

EUROPEAN  
MEDICINES  
AGENCY

## Update on RWE including DARWIN EU®

---

PCWP and HCPWP plenary - 28 June 2023

Presented by Andrej Segec, Kelly Plueschke, Denise Umuhire  
Data Analytics and Methods Taskforce – Real World Evidence

An agency of the European Union



# Towards delivering the 2025 RWE vision

*A tale with three pathways...*

Countdown to 2025

Enabling use



## EMA studies using in-house databases

- **Primary care** health records from the **France, Germany, UK, Italy, Spain** and **Romania**. Some data sources include data on specialist.



## DARWIN EU®

- Coordination Centre launched February 2022
- Onboarded first **10 data partners**
- **First studies** finalised
- Additional 10 data partners are foreseen to **be added each year** for 2023-2025



## 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**

**+** Regulatory authorities also have access to national databases e.g., Nordic registries, SNDS, BIFAP, ...

# RWE report published, with infosheet

**61**  
research topics

**49**

In-house

**8**

DARWIN  
EU

**4**

FWC

RWE needs

- the **needs** for RWE of CxMP and SAWP;
- the **ability** and **capacity** of the current RWE framework;
- the **usefulness** of the RWE provided.

Suitability of data sources

- the **suitability** of available **RWD sources** and **pathways**;
- the **methodological challenges** of data collection, study design and reporting.

Process for RWE studies

- receiving **study requests**;
- **proactively offering** and **conducting** RWE studies;
- identify **opportunities for improvements**.

# Towards delivering the 2025 RWE vision

*A tale with three pathways...*

Countdown to 2025

Enabling use



## EMA studies using in-house databases

- **Primary care** health records from the **France, Germany, UK, Italy, Spain** and **Romania**. Some data sources include data on specialist.



## DARWIN EU®

- Coordination Centre launched February 2022
- Onboarded first **10 data partners**
- **First studies** finalised
- Additional 10 data partners are foreseen to **be added each year** for 2023 and 2024



## Studies procured through EMA FWCs

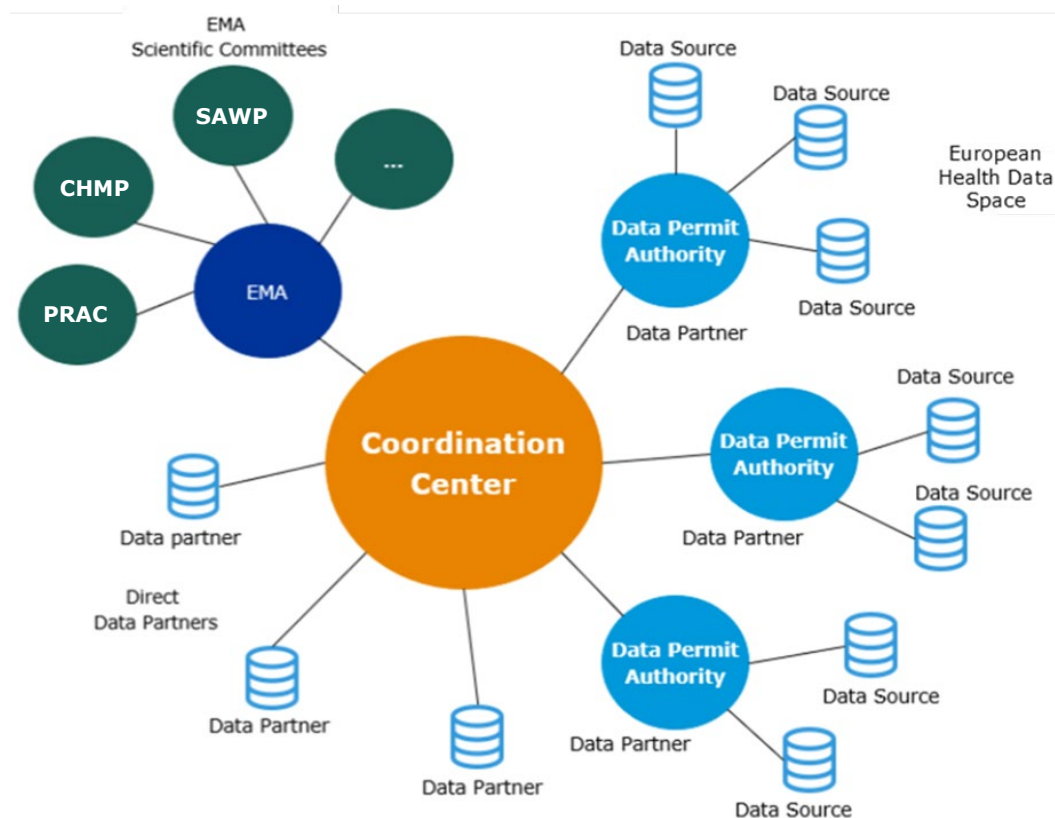
- New framework contract (FWC) since September 2021: services of **8 research organisations** and academic institutes
- Access to **wide network of data sources**: 59 data sources from 21 EU countries
- Ability to leverage external **scientific expertise**

**+** Regulatory authorities also have access to national databases e.g., Nordic registries, SNDS, BIFAP, ...

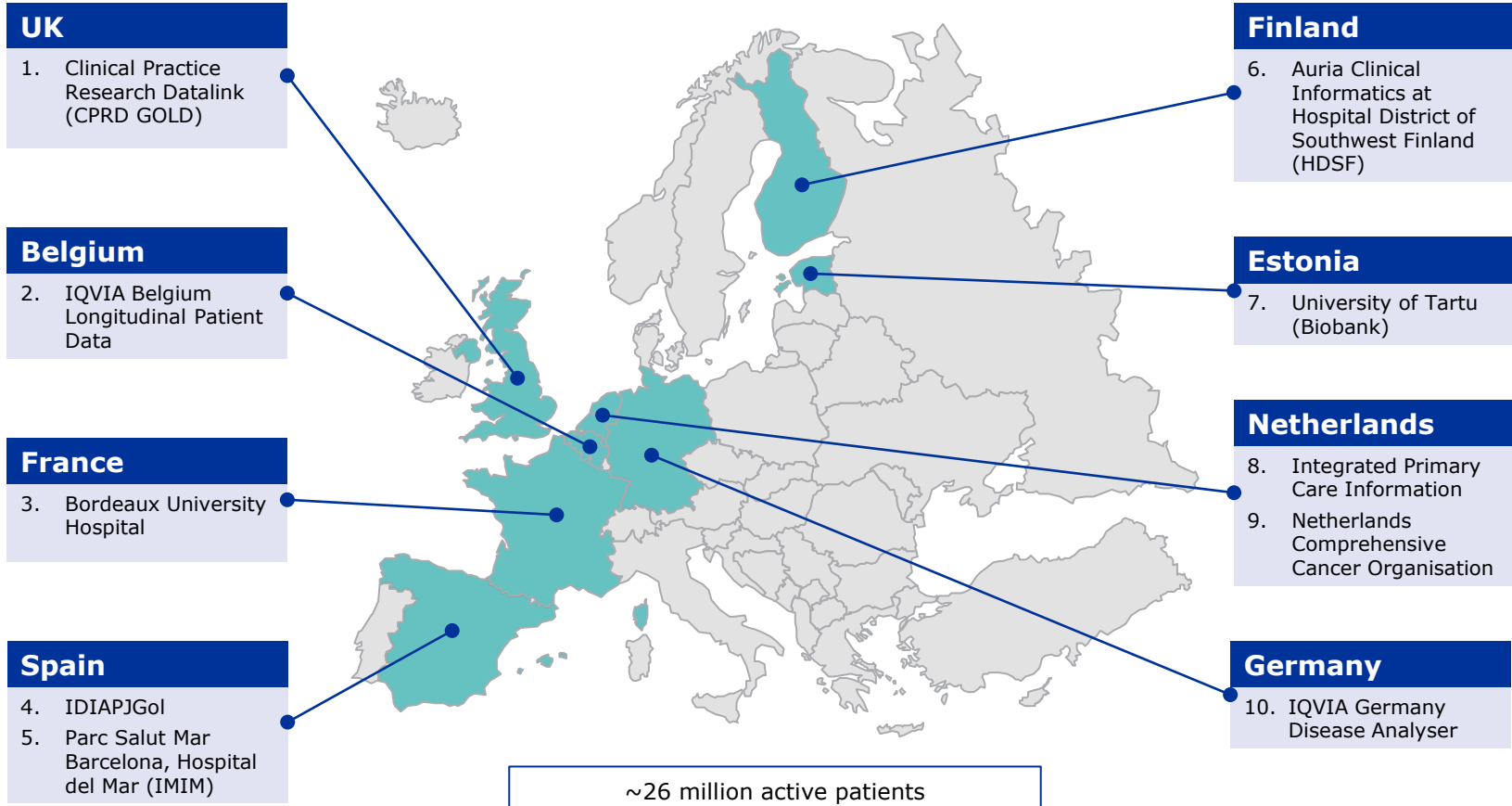
DARWIN EU® is a federated **network of data, expertise and services** that supports better decision-making throughout the product lifecycle by generating reliable **evidence from real world healthcare data**

#### FEDERATED NETWORK PRINCIPLES

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

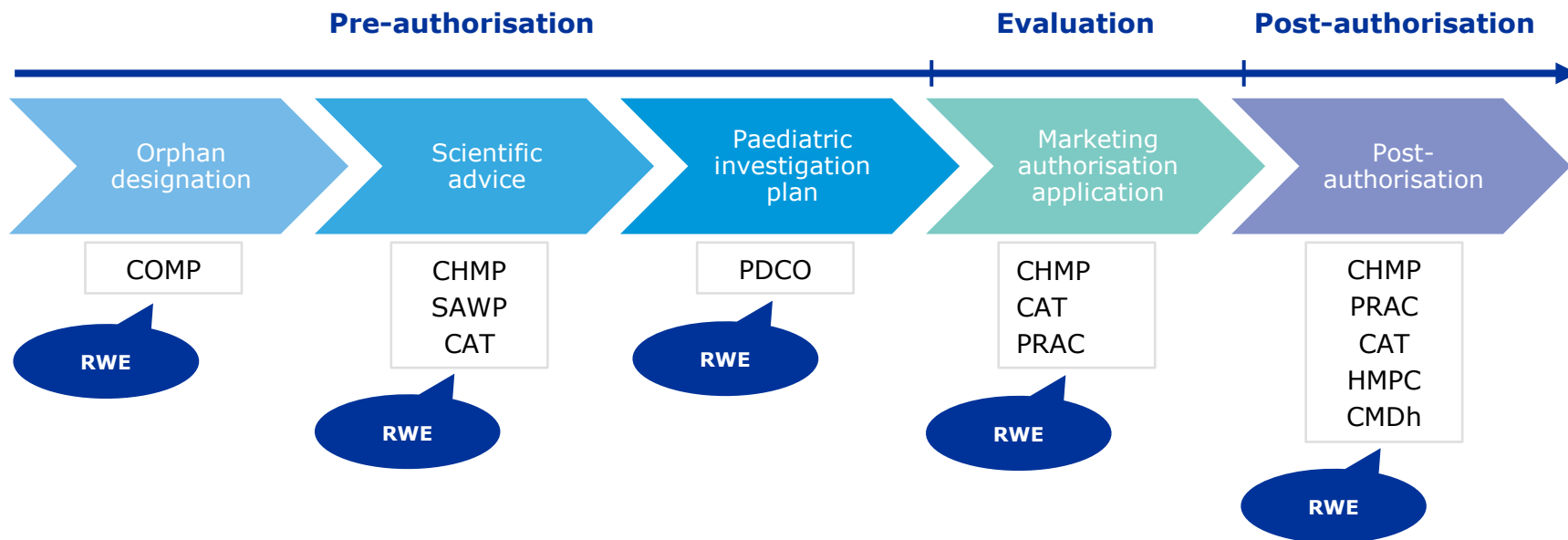


# Data Partners – Phase I



Currently selecting Phase II DPs after [open call for expression of interest](#)

# RWE use across the medicinal product lifecycle



## Milestones completed in 2023

- ✓ Phase II in progress, delivery on target, according to plan
- ✓ Focus on selection of further DPs and study conduct (various use cases)
- ✓ Establishment of analytical pipelines and codes

		Phase I	Phase II	Phase III	Option I	Option II
<b>Studies</b>	<b>Off the shelf</b>	2	6	30	60	60
	<b>Routine repeated</b>	1	6	30	60	60
	<b>Complex study</b>	1	4	12	24	24
	<b>Very complex</b>	0	0	0	1	1
<b>Data Partners (total)</b>		10	20	30	40	40



# DARWIN EU 'ramping up quickly' with more partners coming on board

Regulatory News | 22 March 2023 | J

BASEL, Switzerland – DARWIN EU has welcomed new data partners as an increasing number of stakeholders join the project. Peter Arlett, head of the European Medicines Agency's Real-World Evidence (RWE) Unit, said:

## EMA unveils first projects as data partners join DARWIN EU project



Two years ago, the EMA proposed a set of recommendations to unlock the potential of big data for public health, headlined by the creation of a platform to access and analyse healthcare data from across the bloc.



## High Ambitions For EU DARWIN Platform: Delivery Of First RWE Studies

29 Mar 2023 | NEWS




by Vibha Sharma

@ScripRegVibha | vibha.sharma@informa.com

### Executive Summary

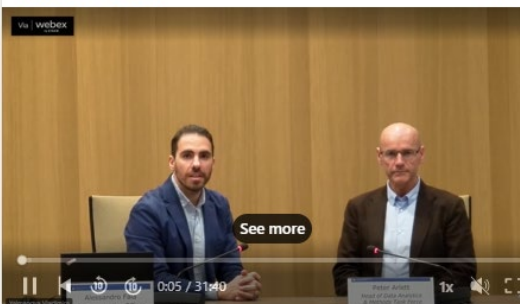
Within one year of its establishment, DARWIN EU has started real-world evidence (RWE) studies, with regulators commissioning studies using real-world data to better understand the uses and effects of medicines. The studies can be performed faster, cheaper and at increased capacity.



European Medicines Agency  
263,829 followers  
1mo · 🌐

How data about medicines from real-world settings can enable more informed regulatory decision making, which can result in safer and more effective use of #medicines by #patients? ...see more

Via webex



See more

0:05 / 31:40

1x

Event ended

Interview with Peter Arlett: Real-world evidence in medicines regulation

LinkedIn Live

Mithra Sophie Gruber, Usbrand den Rooijen and 1,590 other attendees

You and 583 others

100 comments · 102 reposts

# DARWIN EU Coordination Centre website launched

[www.darwin-eu.org](http://www.darwin-eu.org)




**DARWIN EU**

Home About Data Methods Studies FAQs Contact

Home

The European Medicines Agency (EMA) and the European Medicines Regulatory Network established a coordination centre to provide timely and reliable evidence on the use, safety and effectiveness of medicines for human use, including vaccines, from real world healthcare databases across the European Union (EU). This capability is called the **Data Analysis and Real World Interrogation Network (DARWIN EU®)**.

**Expression of Interest Call now open for Data Partners.**

More information can be found [here](#).

**Latest News**

**How to join the network?**  
How to join the data network? The Open Call for DPs described in this document welcomes expressions of interest from any data custodian in... [Read More](#)

**DARWIN EU® Onboards First Data Partners**  
Data Network A strategic priority for DARWIN EU® is to expand the scope of the network for generation of new evidence supporting the... [Read More](#)

**What will DARWIN EU deliver?**

DARWIN EU delivers **real-world evidence** from across Europe on diseases, populations and the uses and performance of medicines. This enables EMA and national competent authorities in the European medicines regulatory network to use these data whenever needed throughout the lifecycle of a medicinal product.



## Off-the-shelf studies

These are mainly characterisation questions that can be executed with a generic protocol. This includes disease epidemiology, for example the estimation of the prevalence, incidence of health outcomes in defined time periods and population groups, or drug utilization studies at the population or patient level.

+ Patient-level characterisation

+ Patient-level DUS analyses

Cohort of newly diagnosed patients or new users of a medicine followed over time. Studies used to characterise disease, patients or use of medicines

+ Population-level DUS analyses

+ Population-level descriptive epidemiology

Used for incidence/prevalence studies. All subjects in the database are eligible based on minimal inclusion criteria.



## Complex

These are studies requiring development or customisation of specific study designs, protocols, analytics, phenotypes. This includes studies on the safety and effectiveness of medicines and vaccines.

+ Prevalent user active comparator cohort studies

+ New user active comparator cohort

+ Self-controlled case risk interval

+ Self-controlled case series

+ Time series analyses and Difference-in-difference studies

+ RMM effectiveness

Studies comparing risk of health outcome in exposed vs unexposed cohorts

Studies comparing risk of health outcome in exposed vs unexposed periods in cohort of cases

Studies to assess the impact of restrictions in the use of medicines

# Studies started in 2022 (year 1/ phase I)

Additional 16 studies to start in 2023 (Phase II) – including HTA/payers, ECDC, EHDS2 pilots

Off the Shelf	<b>Population level epidemiology</b> study on prevalence of <b>rare blood cancers</b> from 2010 <a href="#">EUPAS50800</a>	NL, ES, UK, BE, DE	Support COMP in orphan designation decision making & useful as background rates for other committees
Off the Shelf	Patient level <b>drug utilization</b> study of <b>valproate-containing medicinal products</b> in women of childbearing potential from 2010 <a href="#">EUPAS50789</a>	NL, ES, UK, BE, DE, FI	Assess the use of valproate after safety referral
Off the Shelf	Patient level <b>drug utilisation</b> study of <b>antibiotics</b> on the Watch list of the WHO AWaRe classification, 2010-2021 <a href="#">EUPAS103381</a>	NL, FR, ES, DE, UK	Inform PRAC/CHMP decision making, AMR strategy
Complex	Background all-cause <b>mortality rates in patients with severe asthma aged ≥12 years</b> old <a href="#">EUPAS103936</a>	NL, ES x2, UK, EE	Support CHMP post-authorisation inform future decision making

More detail in protocols + study reports in EU PAS Register + shiny apps

	Study Report for C1-003	
	<b>Author(s):</b> Katia Verhamme, Maria de Ridder, Talita Duarte Salles, Dani Prieto Alhambra, Miguel-Angel Mayer, Romain Griffier	<b>Version:</b> v3.1 <b>Dissemination level:</b> Public

**Table of contents**

<b>1. DESCRIPTION OF STUDY TEAM</b> .....	<b>7</b>
<b>2. DATA SOURCES</b> .....	<b>8</b>
<b>3. ABSTRACT</b> .....	<b>10</b>
<b>4. LIST OF ABBREVIATIONS</b> .....	<b>13</b>
<b>5. AMENDMENTS AND UPDATES</b> .....	<b>13</b>
<b>6. MILESTONES</b> .....	<b>13</b>
<b>7. RATIONALE AND BACKGROUND</b> .....	<b>13</b>
<b>8. RESEARCH QUESTION AND OBJECTIVES</b> .....	<b>14</b>
<b>9. RESEARCH METHODS</b> .....	<b>16</b>
9.1 Study Type and Study Design .....	16
9.2 Study Setting and Data Sources .....	16
9.3 Study Period .....	19
9.4 Follow-up .....	19
9.4.1 Population-level Utilization of antibiotics from the WHO Watch list .....	19
9.5 Study Population with inclusion and exclusion criteria .....	20
9.5.1 Population-level Utilisation of the antibiotics of interest .....	20
9.5.2 Patient-level Utilisation of antibiotics .....	20
9.6 Variables .....	22
9.6.1 Exposure/s .....	22
9.6.2 Outcome/s .....	22
9.6.3 Other covariates, including confounders, effect modifiers and other variables .....	22
9.7 Study size .....	26
9.8 Data transformation .....	26
9.9 Statistical Methods .....	26
9.9.1 Patient privacy protection .....	26
9.9.2 Statistical model specification and assumptions of the analytical approach considered .....	26
9.9.3 Methods to derive parameters of interest .....	27
9.9.4 Methods planned to obtain point estimates with confidence intervals of measures of occurrence .....	28
9.9.5 Methods to control for potential sources of bias .....	30
9.9.6 Methods to deal with missing data .....	30
9.9.7 Description of sensitivity analyses .....	30
9.9.8 Evidence synthesis .....	31
9.10 Deviations from the protocol .....	31
<b>10. DATA MANAGEMENT</b> .....	<b>31</b>
10.1. Data management .....	31
10.2. Data storage and protection .....	31
<b>11. QUALITY CONTROL</b> .....	<b>32</b>
<b>12. RESULTS</b> .....	<b>32</b>
12.1. Population-level DUS .....	32
12.1.1. Participants .....	32
<b>Table 12.1.1:</b> Number of participants in each source population during the study period overall .....	34

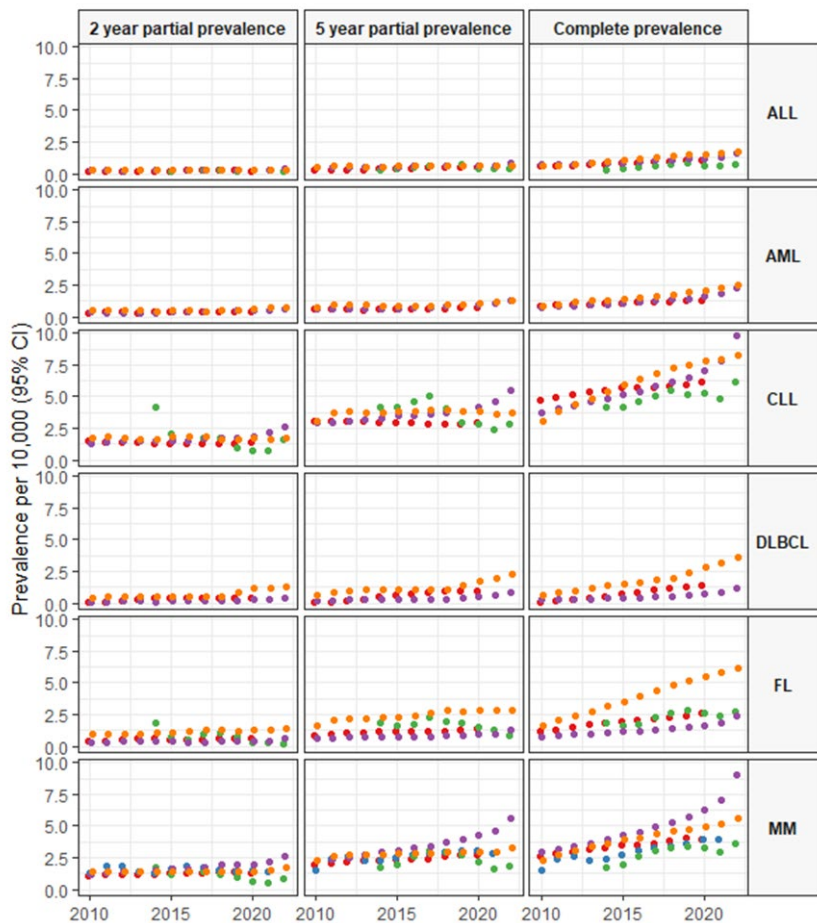
	Study Report for C1-003	
	<b>Author(s):</b> Katia Verhamme, Maria de Ridder, Talita Duarte Salles, Dani Prieto Alhambra, Miguel-Angel Mayer, Romain Griffier	<b>Version:</b> v3.1 <b>Dissemination level:</b> Public

12.1.2. Descriptive Data .....	35
12.1.3. Outcome Data .....	35
12.1.4. Main Results .....	35
Incidence rates of the antibiotics of the WHO Watch list .....	35
Incidence rates of the antibiotics of the WHO Watch list by sex and age groups .....	52
Incidence rates of the antibiotics of the WHO Watch list by route of administration .....	68
Prevalence of the antibiotics of the WHO Watch list .....	68
12.2. Patient-level DUS .....	83
12.2.1. Duration of use .....	83
12.2.2. Indication of use .....	85
12.2.5. Other Analysis .....	86
<b>13. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS</b> .....	<b>86</b>
<b>14. DISCUSSION</b> .....	<b>86</b>
14.1 Key Results .....	86
14.2 Limitations of the research methods .....	87
14.3 Results in context .....	87
14.4 Generalisability .....	88
14.5 Other information .....	88
<b>15. CONCLUSION</b> .....	<b>88</b>
<b>16. REFERENCES</b> .....	<b>89</b>
<b>17. ANNEXES</b> .....	<b>90</b>
<b>Table 1:</b> List with Concept Definitions for indication of use .....	90
<b>Table 2:</b> Lists with concept definitions for exposure .....	92

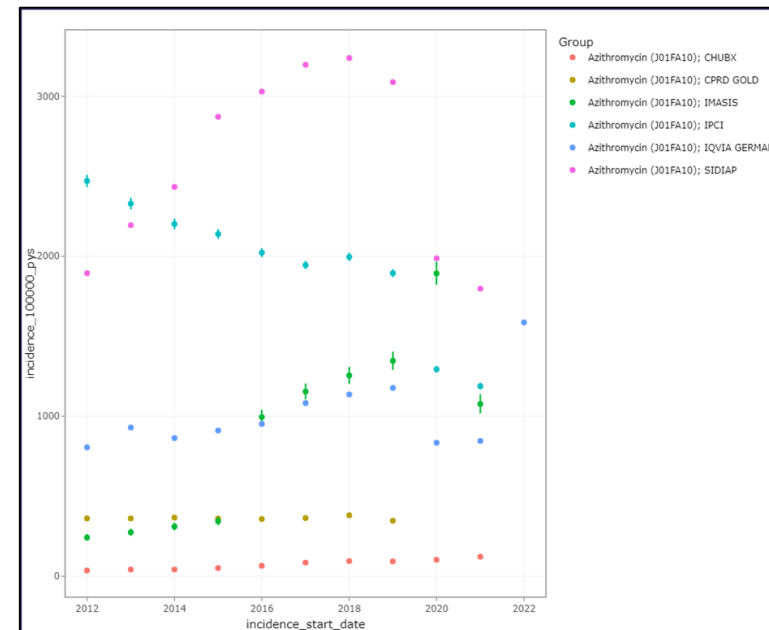
**Document History**

Version	Date	Description
V1.0	23/01/2023	First Version for EMA review
V2.0	06/02/2023	Second Version for EMA review
V3.0	15/02/2023	Final version incorporating EMA comments
V3.1	27/03/2023	Link to Shiny App added

● CPRD GOLD    ● IQVIA Belgium LPD    ● SIDIAP CMBD  
● IPCI    ● IQVIA Germany DA



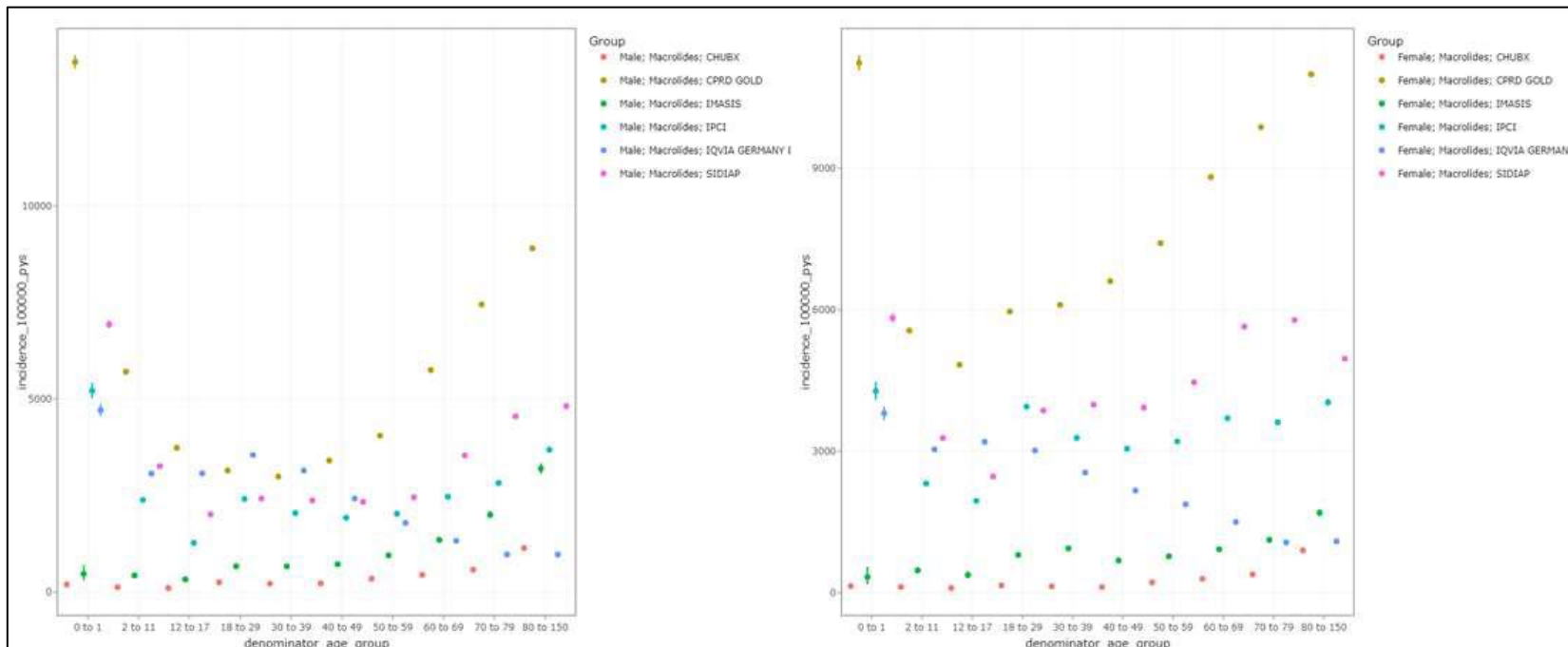
## Incidence rates of azithromycin



Ref. [EUPAS50800](#)  
and [EUPAS103381](#)

# Macrolide (ATB group) use stratified by age/gender

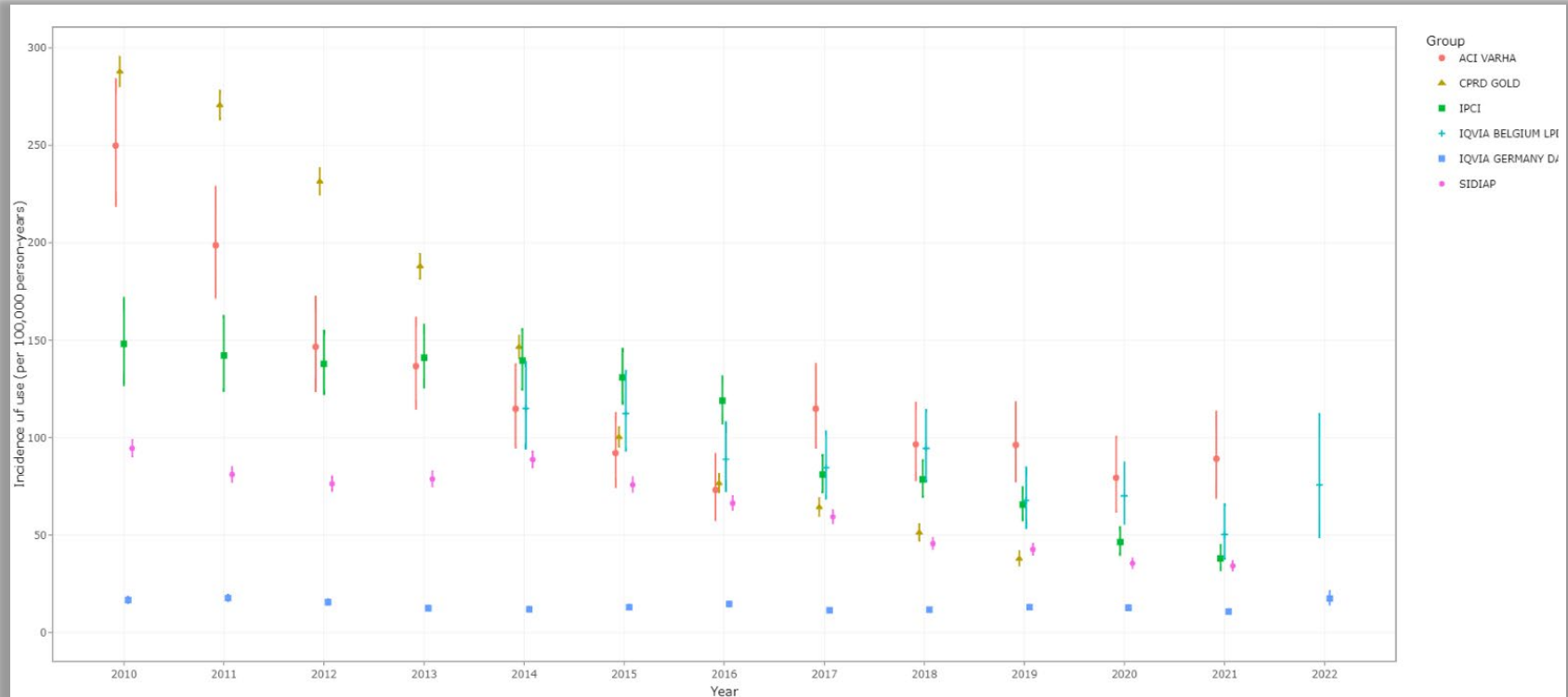
See also shiny app: <https://data-dev.darwin-eu.org/EUPAS103381/>





# EUPAS50789

## New user valproate use incidence in women 12 to 55 yrs



## Studies in progress (various stages)

Background all-cause **mortality rates in patients with severe asthma aged ≥12 years old**  
[\[EUPAS103936\]](#)

CHMP  
 Complex

**Multiple myeloma:**  
 patient characterisation,  
 treatments and survival  
 in the period 2012-2022

HTA/Payers  
 OTS

**Effectiveness of COVID-19**  
 vaccines against  
 severe COVID-19 and  
 post-acute outcomes of  
 SARS-CoV-2 infection.

ECDC/VMP  
 Complex

**Drug utilisation** study on  
 co-prescribing of  
**endothelin receptor  
 antagonists (ERAs)** and  
**phosphodiesterate-5  
 inhibitors (PDE-5is)** in  
 pulmonary arterial  
 hypertension.

CHMP  
 OTS

**Erythromycin** use  
 as prokinetic

NCA  
 OTS

**EHDS** coagulopathy  
 of COVID-19

EC/EHDS  
 Complex

**Naloxone** use in  
 treatment of opioid  
 overdose.

CHMP  
 OTS

Drug utilisation study  
 of prescription  
**opioids.**

PRAC  
 OTS

# Towards delivering the 2025 RWE vision

*A tale with three pathways...*



## EMA studies using in-house databases

- **Primary care** health records from the **France, Germany, UK, Italy, Spain** and **Romania**. Some data sources include data on specialist.



## DARWIN EU®

- Coordination Centre launched February 2022
- Onboarded first **10 data partners**
- **First studies** finalised
- Additional 10 data partners are foreseen to **be added each year** for 2023 and 2024

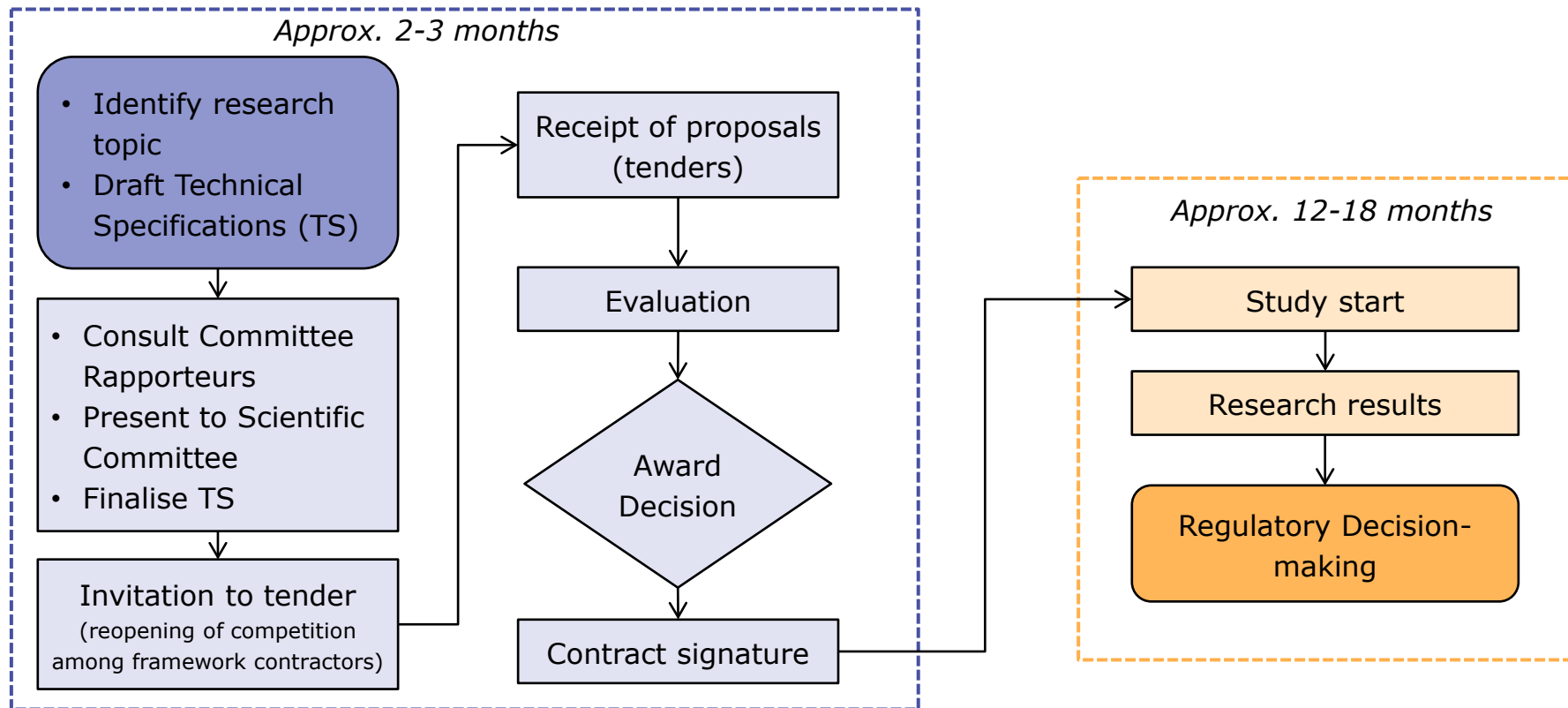


## Studies procured through EMA FWCs

- 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**

**+** Regulatory authorities also have access to national databases e.g., Nordic registries, SNDS, BIFAP, ...

# EMA-funded studies – the process



EMA funded study based on registry data in collaboration with Aetion and TREAT NMD

Home Sitemap Q & A Notice Board Links Contact

Home > View Study

News  
About Us  
ENCePP Documents  
Training in PhEpi and PV

Code of Conduct  
Standards & Guidances  
ENCePP Study Seal  
Public Consultation  
Glossary of terms

Resources Database

Partners forum

EU PAS Register

About EU PAS Register

Administrative Details

Targets of the Study

Methodological Aspects

Documents

Status: Planned

First registered on: 27/01/2023

Last updated on: 08/03/2023

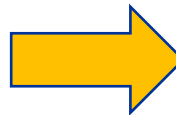
### 1. Study identification

EU PAS Register Number	EUPAS50476
Official title	A registry-based cohort study of Spinal Muscular Atrophy (SMA) disease to describe the natural history of SMA, the evolution of SMA care management and disease progression considering new disease modifying therapies (DMTs).
Study title acronym	
Study type	Observational study
Brief description of the study	To investigate SMA patients' course of disease and standards of care delivery over time in multiple European countries: Objective 1: To describe, by SMA type, the natural history of SMA (the disease and its progression) in the UNTREATED cohort and the TREATED cohort also stratified by DMT, including patients characteristics, disease progression based on motor function assessment as well as respiratory, nutritional and skeletal deformities, post-diagnostic outcomes of interest and serious adverse events of special interest. Objective 2: To describe by SMA type the evolution of diagnosis methods and of medicinal and non-medicinal treatment over time, including adoption of DMTs in the "ALL" cohort and the DMTs patterns.

# EMA priority topics on Registries for 2023/2024

## **Priority topics**

- Leverage the existing [CHMP guideline on registry-based studies](#) (Oct 2021)
- Assess needs for further guidance on registries (Methodology Working Party)
- Better understand the barriers to data access and collaboration
- Promote data quality and discoverability
- SAWP qualification procedure on registries
- Multi-stakeholder workshop Q1 2024

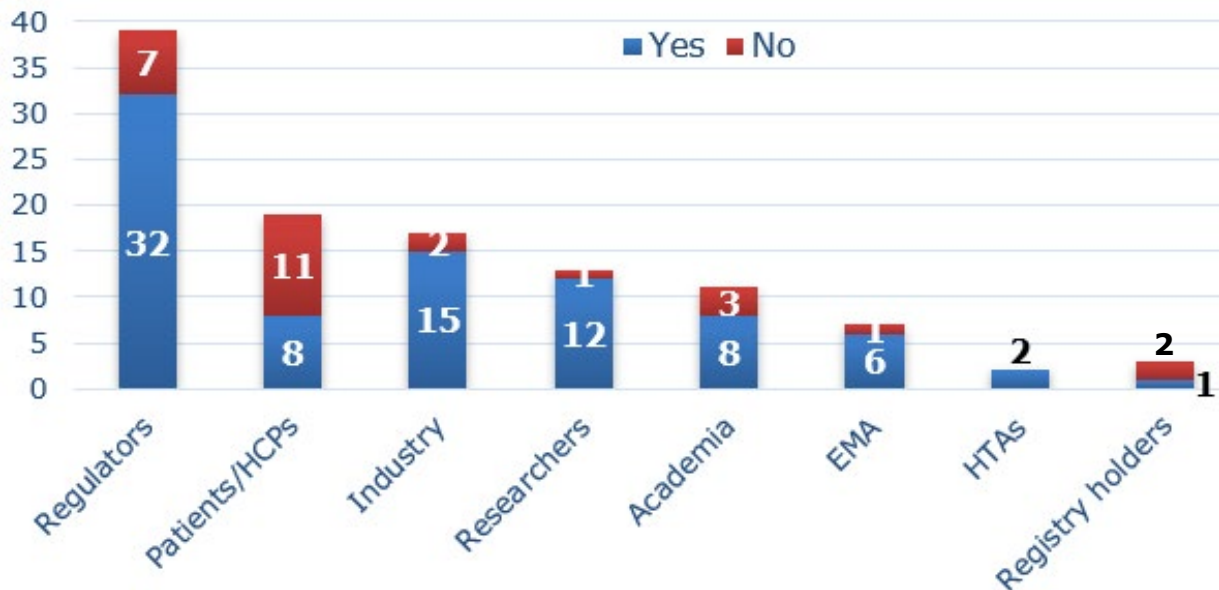
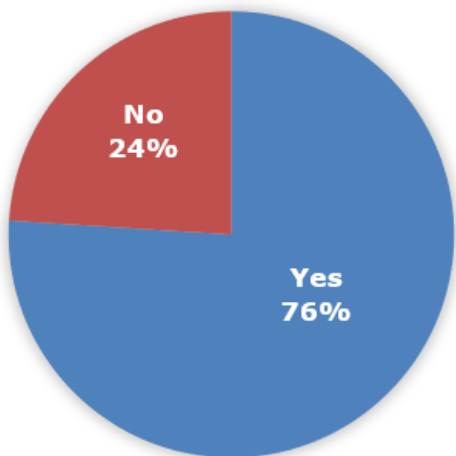


## **Direct actions**

- **Survey on Guideline on registry-based studies**
  - To assess stakeholders' awareness on guideline
  - To identify specific topics requiring clarification
  - To understand training needs
- **Stakeholder communication, engagement and training** through webinars/educational videos with concrete use cases; Q&A
- **PCOs/HCPs to be consulted** on annexes to [DQF](#) and engaged in populating the EMA catalogue
- **Patient angle and patient-experience data** to be a central theme of the workshop

# Main results of survey on Guideline on registry-based studies

## Awareness of the guideline (total: 111)

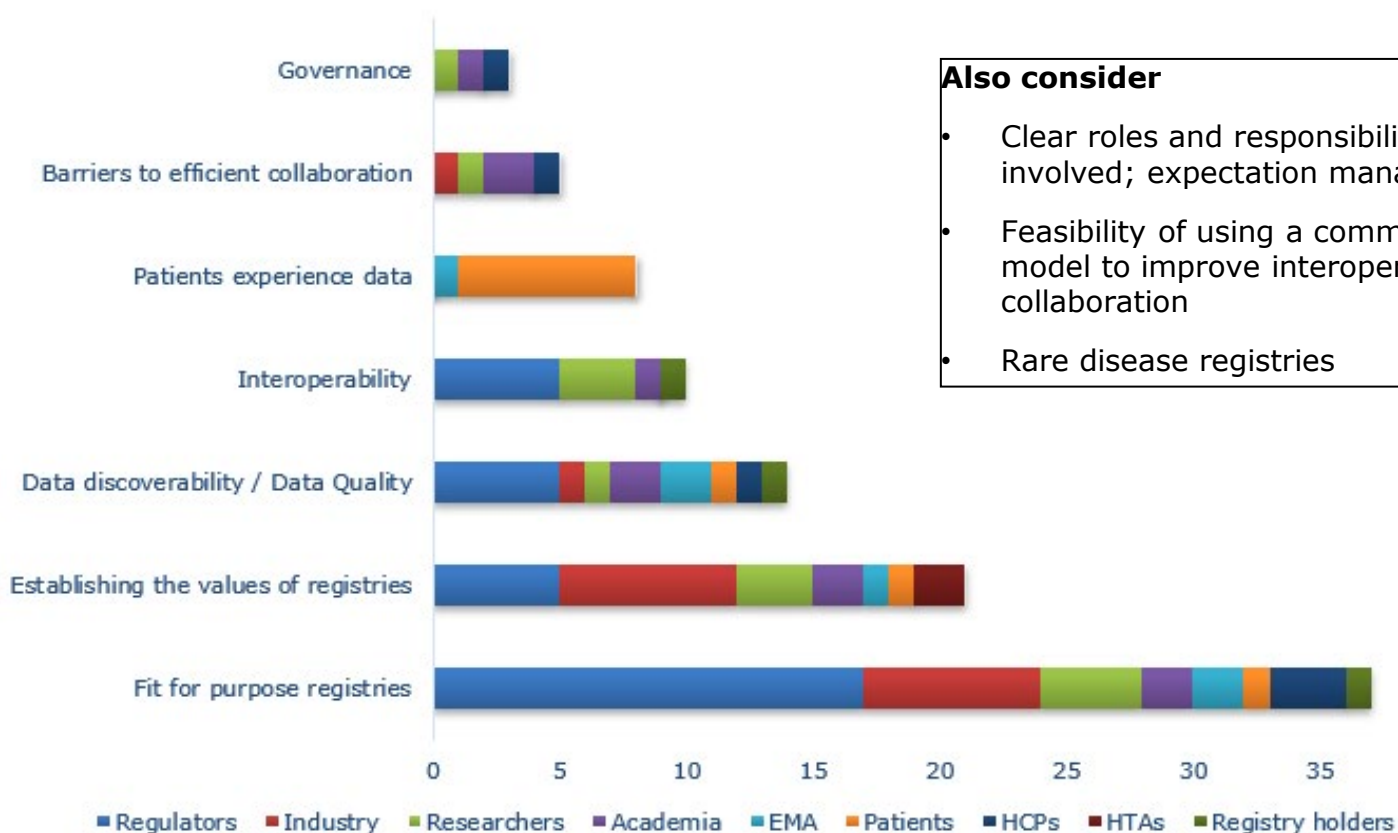


**How?:** EMA website and through interactions with EMA

**Who?:** Regulatory, epidemiology and research teams

**Who else** should know?: Clinical (medical/operational) + analysts

## Priority topics for multi-stakeholder workshop on registries (denominator 111)



### Also consider

- Clear roles and responsibilities of all involved; expectation management
- Feasibility of using a common data model to improve interoperability and collaboration
- Rare disease registries



## Take home messages

- Patients and HCPs are the end-users of medicines and are experts on their disease / condition / treatments  
→ **Patient data are instrumental** in optimising medicines development and regulatory decision-making
- Need to increase patient/HCP involvement at each step of the way → Reinforcing patient relevance in evidence generation is **a key priority** in EMA's **Network Strategy** and the **Regulatory Science Strategy**
- **Understand patient/HCP needs** in terms of training, **consult / integrate their input** on key deliverables → **Identify challenges / opportunities** for enhancing optimal and impactful use of PED and establishing their value in regulatory assessment and decision-making
- Priority topics on Registries: volunteers to collaborate in development of patient communication and engagement strategy + preparation of workshop

# Any questions?

## Further information

---

[Andrej.Segec@ema.europa.eu](mailto:Andrej.Segec@ema.europa.eu), [Kelly.Plueschke@ema.europa.eu](mailto:Kelly.Plueschke@ema.europa.eu),  
[Denise.Umuhire@ema.europa.eu](mailto:Denise.Umuhire@ema.europa.eu)

**Official address** Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

**Telephone** +31 (0)88 781 6000

**Send us a question** Go to [www.ema.europa.eu/contact](http://www.ema.europa.eu/contact)

Follow us on  **@EMA\_News**



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



Coordination Centre website: [www.darwin-eu.org](http://www.darwin-eu.org)

For questions to the Coordination Centre, please contact: [enquiries@darwin-eu.org](mailto:enquiries@darwin-eu.org)



Subscribe [here](#) to receive future issues of the [Big Data Highlights](#)

