

Developments in RWE generation for regulatory decision making

PHUSE CSS 2025

Daniel Morales

Data Analytics and Methods Taskforce



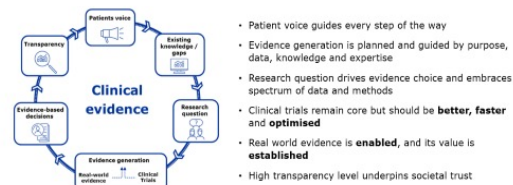
Disclaimer

These slides are copyrighted by the European Medicines Agency. Reproduction is permitted provided the source is acknowledged.

The views expressed in this presentation are personal views and may not be construed or quoted as having been expressed on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working groups.

RWE Generation

Generating clinical evidence: Shared vision towards 2030

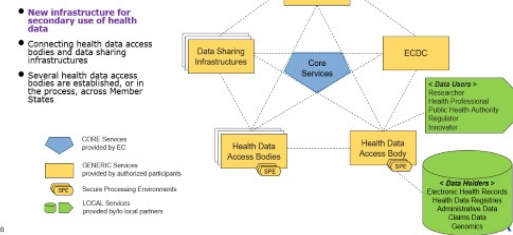


Clinical Evidence 2030: Achter P, Umlauf D, Vignati P, Page F, Hestel Umlauf U, Sordani S, Lomer M, Arnold S, Narmann S, Rapp N, Nappert S, Thoma S, Lomer M, Costa S, Bollen S, Ch. Narmann Ther. 2023 Feb 24; doi: 10.1002/clm2.1006



HealthData@EU

HealthData@EU: A vision



10

Data Quality

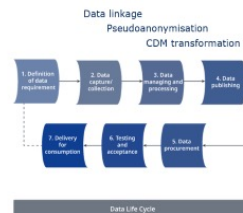
Data Quality

Data quality is important

- Transparency, reliability, efficiency, **trustworthiness**.
- Data used for secondary purposes are not 'perfect', so we need to demonstrate that they are good enough.

Data quality assessment is complex

- RWD are heterogeneous in terms of their structure, format, variables, terminology used and their collection process
- RWD for secondary use have a **lifecycle** in terms of recording, aggregation, transformation, cleaning to become 'research ready'



14



Methodology

Methodological guidance development

Methodology Working Party (MWP)

- Provide product-related support,
- Preparing, reviewing & updating guidelines/concept papers;
- Providing training and workshops to assessors

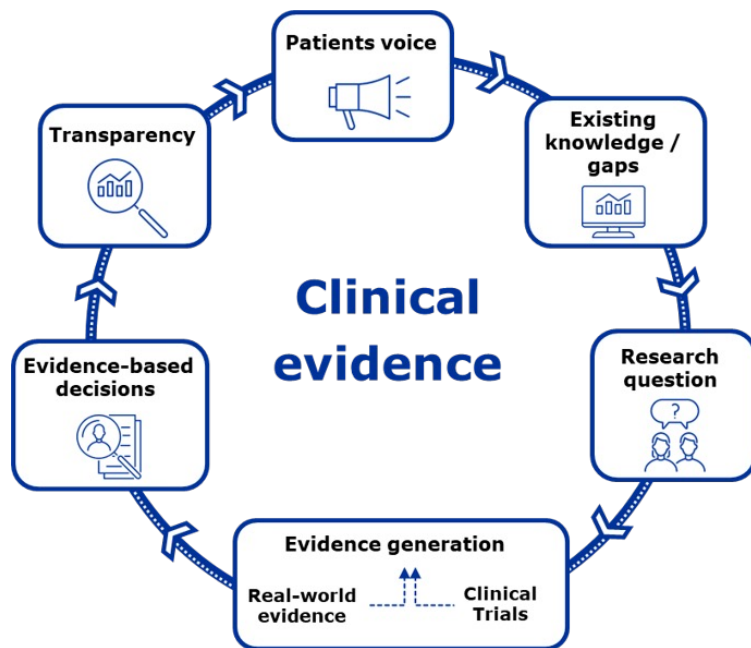
European Specialised Expert Community (ESEC)

- AI & Data science
- Biostatistics
- Clinical Pharmacology
- Modelling & Simulation
- Pharmacogenomics
- Real World Data



19

Generating clinical evidence: Shared vision towards 2030



- Patient voice guides every step of the way
- Evidence generation is planned and guided by purpose, data, knowledge and expertise
- Research question drives evidence choice and embraces spectrum of data and methods
- Clinical trials remain core but should be **better, faster** and **optimised**
- Real world evidence is **enabled**, and its value is **established**
- High transparency level underpins societal trust

3 main pathways to use RWD for generating RWE



Studies using in-house databases

- **Primary and secondary care** health records from **France, Germany and UK**



Studies procured through EMA FWCs

- Framework contract (FWC) since September 2021: services of **8 research organisations** and academic institutions
- Access to **wide network of data**: 59 data sources in 21 EU countries
- Ability to leverage external **scientific expertise**



DARWIN EU®*

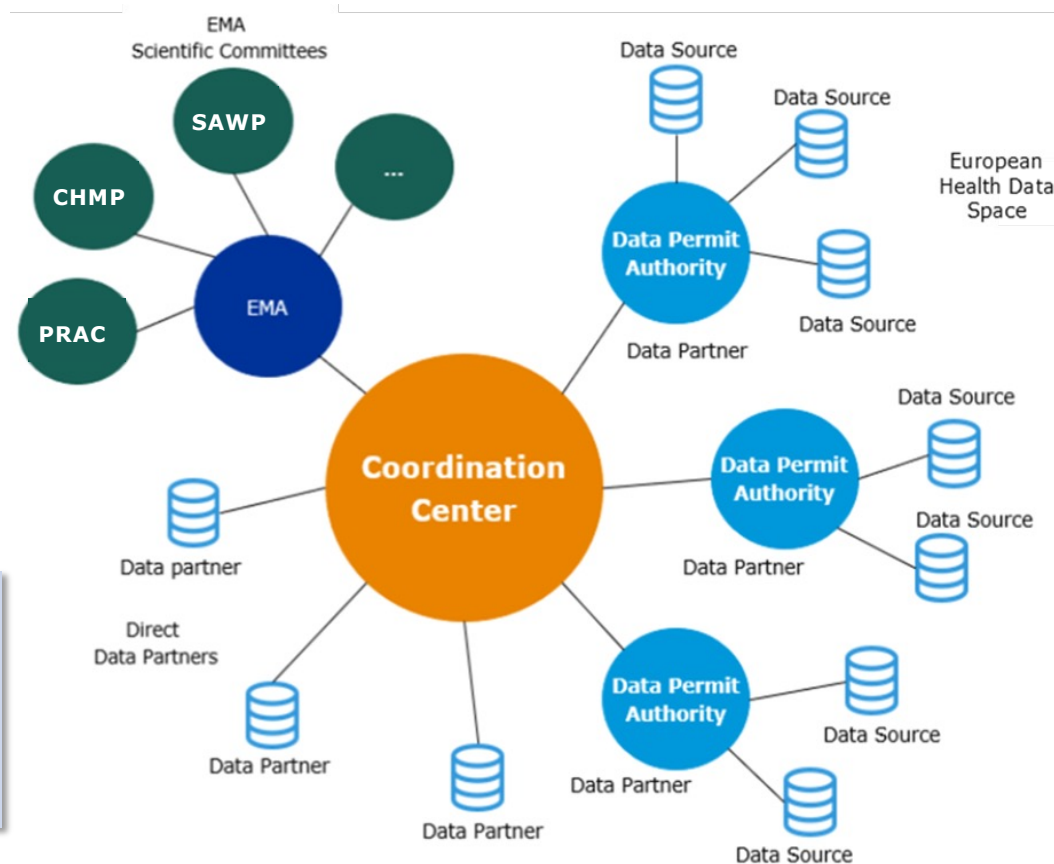
- Coordination Centre launched February 2022
- Onboarded **30 data partners** during the first 3 years
- **50+ studies** finalised
- Additional 10 data partners to **be added** in 2025

DARWIN EU® Data Analysis and Real-World Interrogation Network

Federated **network** of **data**, **expertise** and **services** that supports better decision-making throughout the product lifecycle by generating valid and reliable **evidence from real world healthcare data**

FEDERATED NETWORK PRINCIPLES

- Data stays **local**
- **Use of Common Data Model** (OMOP) to perform studies in a timely manner and increase consistency of results



DARWIN EU Network of Data Partners

International data platform

HARMONY Big Data Platform

The Netherlands

Integrated Primary Care Information
Netherlands Cancer Registry

Belgium

IQVIA Longitudinal Patient Database Belgium

United Kingdom

UK BioBank
Clinical Practice Research Datalink
National Neonatal Research Database

France

Bordeaux University Hospital
Système National des Données de Santé
Health Data Warehouse of Assistance Publique

Portugal

ULSM-RT
Egas Moniz Health Alliance DataBase

Spain

SIDIAP
BIFAP
IMASIS and IMIM
Valencia Health System Integrated Database
H12O
Health Data Research Platform of the Balearic Islands

Norway

Norwegian Linked Health Registry
Cancer Registry of Norway

Sweden

Health Impact

Finland

FinOMOP

Estonia

Estonian Biobank

Denmark

Danish Health Data Registries

Germany

IQVIA Disease Analyzer Germany
InGef Research Database

Hungary

Semmelweis University Clinical Data

Croatia

National Public Health Information System

Greece

Papageorgiou General Hospital

Italy

POLIMI

30 Data Partners as of Feb 2025 in **16 European countries** (~ +10 by end of Feb 2026)

Examples of impactful studies

PRAC



Doxycycline and association with risk of **suicidality**
(PRAC request to facilitate signal assessment)

Safety signal on “suicidality” raised based on cases reported to the Finnish national competent authority and EudraVigilance

Currently available evidence not supporting link between this antibiotic drug and risk of suicidality

—> **No update to doxycycline product information warranted**



CGRP* antagonists and background rates (PRAC request to support 3 signal evaluations - **insomnia, erectile dysfunction, increased blood pressure**)

Signals assessment hard to conclude due to limited evidence on background rates in migraine patients

Results helped to reach a conclusion regarding the 3 different signals and a faster decision.

—> **Signals closed**

*Calcitonin gene-related peptide

Examples of impactful studies

PDCO



Paediatric Systemic Lupus Erythematosus and treatment patterns (PDCO request to support review of upcoming Paediatric Investigation Plan (PIP) submissions in view of clinical trials in the paediatric SLE population being hampered by competitive recruitment)

Informed on the **paediatric SLE population potentially available for clinical trials** (being mainly naive to target therapies) and on the similarity between adults and children, which in turn informs the **extrapolation approach** to be applied



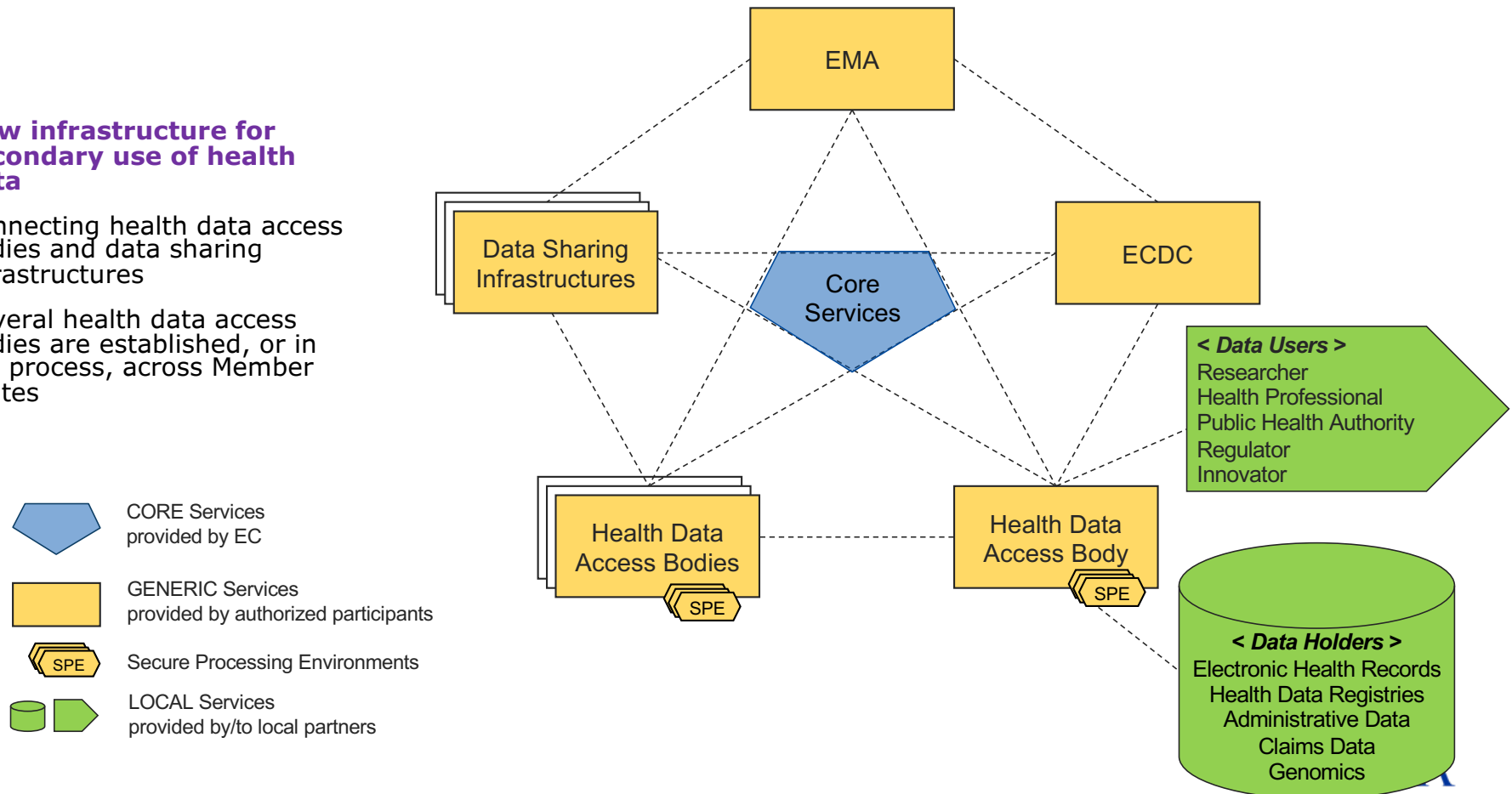
Juvenile polymyositis (JPM) and dermatomyositis (JDM) and disease natural history in adults and paediatric populations (PDCO request to better understand the disease context)

Largest European DM & PM study showing increased prevalence over time and clinical manifestations and treatments prescribed in line with most recent clinical criteria and recommendations

Used by PDCO in a PIP as results suggested sufficient patients available to perform a controlled clinical trial
—> **Request made to the applicant**

HealthData@EU: A vision

- **New infrastructure for secondary use of health data**
- Connecting health data access bodies and data sharing infrastructures
- Several health data access bodies are established, or in the process, across Member States



A European consortium to build and operate a first version of the EHDS



HealthData@EUpilot

17 partners, 9 countries



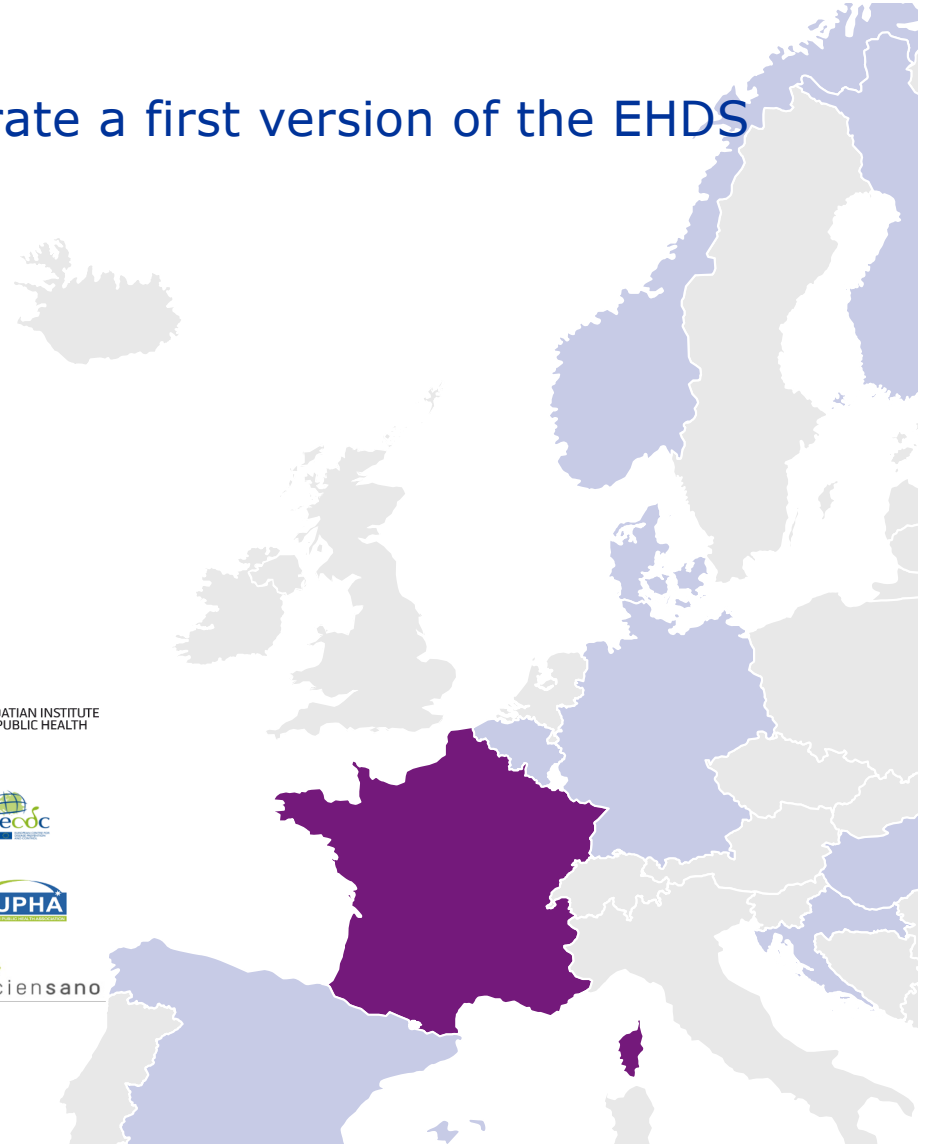
Create and test a beta version of the EHDS



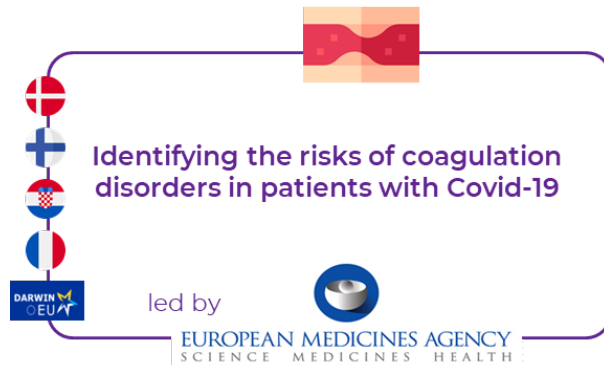
Build a network of data platforms on a European scale...



...tested by concrete cross-border use cases

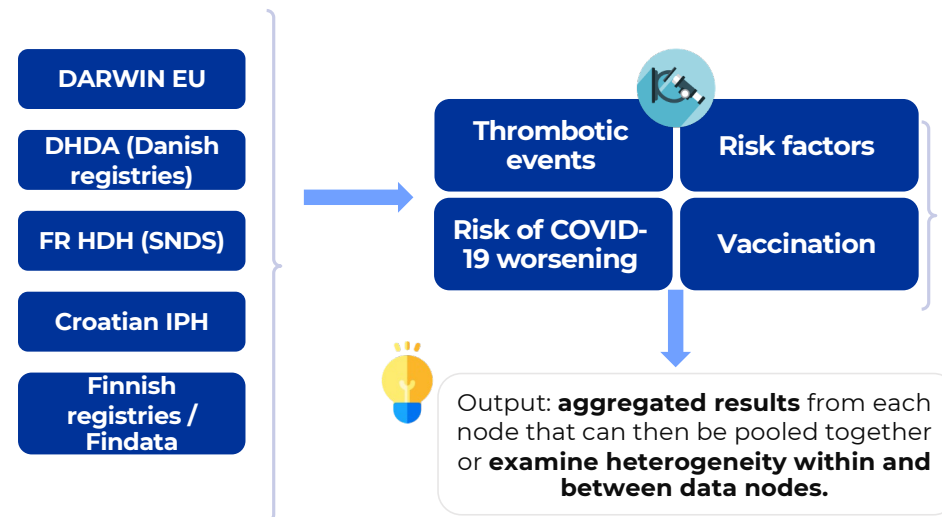


Natural history of coagulopathy in COVID-19 patients and persons vaccinated against SARS-CoV-2 in the context of the Omicron variant



Why?

1. **Inform** about elements needed to build the EHDS
2. **Test** capabilities of data permit authorities acting as HDAB
3. **Demonstrate** performance of an interoperable re-usable network for RWE generation



Aim

To estimate incidence rates of thromboembolic events among patients with Covid-19 and among vaccinated people, compared to general population during the period **when Omicron was the dominant variant.**

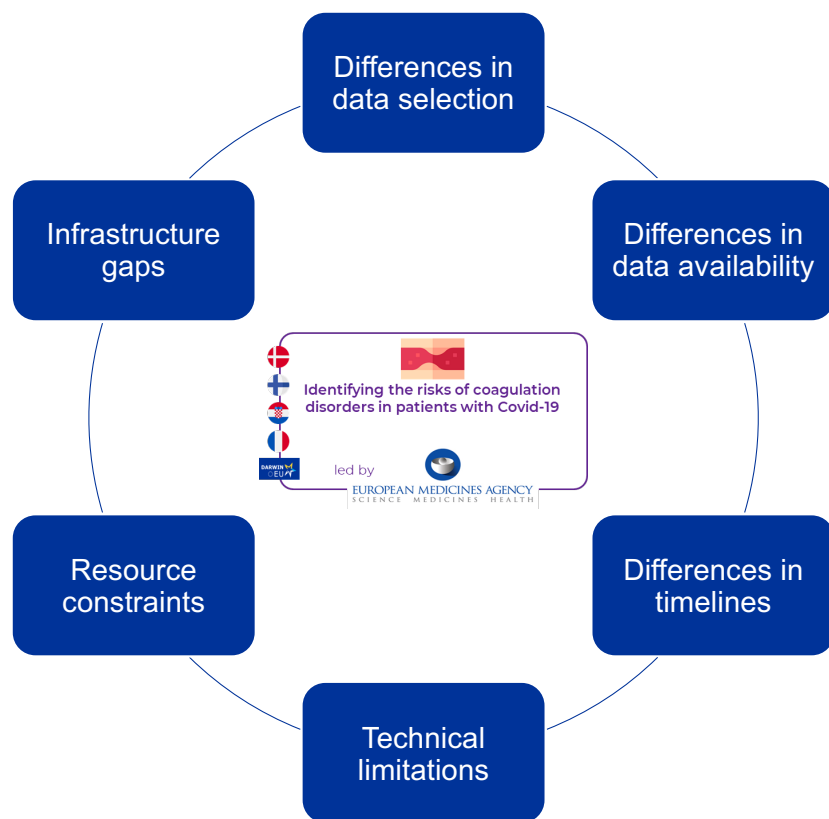


Research approach

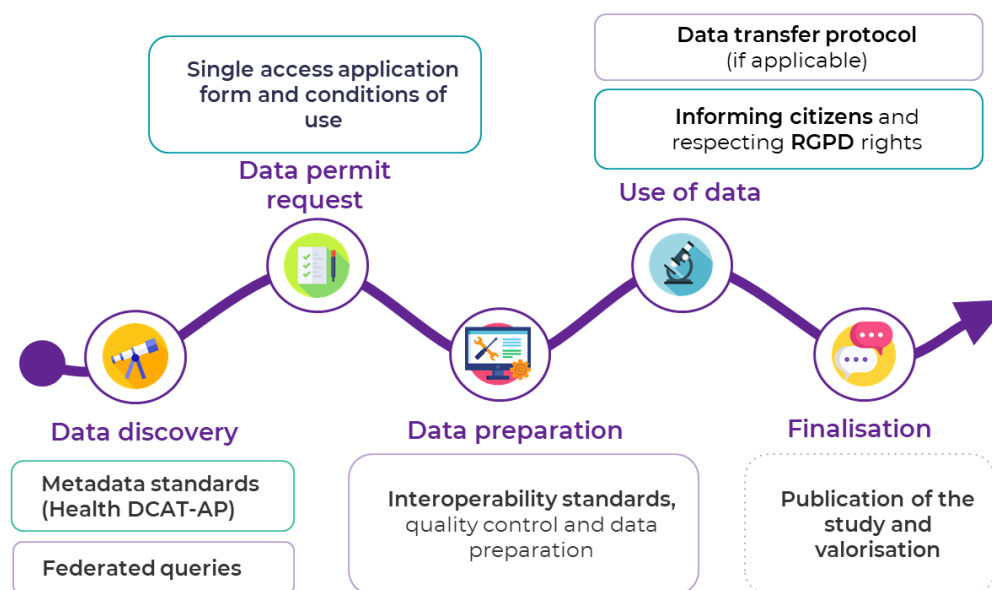
Research methodology:

- Remote implementation of **common protocol** by each node in a **federated analysis model**.
- DARWIN EU CC will use **OMOP** CDM
- Other data nodes will perform **native data analysis AND** execute DARWIN EU CC package on **OMOP** converted data

From learnings to solutions



European Health Data Space



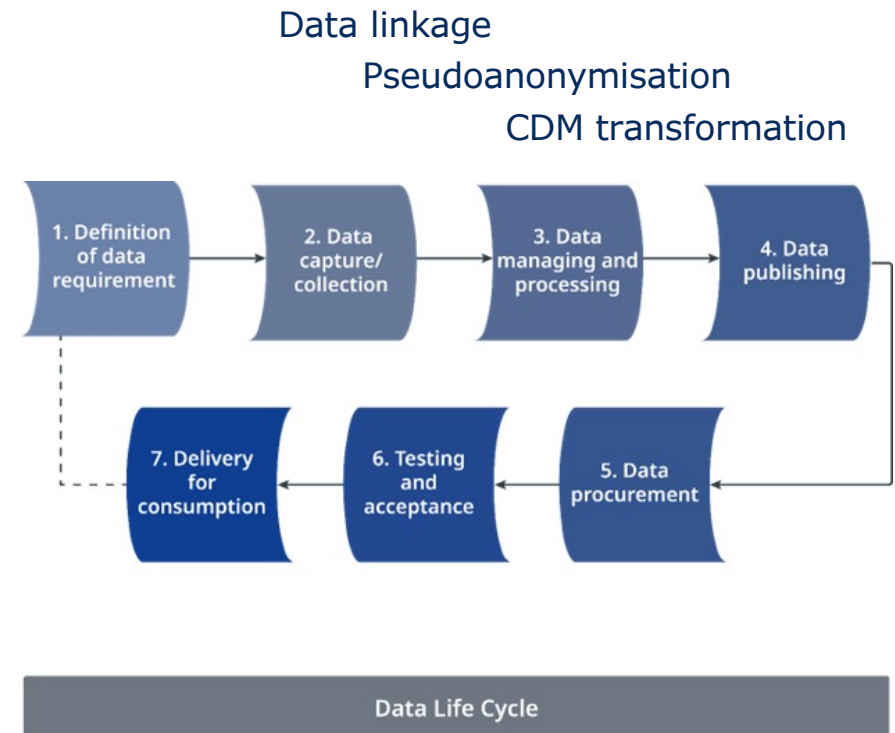
Data Quality

Data quality is important

- Transparency, reliability, efficiency, **trustworthiness**.
- Data used for secondary purposes are not 'perfect', so we need to demonstrate that they are good enough.

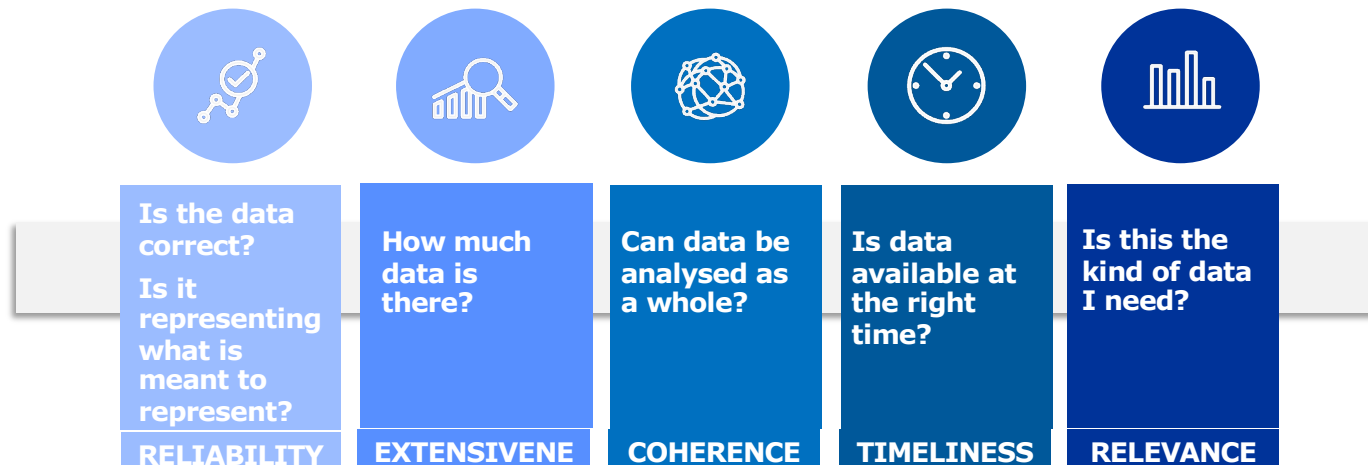
Data quality assessment is complex

- RWD are heterogeneous in terms of their structure, format, variables, terminology used and their collection process
- RWD for secondary use have a **lifecycle** in terms of recording, aggregation, transformation, cleaning to become 'research ready'



EMA Data Quality Framework

Main dimensions



Describes concepts **applicable to all data sources used in medicine regulation**

- Reliability – difficult to control data collection, more focus on error detection
- Extensiveness – measure completeness but not all types of missingness
- Coherence – different collection/recording approaches
- Relevance – suitability of data to a research question



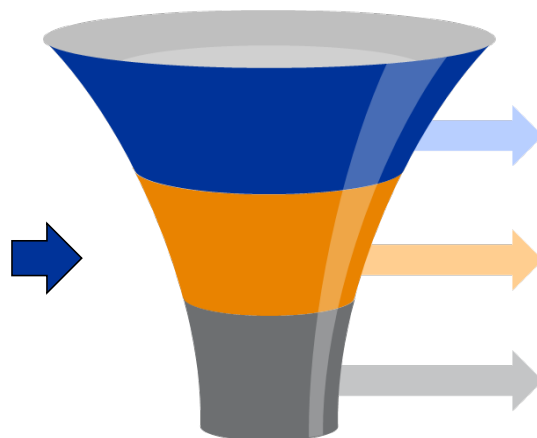
EMA Data Quality Framework: RWD extension

Data source characterization checklist

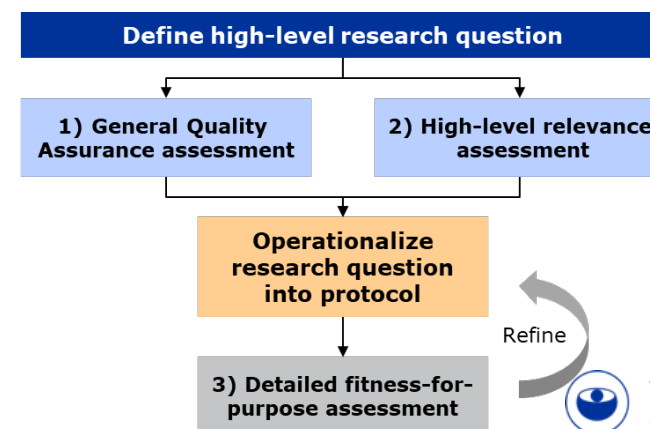
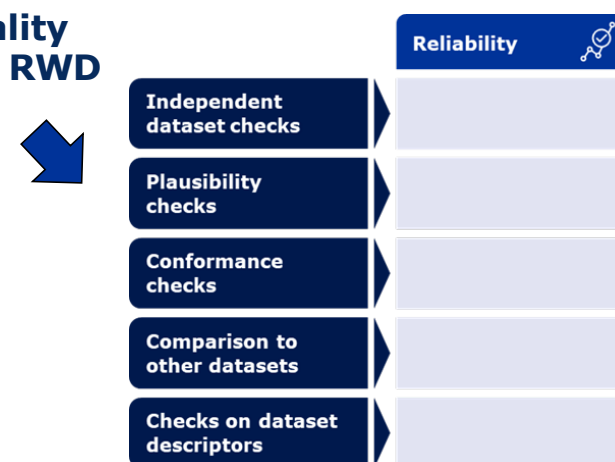
- | | |
|--|---|
| ☐ Rationale and scope for the RWD source creation | ☐ Data augmentation steps |
| ☐ Data collection process | ☐ Known quality issues and independent QA assessment |
| ☐ Selection of data sources and their onboarding | ☐ RWD source data representation |
| ☐ Data management infrastructure | ☐ RWD source declared SLAs |
| ☐ Data management and governance | ☐ RWD source licensing and restrictions |
| ☐ Data manipulation steps | ☐ Feedback |

1. Systems and process characterisation

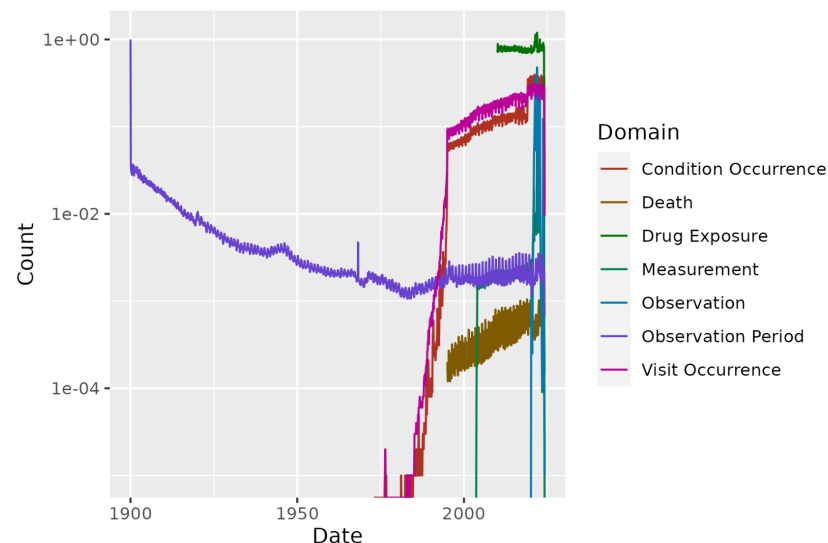
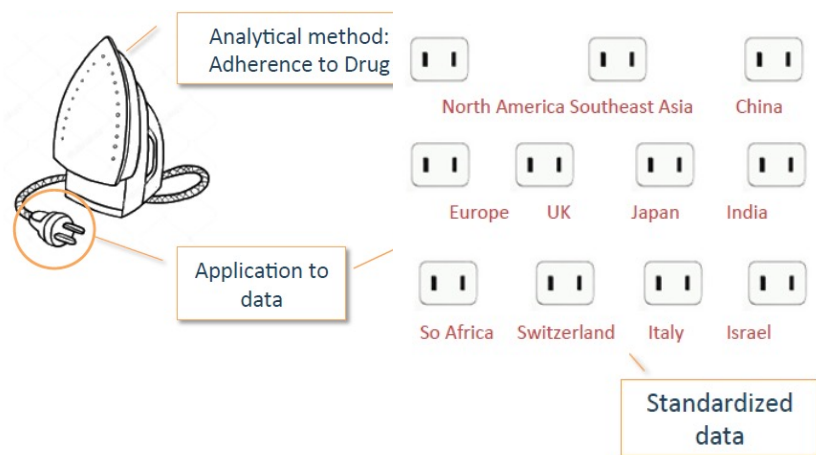
3. Assessing quality in relation to a research question



2. Data quality metrics for RWD



Common data models



Record counts per person over time / per common data model table

Mini/max event start date in each table, within an observation period and at least 5 records

Domain	N	Type	Start date [Min, Max]	End date [Min, Max]
Condition	285,652,418	Registry (S)	[1941-09, 2024-03]	[1995-01, 2019-12]
Death	868,438	Registry (S)	[1991-08, 2024-03]	[NA, NA]
Drug	768,128,860	Registry (S)	[2010-01, 2024-03]	[2009-12, 2064-07]
Measurement	7,026,210	Registry (S)	[1998-12, 2024-03]	[NA, NA]
Obs. Period	9,127,552	Registry (S)	[1898-12, 2500-12]	[1983-11, 2500-12]
Observation	20,984,735	Registry (S)	[2020-02, 2024-03]	[NA, NA]
Visit	351,635,686	Registry (S)	[1941-09, 2024-03]	[1969-09, 2024-03]

Characterising pregnancy data in DARWIN EU

Questions

1. Can we identify data partners with source data on pregnancies?
 - Pregnancy start and end dates, pregnancy outcomes and mother-child linkage.
2. How do OMOP pregnancy algorithms perform and is further development needed?
3. Should we use the OMOP pregnancy expansion table?

Expected outcomes

- Establish conventions, understand data quality, support feasibility, allow characterization.

RESEARCH ARTICLE

Inferring pregnancy episodes and outcomes within a network of observational databases

Amy Matcho^{1*}, Patrick Ryan², Daniel Fife², Dina Gifkins², Chris Knoll¹, Andrew Friedman³

Expanding the OMOP Common Data Model to Support Perinatal Research in Network Studies

Alicia Abellan¹ | Edward Burn^{1,2} | Nhung T. H. Trinh³ | Theresa Burkard² | Alison Callahan⁴ | Sergio Fernández-Bertolin¹ | Eimir Hurley³ | Clara Rodriguez¹ | Elena Segundo⁴ | Daniel R. Morales⁵ | Hedvig M. E. Nordeng^{1,6} | Talita Duarte-Salles^{1,7}

CDM Field / Description

Required fields

person_id Unique identifier of the pregnant person

pregnancy_id Unique identifier of each pregnancy episode

pregnancy_start_date Date when the pregnancy episode started (based on ultrasound last menstrual period if ultrasound information is missing)

pregnancy_end_date Date when the pregnancy episode ended (based on the date of t

gestational_length_in_day Length of gestation in days

pregnancy_outcome Outcome of the pregnancy: livebirth, miscarriage (<20 weeks), termination of pregnancy, discordant (different outcomes in multiple pregnancies), un

pregnancy_mode_delivery How the delivery was initiated: vaginal, c-section, unkno

pregnancy_single Single pregnancy: yes if single, no if multiple, unknown

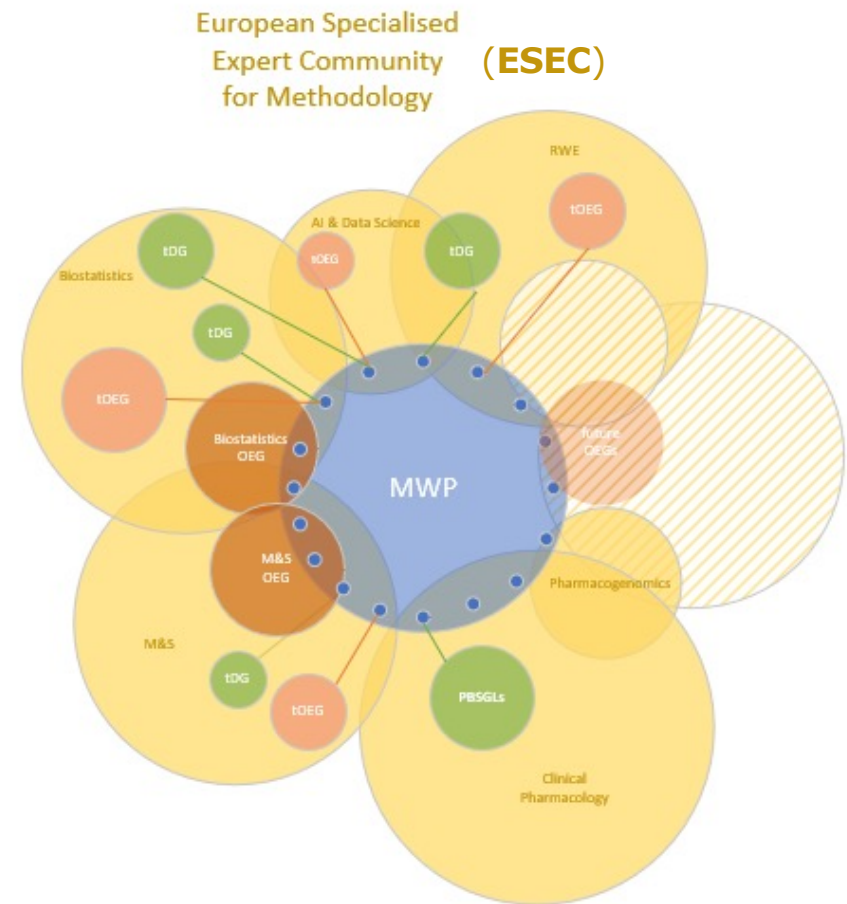
Methodological guidance development

Methodology Working Party (MWP)

- Provide product-related support,
- Preparing, reviewing & updating guidelines/concept papers;
- Providing training and workshops to assessors

European Specialised Expert Community (ESEC)

- AI & Data science
- Biostatistics
- Clinical Pharmacology
- Modelling & Simulation
- Pharmacogenomics
- **Real World Data**



EMA Reflection paper on the use of real-world data in non-interventional studies



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 March 2025
EMA/99865/2025
Committee for Human Medicine Products/
Methodology Working Party (CHMP/MWP)

Reflection paper on use of real-world data in non-interventional studies to generate real-world evidence for regulatory purposes

Draft agreed by Methodology Working Party (MWP)	October 2023
Adopted by CHMP PROM for release for consultation	15 April 2024
Start of public consultation	3 May 2024
End of consultation (deadline for comments)	31 August 2024
Agreed by Methodology Working Party (MWP)	March 2025
Adopted by CHMP PROM	17 March 2025

The target trial emulation (TTE) framework should be considered as a strategy that uses existing tools and methods to formalise the design and analysis of NIS using RWD with causal objectives.

The estimand framework described in the ICH E9 (R1) Addendum on Estimands and Sensitivity Analysis in Clinical Trials should be considered in the design of the hypothetical trial, such as the attributes of the estimand, intercurrent events and strategies to handle intercurrent events.

This will help increase the coherence between definitions...between the NIS and the target trial

The lack of randomisation and blinding still requires attention....

ROC19: TARGET-EU

Comparative effectiveness and safety studies using the target trial emulation and estimand frameworks

Specific Contract 04 implementing FWC EMA/2020/46/TDA/L5.06

Concept paper on external controls

Motivation

- Relevant proportion of dossiers with pivotal data from single-arm trials (SATs)
 - Across different therapeutic areas (incl. rare diseases)
 - Recurring challenges for regulatory assessment
 - No dedicated regulatory guidance on role of external controls
- Need to (1) communicate challenges with ECs, and (2) improve design, conduct, analysis, interpretation and assessment
 - Clarify under which circumstances ECs can be used to generate fit-for-purpose pivotal evidence for regulatory decision making


EUROPEAN MEDICINES AGENCY
SCIENCE · MEDICINES · HEALTH

1 17 April 2023
2 EMA/CHMP/564424/2021
3 Committee for Medicinal Products for Human Use (CHMP)

4 [Reflection paper on establishing efficacy based on single-arm trials submitted as pivotal evidence in a marketing authorisation](#)
5
6
7 Considerations on evidence from single-arm trials

8 Draft

Draft agreed by Drafting Group on single-arm trials	27 January 2023
Adopted by CHMP for release for consultation	17 April 2023
Start of public consultation	21 April 2023
End of consultation (deadline for comments)	30 September 2023

9 Comments should be provided using this [template](#). The completed comments form should be sent to BP-SATs@ema.europa.eu

10

11

Keywords	Single-arm trials, non-randomised trials, regulatory decision making
----------	--

Official address: Domenico Scarlati laan 6 • 1083 HS Amsterdam • The Netherlands
Address for visits and deliveries: Refer to www.ema.europa.eu/how-to-find-us
Send us a question: Go to www.ema.europa.eu/contact Telephone +31 (0)88 781 6000 An agency of the European Union



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Thank you

daniel.morales@ema.europa.eu

Follow us

