TURNING DATA INTO EVIDENCE

Real-World Evidence for Regulatory Decision-making

DCVMN: Regulatory Working Group Workshop

Singapore 24-25 November2023

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FDA: Real-World Evidence (1/2)

- **Real World Evidence (RWE)** [FDA][1,2]: RWE is the clinical **evidence** about the usage and potential benefits or risks of a medical product **derived from** analysis of **Real-World Data** (RWD).

- **Real World Data (RWD)** [FDA][1,2]: RWD is data relating to patient health status and/or the delivery of health care **routinely** collected from a variety of sources.

1. Food and Drug Administration. Framework for FDA's real-world evidence program. December 2018 (https://www.fda.gov/ media/120060/download).
2. Food and Drug Administration. August 2023. Considerations for the use of RWD and RWE to support regulatory decision-making for Drugs and Biological Products, Guidance for Industry

FDA: Real-World Evidence (2/2)

RWD:data on patients health **routinely** collected

- Electronic health records (EHRs)
- Medical claims data
- Product and disease registers
- Patient-generated data
- Digital health (wearables)

RWE: clinical **evidence** generated using RWD

- Study designs: pragmatic trials, observational studies (case-control, cohort)
- Type of data: primary data collection or secondary data use
- Timing: prospective or retrospective

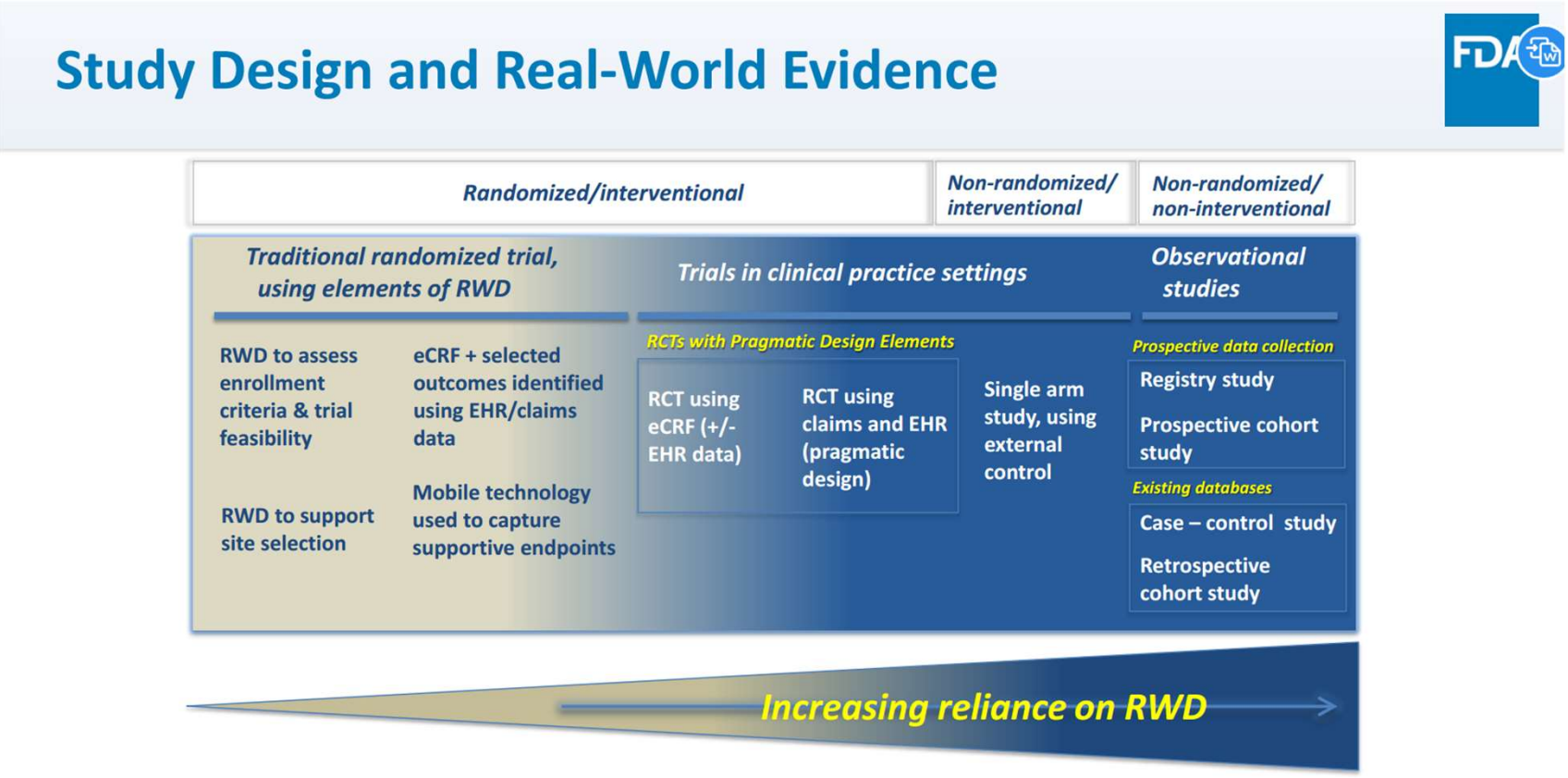
Concato J, Stein P, Dal Pan GJ, Ball R, Corrigan-Curay J. Randomized, observational, interventional, and real-world-What's in a name? Pharmacoepidemiol Drug Saf. 2020 Nov;29(11):1514-1517. doi: 10.1002/pds.5123. Epub 2020 Sep 17. PMID: 32940401

Clinical Trials vs Observational Studies (1/2)

- **Dichotomization 'randomized versus observational' fails to recognize the broad spectrum of data that generates RWE.**
  - **Interventional study (or Clinical Trial)** [1] : is a study in which participants are **assigned** to one or more interventions, according to a study **protocol**, to evaluate the effects of those interventions on subsequent health-related outcomes. Examples are randomized controlled trials, trials with pragmatic elements, single-arm trials.
  - **Non-interventional study (or observational study)** [1]: a type of study in which patients **received** the marketed drug of interest during **routine medical practice** and are not assigned to an intervention according to a protocol. Examples are observational cohort studies and case-control studies.

1. Food and Drug Administration. August 2023. Considerations for the use of RWD and RWE to support regulatory decision-making for Drugs and Biological Products, Guidance for Industry

Clinical Trials vs Observational Studies: Use of RWE (1/2)



https://www.fda.gov/media/148543/download

EMA: Real-World Evidence (1/2)

- **Real World Evidence (RWE)** [FDA][1]: information derived from analysis of Real-World Data (RWD).

- **Real World Data (RWD)** [FDA][1]: **routinely collected** data relating to patient's health status or the delivery of health care from a variety of sources **other than traditional clinical trials.**

1. Cave A, Kurz X, Arlett P. Real-World Data for Regulatory Decision Making: Challenges and Possible Solutions for Europe. Clin Pharmacol Ther. 2019 Jul;106(1):36-39. doi: 10.1002/cpt.1426. Epub 2019 Apr 10. PMID: 30970161; PMCID: PMC6617710.
2. Arlett P, Kjaer J, Broich K, Cooke E. Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value. Clin Pharmacol Ther. 2022 Jan;111(1):21-23. doi: 10.1002/cpt.2479. Epub 2021 Nov 19. PMID: 34797920; PMCID: PMC9299492.

EMA: RWD/RWE vision and experience gained

- "Our (EMA) vision, anchored in the European Medicines Regulatory Network (EMRN) strategy to 2025, is that by 2025 the use of RWE will have been enabled and the value will have been established across the spectrum of regulatory use cases." [1]

- Traditional RCTs and RWD/RWE are complementary, and the use of RWD/RWE can speed up medicine development and support post marketing safety and effectiveness monitoring. [1]

- RWD/RWE pilot studies ongoing and review available [2]: Use of real-world evidence in regulatory decision making – EMA publishes review of its studies | European Medicines Agency (europa.eu)

1. Arlett P, Kjaer J, Broich K, Cooke E. Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value. Clin Pharmacol Ther. 2022 Jan;111(1):21-23. doi: 10.1002/cpt.2479. Epub 2021 Nov 19. PMID: 34797920; PMCID: PMC9299492.
2. EMA: Real-world evidence framework to support EU regulatory decision-making. Report on the experience gained with regulator-led studies from September 2021 to February 2023.

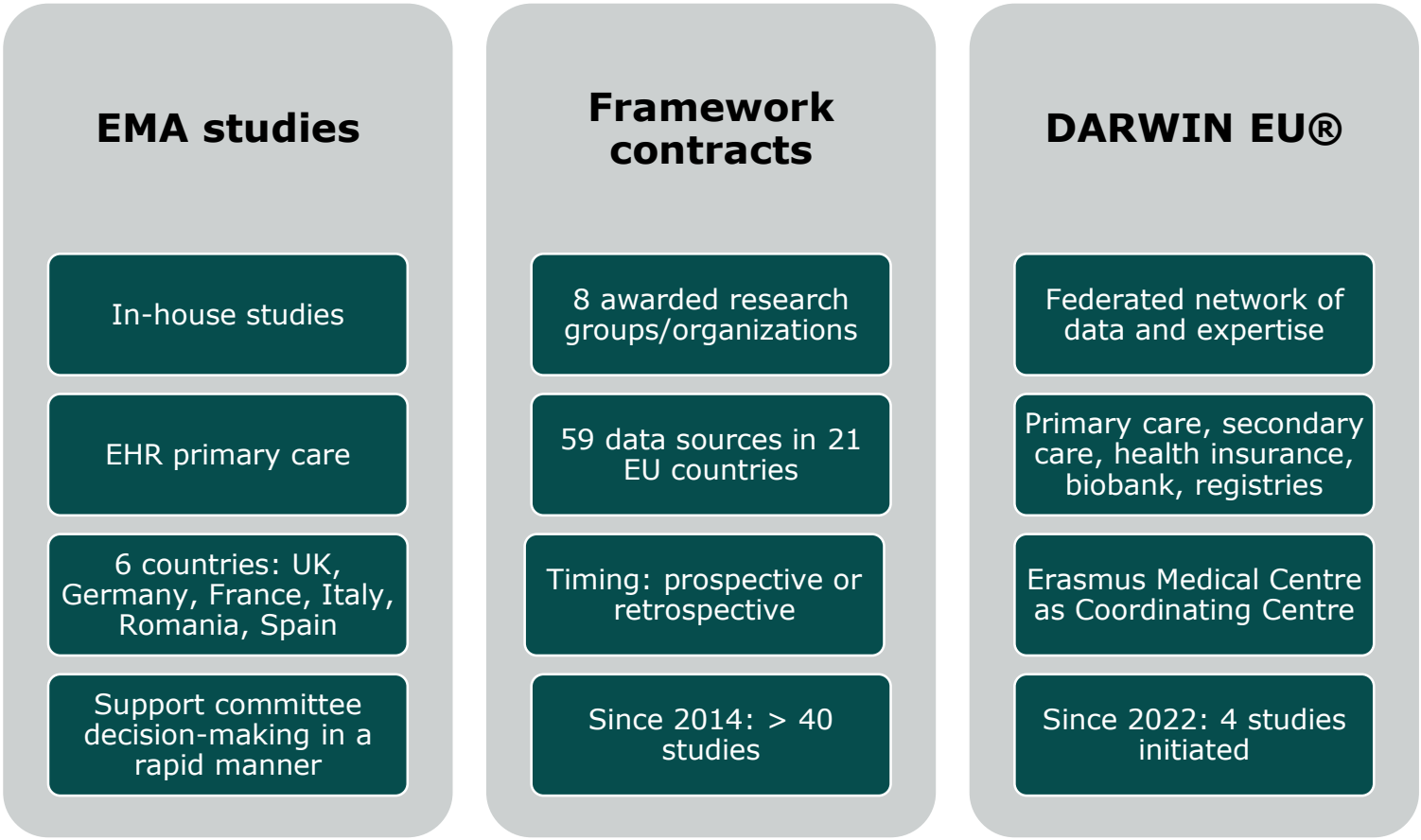
EMA: Research topics for RWD studies

Research topics can emerge from regulatory procedures such as

- Initial marketing authorization applications
- Period safety update reports (PSURs)
- Safety signals
- Referrals
- Variation application
- Scientific advice requests
- Application for PIP or waiver
- Application/maintenance of orphan designation

EMA: Real-world evidence framework to support EU regulatory decision-making. Report on the experience gained with regulator-led studies from September 2021 to February 2023.

FDA: Pathways for RWD studies



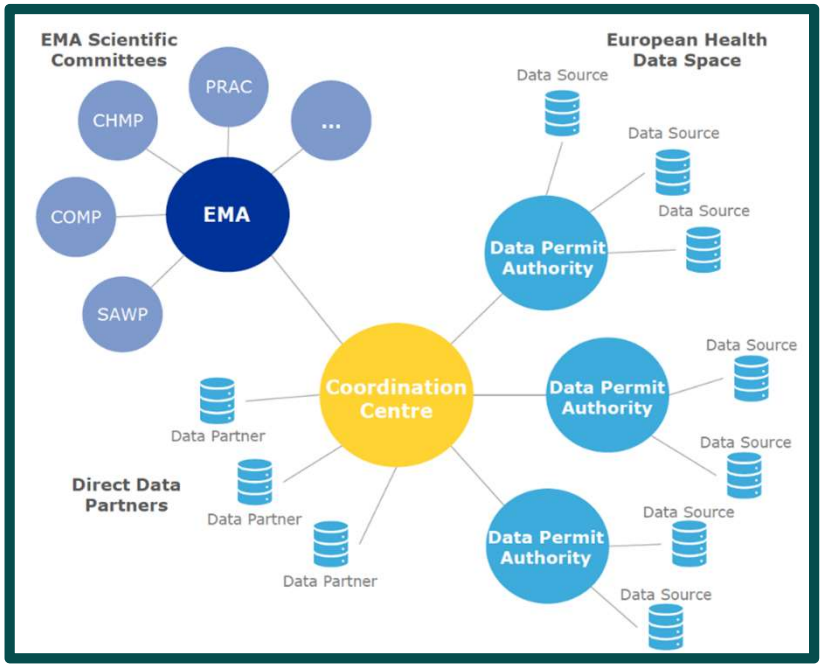
1. EMA: Real-world evidence framework to support EU regulatory decision-making. Report on the experience gained with regulator-led studies from September 2021 to February 2023.

DARWIN EU®

https: www.darwin-eu.org

DARWIN EU supports regulatory decision-making by

- Expanding a catalogue of observational data sources
- Providing a source of high-quality validated data sources
- Carrying-out non-interventional studies



EMA: Pilot studies – examples #1

Pediatric Committee (PDCO): prevalence of hypereosinophilia	
Problem	The applicant requested for a partial PIP waiver for children< 6yrs. The applicant claimed that studies would not be feasible as the condition is too rare. Contrasting data was available. To decide on the waiver request, the PDCO requested additional European data to better inform the feasibility of clinical trials
Study	EHR study (GE, FR) showing cases with possible HES were rare in children aged 0-5 years with an estimated yearly prevalence between 0.0 and 6.2 per million children.
Useful	Results supported decision to grant waiver for children < 6yrs

EMA: Pilot studies – examples #2

Pharmacovigilance Risk Assessment Committee (PRAC): Comirnaty and vulval ulceration	
Problem	During routine signal detection, cases of genital ulceration (including vulval ulceration, vaginal ulceration, vulvovaginal ulceration, genital ulceration) in close temporal association to Comirnaty vaccination were identified.
Study	EHR study to: (a) describe the use of the vaccine in the general population, and (b) estimate incidence rates of vulval ulceration in the general and exposed female population. The study found no difference in post-vaccination incidence rates of vulval ulceration compared to the background incidence rates.
Useful	Supported the PRAC conclusion that at the moment there is not sufficient evidence to conclude a causal association between vulval ulceration and Comirnaty exposure

Real-World Evidence is a reality in regulatory decision-making

Real-World Evidence will continue to grow in importance

Questions?