-World Data with AI

- Development, optimisation & implementation of AI-methods for RWD analyses in regulatory decision-making & HTA along the product life-cycle
- To support regulatory decisions by taking advantage of new technologies
- To facilitate the implementation of the effective use of RWD in regulatory decision-making and HTA

- Duration: 2023-2026, ~ 7 Mio €
- Consortium: 10 Partners, 6 EU countries
- Lead: Prof. Britta Hänisch (BfArM)

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Real4Reg Methodology

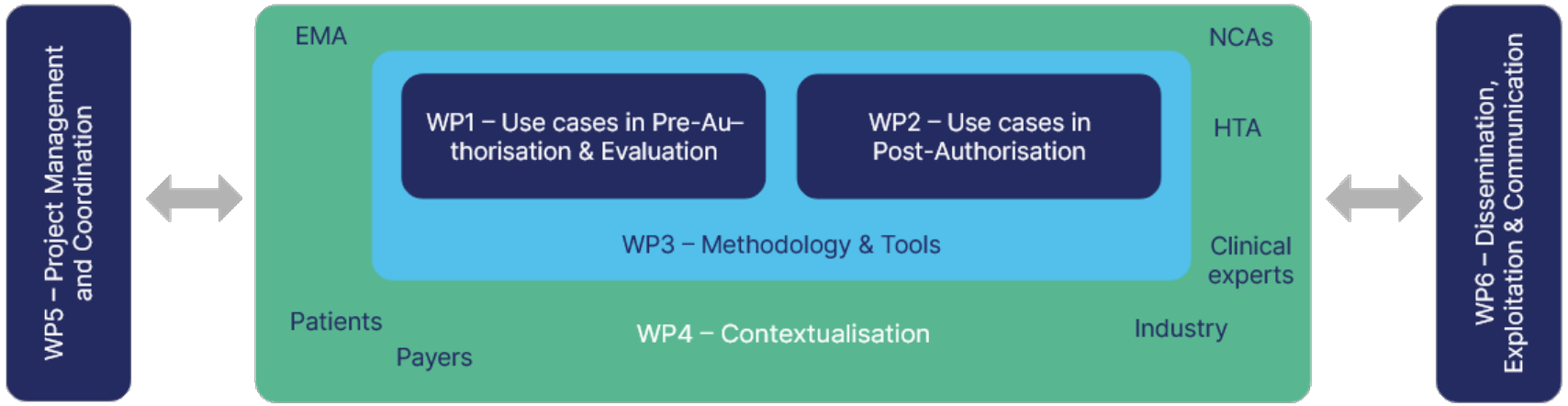

Figure 7. The Real4Reg project: methodology (https://www.real4reg.eu/)

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How does Real4Reg support complementary data sources and new approaches for decision-making process?

- Common data model
  - description and understanding of the heterogeneity of RWD sources and patient characteristics
  - enable more standardised use of different RWD
  - enable data FAIRification (Findable, Accessible, Interoperable, Reusable) by metadata catalogue

- AI/ ML approaches regarding
  - Construction of synthetic control arms
  - Propensity score methods
  - Conditional average treatment effect
  - Clustering disease trajectories

➢ Guidance and training concept, analytical workflows and templates

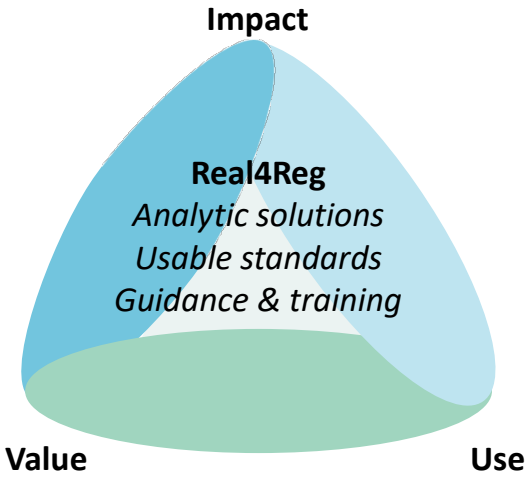

Figure 8. The Real4Reg project: objectives (https://www.real4reg.eu/)

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Real4Reg Survey

Survey on key stakeholders‘ knowledge, opinions and interests about the use of RWD, RWE, and AI/ML

„What issues did you encounter when making use of RWD/RWE for regulatory affairs and/or HTA purposes“?

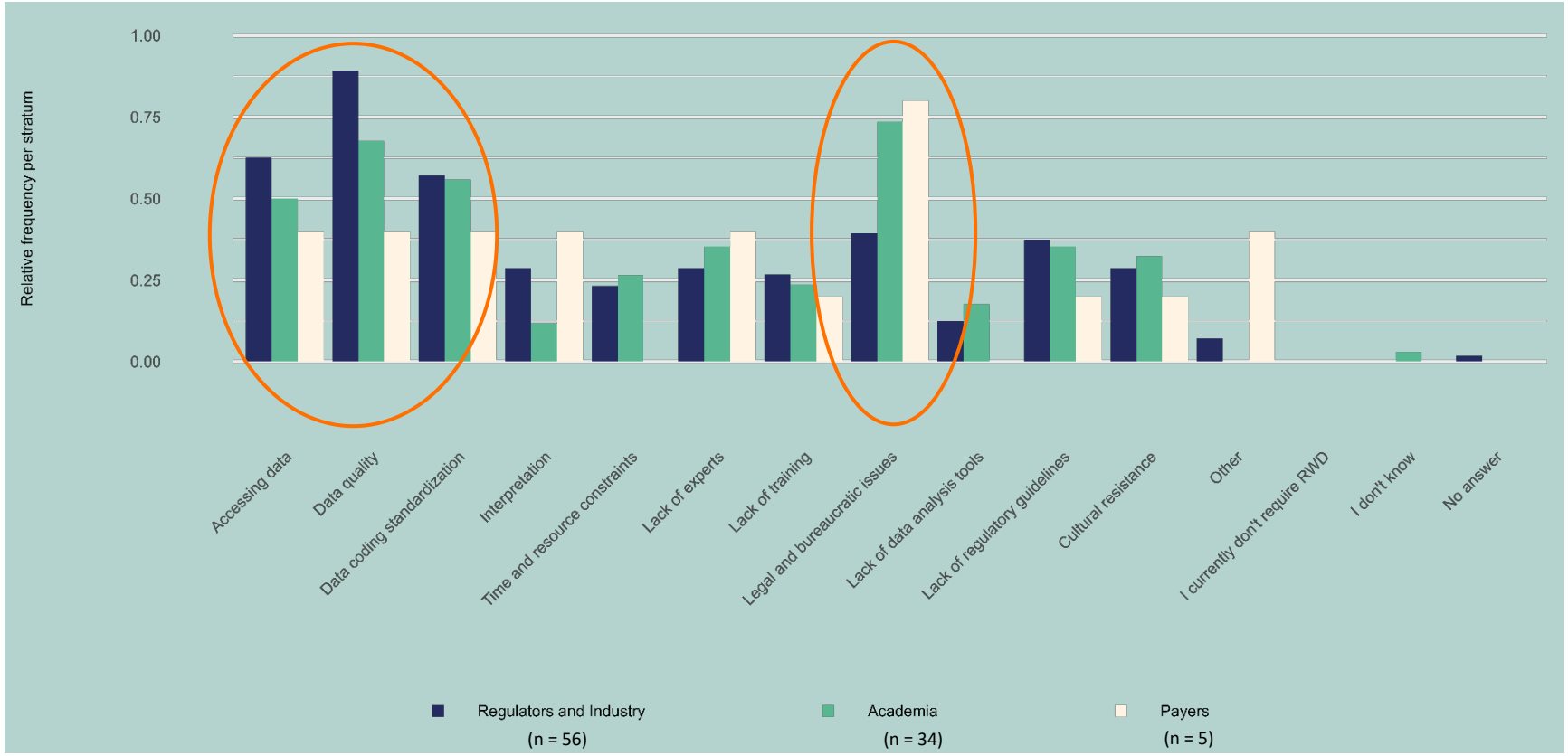

Figure 9. Real4Reg Survey, issues encountered in the use of RWD for regulatory decision-making: all participants (source: Real4Reg 2025)

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Real4Reg Survey

Subgroup „Regulators & Industry“ stratified by employer:

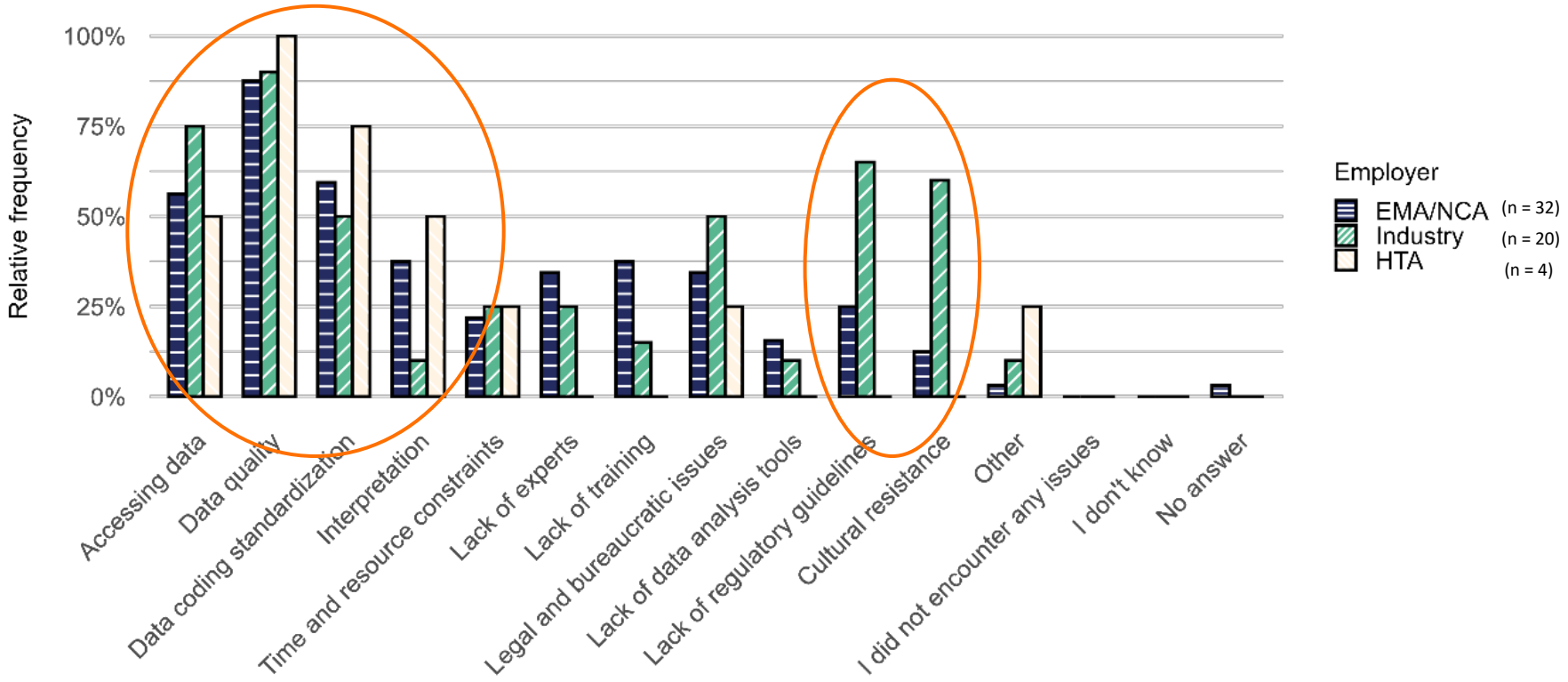


Figure 10. Real4Reg Survey, issues encountered in the use of RWD for regulatory decision-making: regulators and industry employees (source: Real4Reg 2025)

Challenges and perspectives of observational data for regulatory research

A conclusion

Conclusion

- Data quality
  - Heterogeneity aspect needs to be differentiated:
    - Clinical
    - Information
    - Measurement
  - Understanding of "*how data points become data points*" needs to be improved
  - Validation of data sources is needed to improve trust and consideration for decision-making
  - Standardisation of data preprocessing and analytic approaches

- Information regarding adequate use of the variety of data sources
  - Depending on the specific research question a specific granularity of data is needed
  - Transparency for reproducibility
  - Perspective of cross-national analyses (*EHDS*), large sample sizes, lower costs, high completeness

References

[1] Cave A., Kurz X., and Arlett P., “Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe,” Clinical Pharmacology & Therapeutics, 2019: 36–39, 10.1002/cpt.1426.

[2] US FDA, “Real-World Evidence,” 2024, https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

[3] Berger M. L., Sox H., Willke R. J., et al., “Good Practices for Real-World Data Studies of Treatment and/or Comparative Effectiveness: Recommendations From the Joint ISPOR-ISPE Special Task Force on Real-World Evidence in Health Care Decision Making,” Pharmacoepidemiology and Drug Safety, 2017: 1033–1039, 10.1002/pds.4297.

[4] Hennessy S, Atsuta Y, Hill S, Rägo L, Juhaeri J; Council for International Organizations of Medical Sciences (CIOMS) Working Group XIII. Real-World Data and Real-World Evidence in Regulatory Decision Making: Report Summary From the Council for International Organizations of Medical Sciences (CIOMS) Working Group XIII. Pharmacoepidemiol Drug Safety, 2025:e70117, 0.1002/pds.70117.

References

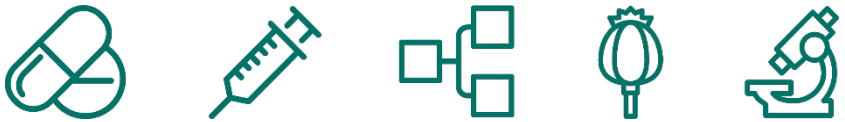
[5] Flynn R, Plueschke K, Quinten C, Strassmann V, Duijnhoven RG, Gordillo-Marañon M, Rueckbeil M, Cohet C, Kurz X. Marketing Authorization Applications Made to the European Medicines Agency in 2018-2019: What was the Contribution of Real-World Evidence? Clin Pharmacol Ther., 2022:90-97, 10.1002/cpt.2461.

[6] 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 Ther., 2023:135-151. 10.1002/cpt.2766.

[7] 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 Ther., 2022:310-320, 10.1002/cpt.2462.

[8] Schneeweiss S, Rassen JA, Brown JS, Rothman KJ, Happe L, Arlett P, Dal Pan G, Goettsch W, Murk W, Wang SV. Graphical Depiction of Longitudinal Study Designs in Health Care Databases. Ann Intern Med., 2019:398-406, 10.7326/M18-3079.

Vielen Dank für Ihre Aufmerksamkeit!



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