Update on Real-World Evidence and DARWIN EU

CAT Industry Interested Parties Meeting
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Disclaimer

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Outline

• Real-World Evidence (RWE) definition

• European Medicine Regulatory Network approach to RWE
  • RWE in marketing authorisation applications
  • RWE provided by the network to support regulatory decision making

• How the vision will be delivered
  • DARWIN EU
  • Piloting with the committees
Real-World Data and Real-World Evidence

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

**Real-World Evidence (RWE):** information derived from analysis of real-world data.
Use of RWD/RWE and the European Medicines Regulatory Network (EMRN) role

**RWD/RWE provided by**

- Pharmaceutical companies

**RWD/RWE used to**

- Support marketing authorisation submissions

**EMRN role**

- Guidance

**National competent authorities or EMA**

- Support committees’ decision making

- Advice

- Analyses/studies
RWD/RWE in marketing authorisation submissions

**Aim**

- To support submission of RWE of high validity and relevance and therefore optimal use of the RWE to support regulatory decision-making

**How**

- To support marketing authorisation applicants (MAAs) by providing guidance on the format and content of submission of RWE, e.g. *Guideline on registry-based studies (Oct 2021)*

- Templates and check-lists for feasibility analyses on appropriateness of RWE data sources (e.g. registries and electronic health care records)

- Standard definitions (internationally agreed), quality assessment criteria,...

**On going initiative**

- Study to characterise RWD/E included in applications and explore its contribution to decision making
RWE by EMRN

- International regulators have been establishing systems for generating the evidence needed, e.g. FDA Sentinel system, Health Canada CNODES, PMDA MID-NET,...
Data (and studies) discoverability and characterisation

A catalogue of data sources (including registries) is being developed - Q4 2022 (TBC)

• The catalogue will be a newer and better version of the current ENCePP Resources Databases, focusing on data sources available in EU

• The catalogue will be searchable, and will include metadata describing the main characteristics of each data source
  • E.g. population size, demographics, type of care covered, diseases of interest covered,…

• In the future, information on quality of the data source might also be included

A catalogue for studies based on EU PAS Register will also be delivered - Q4 2022 (TBC)

• Useful to identify what studies have been done on a disease/product and which data sources have been used
Sources of evidence for regulatory committees

1. **Studies** on the electronic health databases accessible in-house

2. **Studies procured** through the EMA framework contracts

3. **DARWIN EU** (starting from 2022)

- Requests or obligations to pharmaceutical companies
- Analysis of public information including public scientific literature
Coming in 2022: Data Analysis and Real-World Interrogation Network - DARWIN EU®

DARWIN EU is a federated network of data, expertise and services

**EU Medicines Regulatory Network**

- **EMA** - provides leadership, setting standards, contracting studies, overseeing
- **EMRN** - including EMA scientific committees and working parties, national competent authorities (NCAs) and the European Commission: *request studies* via EMA

**The Coordination Centre**

- Establishes and *maintains the network* (including onboard/maintain data sources), manage the *execution of scientific studies*

**Data Partners, incl. Data Permit Authorities**

- **Partners** who have access to data, or who may request analyses in a data source and provide results to the Coordination Centre
- This includes **Data Permit Authorities** (DPAs), already existing or to be created as part for the European Health Data Space (EHDS)
DARWIN EU® - High level timelines

**2021**
- Selection of the Coordination Centre provider

**Phase I and II - 2022/2023**
- Establish connectivity with EHDS and existing Data Permit Authorities
- Start recruiting and onboarding the data partners
- First catalogue of standard data analyses available
- Start running pilot studies to support EMA committees - first benefits delivered

**Phase III - 2024**
- DARWIN EU® to be fully operational and routinely supporting the scientific evaluation work of EMA and NCAs’ scientific committees

**Operation - 2025/2026**
- DARWIN EU® to continue to evolve
- Full integration with the EHDS
3 DARWIN EU® Advisory Board

• Mandate
  
  • Provide **strategic advice** and **recommendations** to the project team on the **establishment** of the DARWIN EU capability and its **use of the European Health Data Space**
  
  • **Ensure continued coordination and alignment** with relevant European initiatives and policy
  
  • Support **two-way communication** with the stakeholders

• Stakeholders

  • **European Commission, National Competent Authorities (NCA), HTA, Payers association, Data Permit Authorities, Joint Action TEHDAS, EU patient associations, EU healthcare professional associations, European Centre for Disease Prevention and Control agency (ECDC), and European pharmaceutical industry** (as observer)

  • Through **collaboration**, we will deliver more for public health
DARWIN EU® - Benefits

- National and EU regulation of medicines
  - **Drug development** – disease epidemiology, unmet need, historical controls, planning
  - **Authorisation** – contribution to BR, controls, extrapolation to general and/or special populations
  - **Post-authorisation** – benefit-risk monitoring, extension of indication, risk minimisation measures

DARWIN EU will significantly **increase the capacity** of the Network to undertake high-quality observational studies based on real-world data

- **Additional benefits** as EU partners participate and access the platform:
  - **European Commission** – key use case for the European Health Data Space
  - **National governments** to support health policy and delivery of healthcare systems
  - **HTA bodies and payers** to support better quality decisions on cost-effectiveness
  - **EU health agencies** - use cases specific for EFSA, ECDC, ECHA, JRC
  - **EU patients** - faster access to innovative medicines and safe and effective use
# RWE generated through regulators – Use cases

From a regulatory perspective, RWE aims to support committees’ decision-making in three main areas:

<table>
<thead>
<tr>
<th>Use case category</th>
<th>Use case objective</th>
<th>Support the planning &amp; validity of applicant studies</th>
<th>Understand clinical context</th>
<th>Investigate associations and impact</th>
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<tbody>
<tr>
<td></td>
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<td>Design and feasibility of planned studies</td>
<td>Disease epidemiology</td>
<td>Effectiveness and safety studies</td>
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<td>Representativeness and validity of completed studies</td>
<td>Clinical management &amp; drug utilisation</td>
<td>Impact of regulatory actions</td>
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Pilot-based approach to iteratively refine and implement RWE processes and use cases

Interacting with scientific committees to agree PoC and pilots

- **PRAC**: implementing the lessons learnt from 2019-21 pilot
- **SAWP**: pilot starting in 2021
- **CAT, COMP, PDCO**: PoC in 2021, pilot starting in 2022
- **CHMP**: Pilot starting in 2022

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<tr>
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<th>Q4 2021</th>
<th>Q1-Q4 2022</th>
<th>From 2023</th>
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<tbody>
<tr>
<td><strong>Proof of concept phase</strong></td>
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<tr>
<td>Studies on databases accessible <strong>in-house</strong></td>
<td>●</td>
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<tr>
<td><strong>Procured</strong> studies through framework contracts</td>
<td>●</td>
<td></td>
<td>(additional data sources from Dec 2021)</td>
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<td>Studies via <strong>DARWIN EU</strong></td>
<td>●</td>
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<td>(first pilot studies)</td>
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<tr>
<td><strong>Pilot phase</strong></td>
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<td>●</td>
<td>●</td>
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<tr>
<td><strong>Routine support</strong></td>
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Aim to support the majority of Committees in their decision-making with valid and reliable evidence at EU level by 2023
Conclusions

**Aim**

Pharmaceutical companies

Support marketing authorisation submissions

National competent authorities or EMA

Support scientific committees’ decision-making with valid and reliable evidence at EU level

**On-going work**

Further analysis ongoing to evaluate the impact and usefulness of RWE in MA

On-going initiatives to increase both the generation and the use of RWE

Pilot-based approach to iteratively refine and implement RWE processes and use cases

**Vision 2025**

Role of RWE established across spectrum of regulatory use cases

Regulation more data-driven: includes analysis of CTs and RWD

Better evidence supports better decisions on medicines for patients
Any questions?

Further information

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What should be the criteria for acceptability of RWE?

**WHAT**

**Data source**
- **Adequate**: amount of information needed for regulatory decision-making, e.g. sufficient **sample size** and sufficient **information** on patient characteristics, treatments (doses, duration of prescription, formulation), morbidities and risk factors
- **High quality**: derived from real-data sources of demonstrated quality and **accuracy** (validation)

**Methods**
- Internal **validity**: accurate representation of what it intended to measure (i.e. no bias)

**Consistency**
- Across countries/data sources, or differences can be explained

**HOW**

**Transparency**
- **Replicability**: A priori specification

**Timeliness**
- We finally got the results of your data query. Sorry it took so long.
Studies on electronic health databases accessible in-house (EMA)

- Currently **three primary care databases** (UK, FR, DE)
- **99** EMA in-house analyses or studies performed from 2013
  - The studies supported evidence needs of EMA Committees, mainly Pharmacovigilance (PRAC)
- **PRAC pilot**: November 2019 - January 2021
- On-going procurement to increase **geographical representation** and access to **hospital** prescribing

Studies procured through the EMA framework contracts

- Allows access to **different data sources** and **scientific expertise**
- **30 studies** funded from 2010, e.g.
  - **vAACine covid-19 monitoring readinESS (ACCESS)**: background rates for adverse events of special interest
  - Ranitidine - potential risk of cancer associated with N-nitrosodimethylamine (NDMA)
- A **new framework contract**, with a broader set of organisations and **data sources** from October
3 DARWIN EU® - Process for conducting analyses and studies

NCA/EMA Committee

- Question that impacts committee opinion
- Integrate data and reports in the assessment report

NCA/EMA

- Evaluates relevance and feasibility of RWD
- Define the research questions

Coordinating centre in consultation with EMA

- Create protocol and programming code
- Contact relevant Data partners
- Manage specific study governance (ethics, ...)

Data Partners (may include NCA/EMA)

- Receive and run the code on their own DBs
- Aggregate data and results sent to the coordinating centre

Key principles
- Data stays local
- A common data model will help performing studies timely and increasing consistency of results