DARWIN EU ® – first experience and regulatory use cases

EMA/HMA Big Data Stakeholder Forum 2022

1st December 2022

Presented by Xavier Kurz
Data Analytics and Methods Taskforce, European Medicines Agency

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DARWIN EU

EUROPEAN MEDICINES AGENCY

By 2025 the use of Real-World Evidence will have been enabled and the value will have been established across the spectrum of regulatory use cases

- European Medicines Regulatory Network (EMRN) strategy to 2025 -

Three main areas for which RWD analyses can support EMA scientific committees for decision-making

1 Support the planning and validity of applicant studies

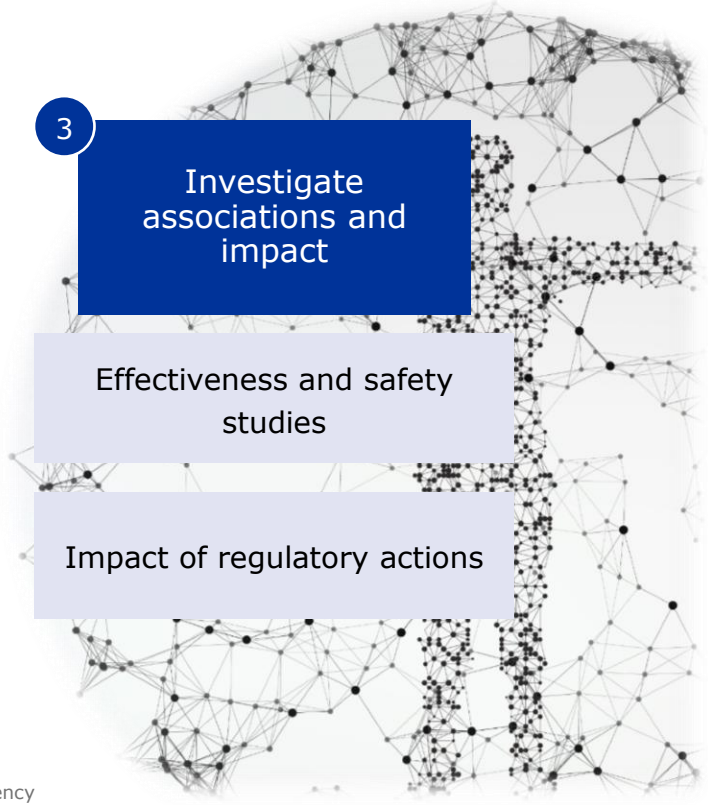
- Design and feasibility of planned studies
- Representativeness and validity of completed studies

2 Understand the clinical context

- Disease epidemiology
- Clinical management
- Drug utilisation

3 Investigate associations and impact

- Effectiveness and safety studies
- Impact of regulatory actions



How does EMA can generate Real-World Evidence

EMA studies using in-house databases

- Primary care health records from the **UK, France**, and **Germany**
- In progress - **four extra databases**: primary care from **Italy, Spain and Romania** and hospital data from the **UK**
- By Q3 2022 hospital prescribing from **France**

Studies procured through EMA FWCs

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

DARWIN EU®

- Federated network of **data sources** providing **evidence from real world healthcare data**
- **Data stay local**
- **Use of common data model** to perform studies in a timely manner and increase consistency of results
- Coordination centre : Erasmus University Medical Centre Rotterdam

DARWIN EU: Implementation roadmap

Phase I - 2022

- Start running pilot studies to support EMA committees – **first benefits delivered**
  - Coordination Centre set-up
  - Data Protection Impact Assessment
  - Start recruiting and onboarding 10 data partners
  - Pilot with the EHDS model and existing Data Permit Authorities
- Consultation of stakeholders

Phase II - 2023

- Support the majority of Committees in their decision-making with reliable RWE by 2023

Phase III - 2024

Up scale delivery and capacity to routinely support the scientific evaluation work of EMA's scientific committees and NCAs by delivering studies and maintaining data sources.

Operation - 2025/2026

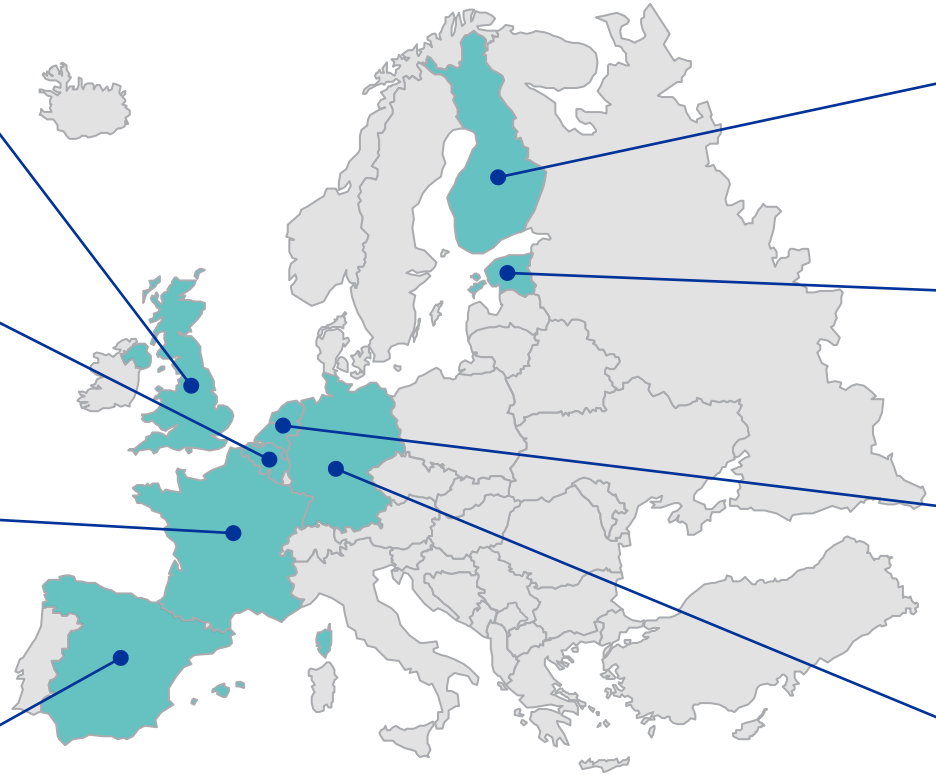
- DARWIN EU® to be fully operational and yearly evolves to meet the needs from the EU Regulatory Network
- **Integration with the EHDS**

- Total of 40 databases are foreseen to be recruited in 4 years
- Over 5 years, ~380 studies will be conducted

Benefits of DARWIN EU®

- Provide scientific expertise in formulating and executing studies and analyses
- Maintain a catalogue of known, relevant data holders, continually ensuring the discoverability & quality of data held by data holders
- Maintain & expand the federated network of data partners, assisting new data holders in conforming with required standards for usage in regulatory context
- Conduct scientific studies and analyses on behalf of the EMRN and EMA scientific committees
- Deliver training, governance, support of business services
- Enable the EMRN, EMA and the scientific committees to make use of the EHDS in the context of medicines regulation, acting as EHDS 'pathfinder'

Data Partners – Phase I



UK

1. Clinical Practice Research Datalink (CPRD GOLD)

Belgium

2. IQVIA Belgium Longitudinal Patient Data

France

3. Bordeaux University Hospital

Spain

4. IDIAPJGol
5. Parc Salut Mar Barcelona, Hospital del Mar (IMIM)

Finland

6. Auria Clinical Informatics at Hospital District of Southwest Finland (HDSF)

Estonia

7. University of Tartu (Biobank)

Netherlands

8. Integrated Primary Care Information
9. Netherlands Comprehensive Cancer Organisation

Germany

10. IQVIA Germany Disease Analyser

~26 million active patients

Experience from the onboarding of the first set of data partners

* Use of selection criteria

- Data sources collecting health data routinely and different types of real-world data √
- Data sources which collectively provide a broad geographical cover √
- Data sources containing patient-level data √
- Medicines prescribed or dispensed identifiable with quantities (e.g. doses, package size) and dates and linked to individual but unidentifiable patients √
- Clinical events formally coded, with accurate dates and linked to individual patients √
- Data already converted or planned to be converted into a common data model (OMOP) √

Experience from the onboarding of the first set of data partners

* Considerations for Year 2

- Balance between onboarding of "general purpose" population-based datasets (without restriction as to products and diseases) and specialised datasets such as specific disease registries
- Research questions from EMA Committees and other stakeholders may guide the selection of suitable data partners
- Selection of non-EU data partners if they add value (e.g. large drug utilisation databases and hospital databases from the US)
- Some data sources may need to be converted into OMOP common data model

What analyses and studies will DARWIN EU® deliver?

Category of observational analyses and studies	Description
Routine repeated analyses	Routine analyses based on a generic study protocol • Periodical estimation of drug utilisation • Safety monitoring of a medicinal product • Estimation of the incidence of a series of adverse events
Off-the-shelf studies	Studies for which a generic protocol is adapted to a research question • Estimate the prevalence, incidence or characteristics of exposures • Estimate the prevalence, incidence or characteristics of health outcomes • Describe population characteristics
Complex Studies	Studies requiring development or customisation of specific study designs, protocols and Statistical Analysis Plans (SAPs), with extensive collection or extraction of data • Etiological study measuring the strength and determinants of an association between an exposure and the occurrence of a health outcome considering sources of bias, potential confounding factors and effect modifiers
Very Complex Studies	Studies which cannot rely only on electronic health care databases, or which would require complex methodological work • Studies where it may be necessary to combine a diagnosis code with other data such as results of laboratory investigations, or studies requiring additional data collection

DARWIN EU® Studies – Phase I

Type	Studies	Data Partners	Planned RWE use	Committee	
OTS	**Population level epidemiology** study on prevalence of **rare blood cancers** from 2010.	NL, ES, UK, BE, DE	Support COMP in orphan designation decision making	COMP	Ongoing
OTS	Patient level **drug utilisation** study of **valproate-containing medicinal products** in women of childbearing potential from 2010	NL, ES, UK, BE, DE, FI	Assess the use of valproate after safety referral	PRAC	
OTS	Patient level **drug utilisation** study of **antibiotics** on the Watch list of the WHO AWaRe classification, 2010-2021	NL, FR, ES, DE, UK	Inform PRAC/CHMP decision making	PRAC – CHMP AMR strategy	
Com plex	Background all-cause **mortality rates in patients with severe asthma aged ≥12 years** old		Support CHMP evaluation and post-authorisation informing future decision making	CHMP	Draft protocol

Timelines Study – C1-002 (valproate study)

Network operations

Interaction with Databases for Onboarding

Start Onboarding Process: Onboarding document + QC package

Onboarding documents sent to EMA for review: **September-October 2022**

Greenlight from EMA on onboarding of databases from Y1

Framework Contract Signature initiated

Datasources for C1-002:
IPCI: approved and **framework contract signed**
SIDIAP: approved and **framework contract signed**
CPRD Gold: approved and **framework contract signed**
IQVIA Germany: onboarding approved
IQVIA Belgium: onboarding approved
HDSF: approved and **framework contract signed**

IRB approval
IPCI (umbrella): approved 4th November 2022
SIDIAP: Scientific committee approved 2nd November 2022 – Meeting for ethical approval planned end of November 2022
CPRD Gold Specific protocol: approved in November 2022
IQVIA Germany: Not needed
IQVIA Belgium: Not needed
HDSF: Submitted to IRB board on the 11th November 2022

Signature of work order contract **(study specific)** generated

Study operations

Study Request
4th July 2022

Feasibility Assessment
15th July 2022

Greenlight from EMA to conduct study
26th July 2022

Study Outline Creation

Protocol Generation
August 2022

Draft Study Outline and Protocol sent to EMA
1st September 2022

EMA review max 15 working days
EMA approval of protocol - 29th September 2022

Governance board approval process (IPCI, SIDIAP, CPRD GOLD, HDSF) (not needed for IQVIA)
November 2022

Study Execution: planned for **November 2022 – December 2022**

Study Report: December 2022

EMA review Max 15 working Days

Parametrisation of general study package on drug prevalence to study specific parameters (valproate, dosing, indication of use)

Deadline for report 17th January 2023

KOM – 18th November 2022

Today:22nd November 2022

DEVELOPMENT ACTIVITIES

Experience from the first set of studies

- Simultaneous onboarding of data partners and pilot testing of study processes (e.g. feasibility assessment, protocol development and assessment)
- Fast delivery of results anticipated after acceptance of protocol
- Number of studies to increase on a yearly basis
- Many research questions already submitted for Year 2 – need for prioritisation
- Drug classes for routine repeated analyses: antibiotics, opioids

European Health Data Space (EHDS)

OBJECTIVES

Effective use of health data

SCOPE & EXPECTED IMPACT

Use of health data (primary, MyHealth@EU)	• Empower individuals to control their data • Standardization and mandatory certification of EHR systems • Voluntary labelling of wellness apps • European Electronic Health Record Exchange Format	**Single market for health data, data protection, free movement of people, digital goods and services**
Re-use of health data (secondary, HealthData@EU)	• Health data access bodies • Purposes for use and forbidden use • Data permits, secure environments, no identification	**Facilitated Research & Innovation** **Better Policy Making**

MEANS

Legal / Governance

Quality of data

Infrastructure

Capacity building/digitalisation

EHDS2 Pilot phase: Use cases at a glance (WP9)

1

Surveillance of antimicrobial resistance

Led by ecdc

2

Natural history of coagulopathy (blood clotting) related events in COVID-19 patients and risk factors

Led by EUROPEAN MEDICINES AGENCY

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3

Population uptake metrics: COVID-19 test positivity, vaccination and hospitalization

Led by sciensano

4

Comparing Nationwide Health trajectories to evaluate European Health Data interoperability: an application to cardiometabolic diseases

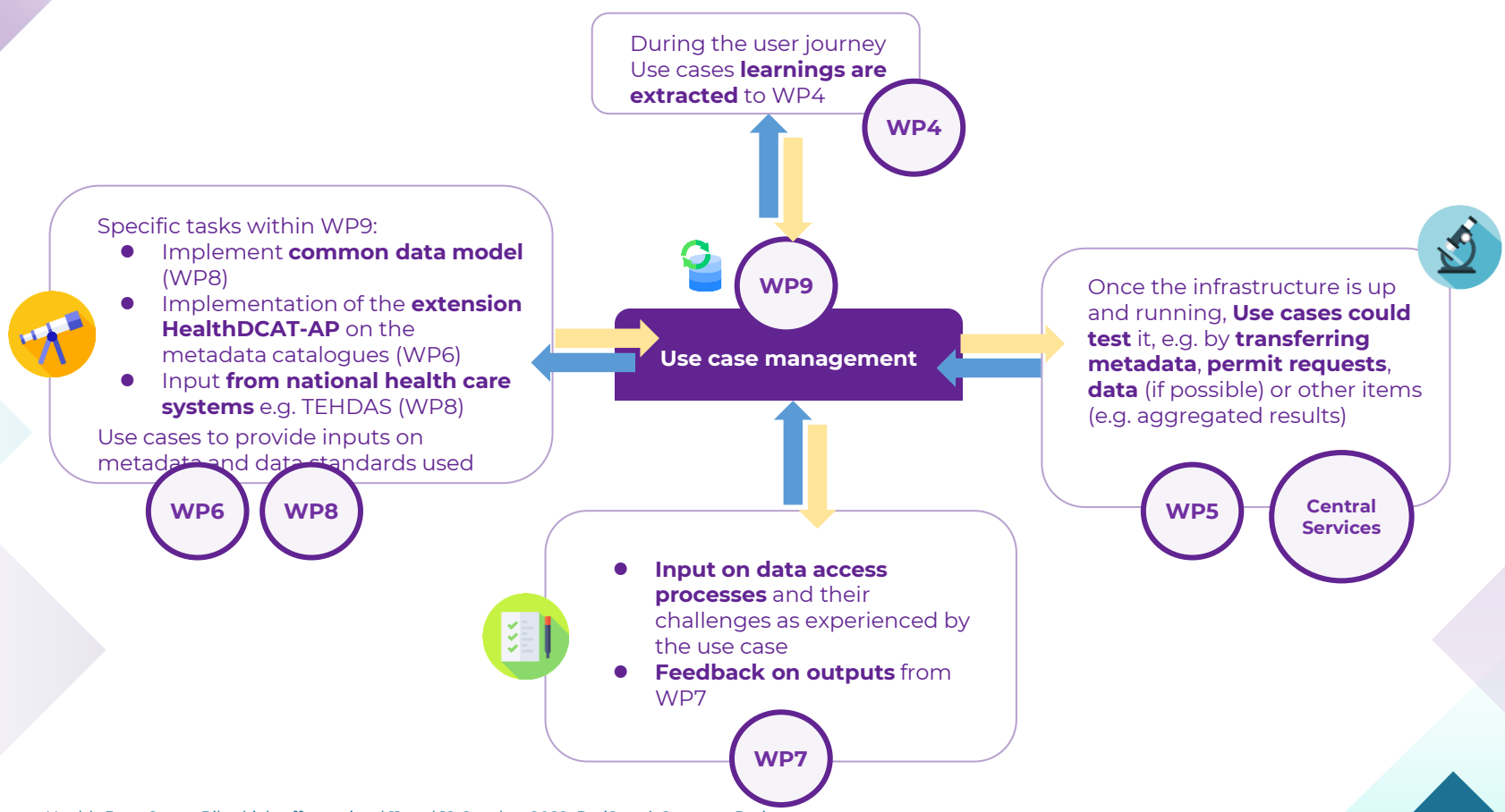
Led by HEALTH DATA HUB

5

Genomic data linked to health data, with a focus on

Led by elixir

How WP9 relates & interconnects with the other technical work packages



Involvement of HTA bodies and payers
(discussion at the DARWIN EU workshop with HTA/Payer representatives)

Suggested domains of interest

- Natural history of disease, which allows to validate the assessment of the control arm, are of interest.
- RWD on chronic diseases based on remote patient monitoring
- Current standard of care – different lines of treatment and follow-up data on long-term effects
- Effects of new drugs – importance of data collection in registries
- Effectiveness studies

Suggested topics

Orphan Medicinal Products (OMPs), Advanced therapy medicinal products (ATMPs), therapies for rare cancers (e.g. multiple myeloma) and blood disorders

Discussion to be continued

Thank you!

Further information

Data Analysis and Real World Interrogation Network (DARWIN EU) | European Medicines Agency (europa.eu)

Official address Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands
Telephone +31 (0)88 781 6000
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