RWE generation at EMA

DARWIN EU® update

Andrej Segec, EMA TDA-RWE

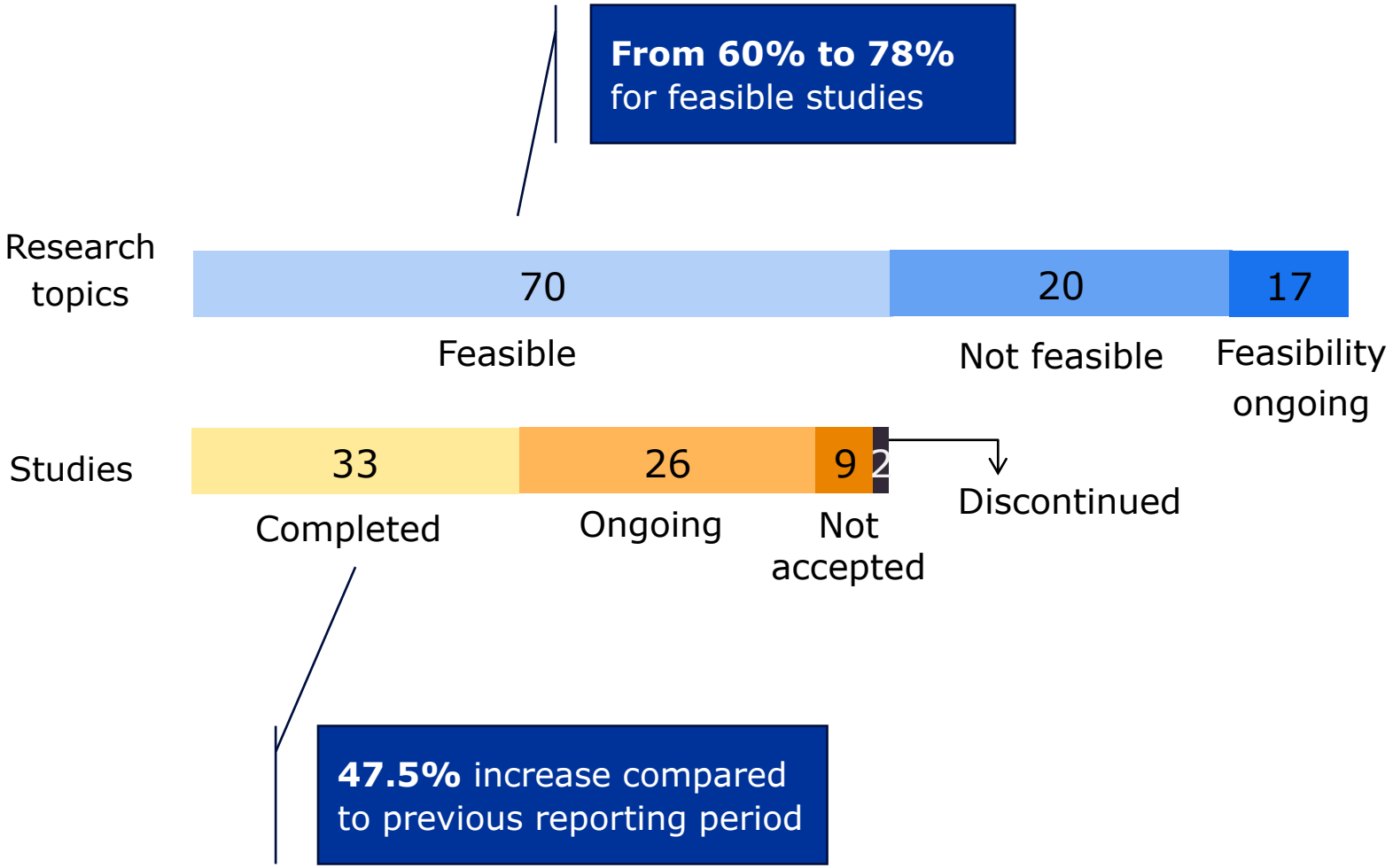
Current reporting period to Feb 2025:

107

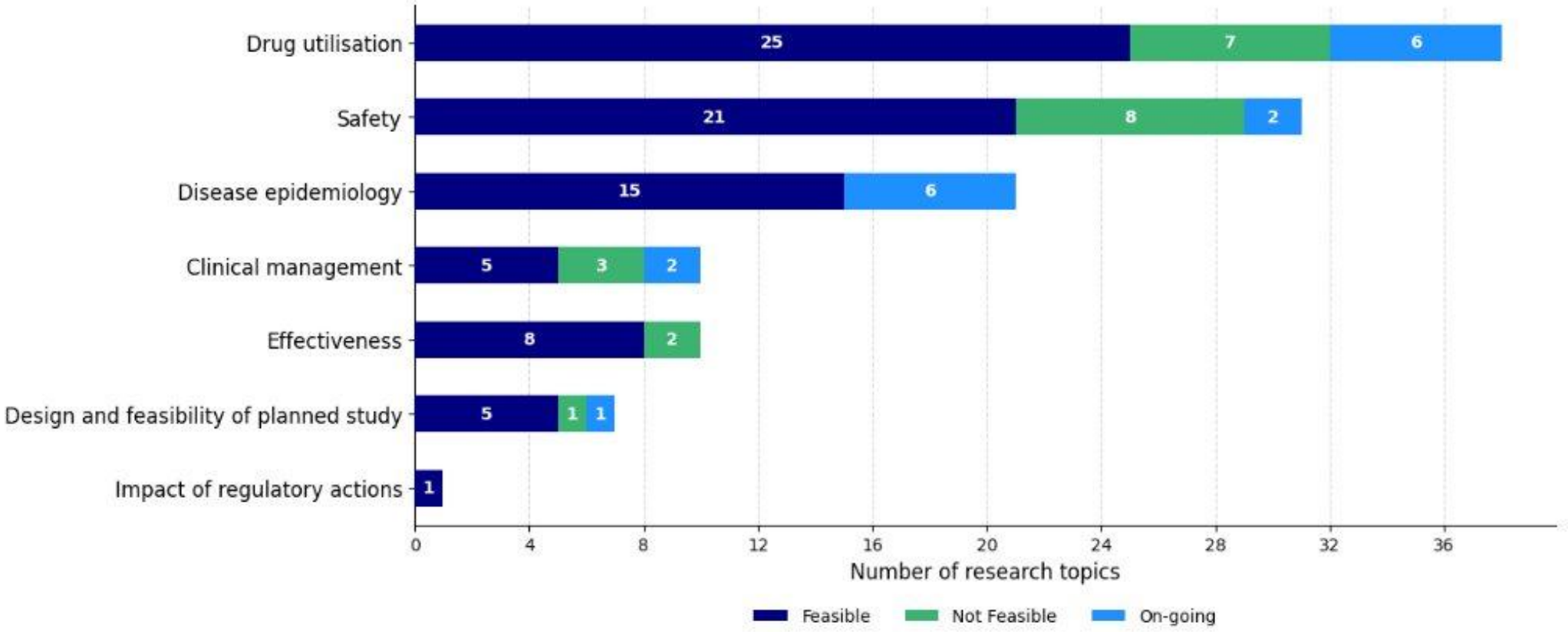
Research topics

(Feb '24 – Feb '25)

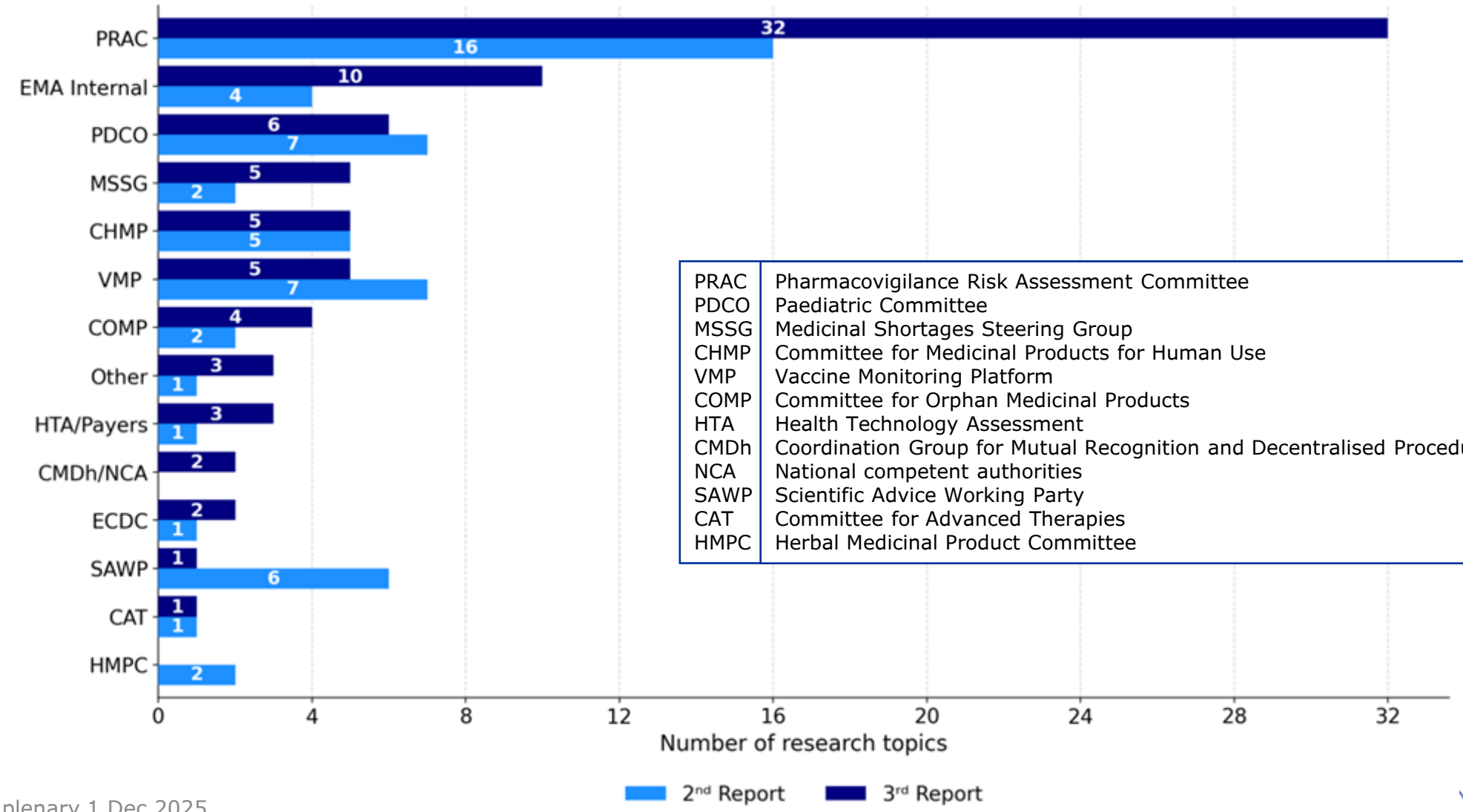
89	9	9
DARWIN EU	I-H	FWC



Feasibility of research topics by use case

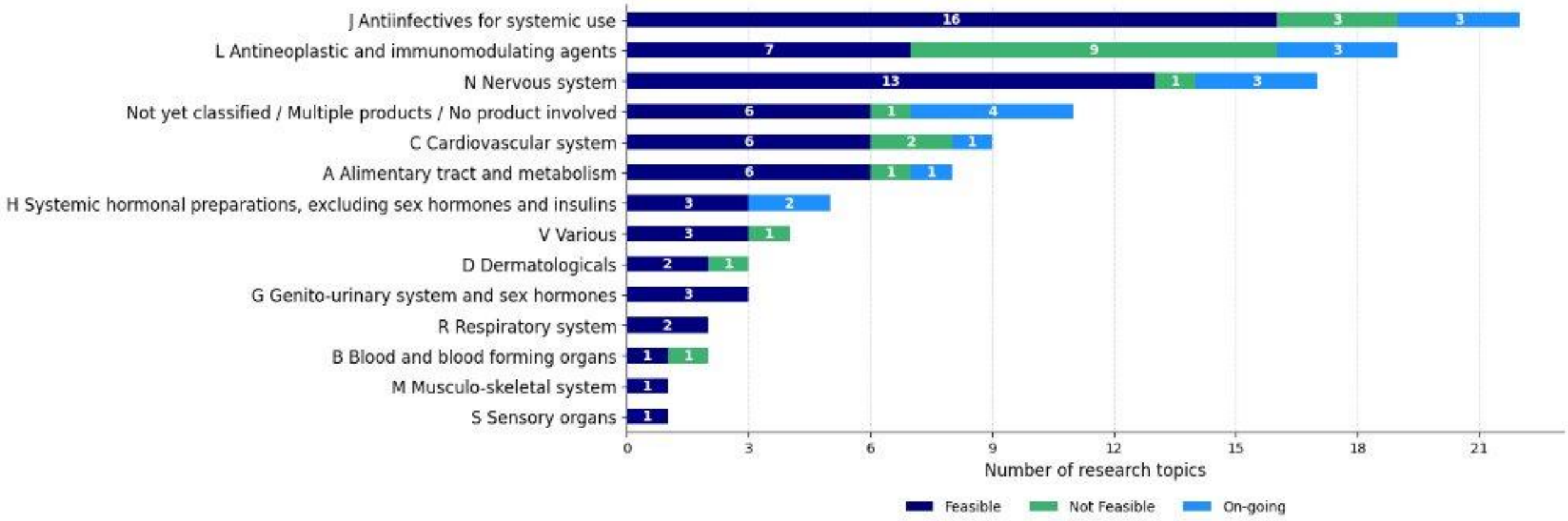


Requesters dynamic over time

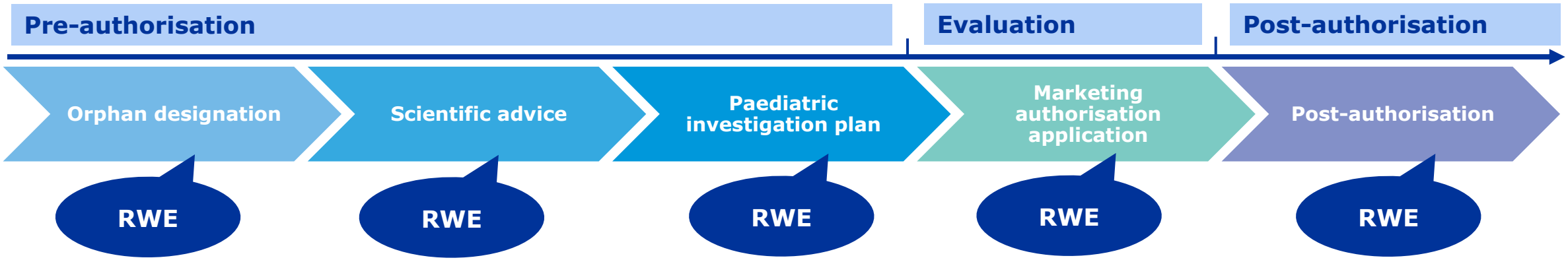


PRAC	Pharmacovigilance Risk Assessment Committee
PDCO	Paediatric Committee
MSSG	Medicinal Shortages Steering Group
CHMP	Committee for Medicinal Products for Human Use
VMP	Vaccine Monitoring Platform
COMP	Committee for Orphan Medicinal Products
HTA	Health Technology Assessment
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures
NCA	National competent authorities
SAWP	Scientific Advice Working Party
CAT	Committee for Advanced Therapies
HMPC	Herbal Medicinal Product Committee

Feasibility of research topics by Anatomical Therapeutic Chemical (ATC) classification



RWE use across the medicinal product lifecycle



- ✓ Generate prevalence data to inform orphan designation

- ✓ Advise companies on use of RWE in product development based on feasibility and relevance of studies

- ✓ Identify needs in children to support waivers/ deferrals

- ✓ Supplement, validate and contextualise clinical trial results
- ✓ Inform decision-making on post-authorisation studies

- ✓ Assess benefit and risks in real world and inform decision-making
- ✓ Monitor safety and effectiveness in special populations, off-label use
- ✓ Characterise safety profile and monitor the effectiveness of risk minimisation measures
- ✓ Assess extension of indication and repurposing of medicines

COMP	CHMP / SAWP / CAT	PDCO	CHMP / CAT / PRAC	CHMP / PRAC / CAT / HMPC

Three main areas where RWD analyses support decision-making: all use cases completed

1 Understand the clinical context

- ✓ **Disease epidemiology**
- ✓ Clinical management
- ✓ **Drug utilisation**

2 Support the planning and validity

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

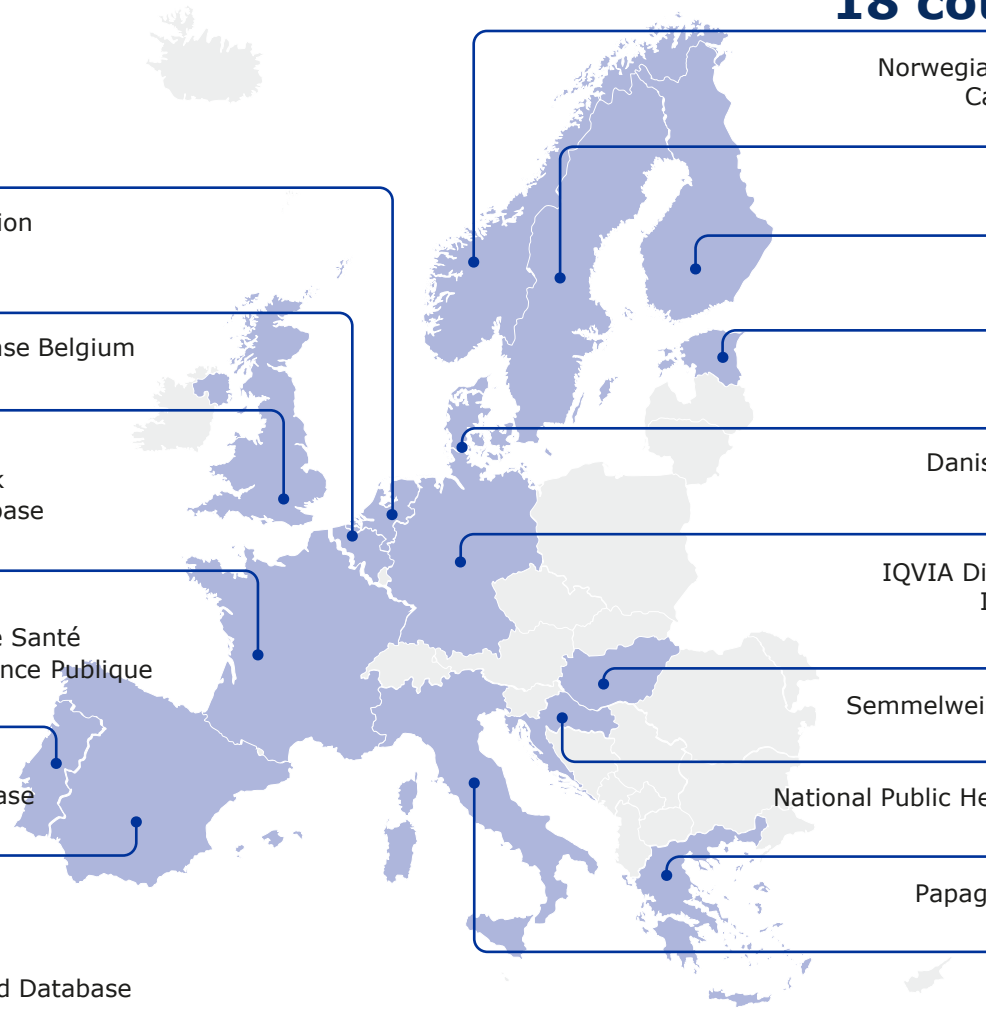
3 Investigate associations and impact

- ✓ (**Comparative**) **Effectiveness** and **safety** studies
- ✓ Impact of regulatory actions

Overview of Data Partners

188 million patients

31 data partners
40 data sources
18 countries



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

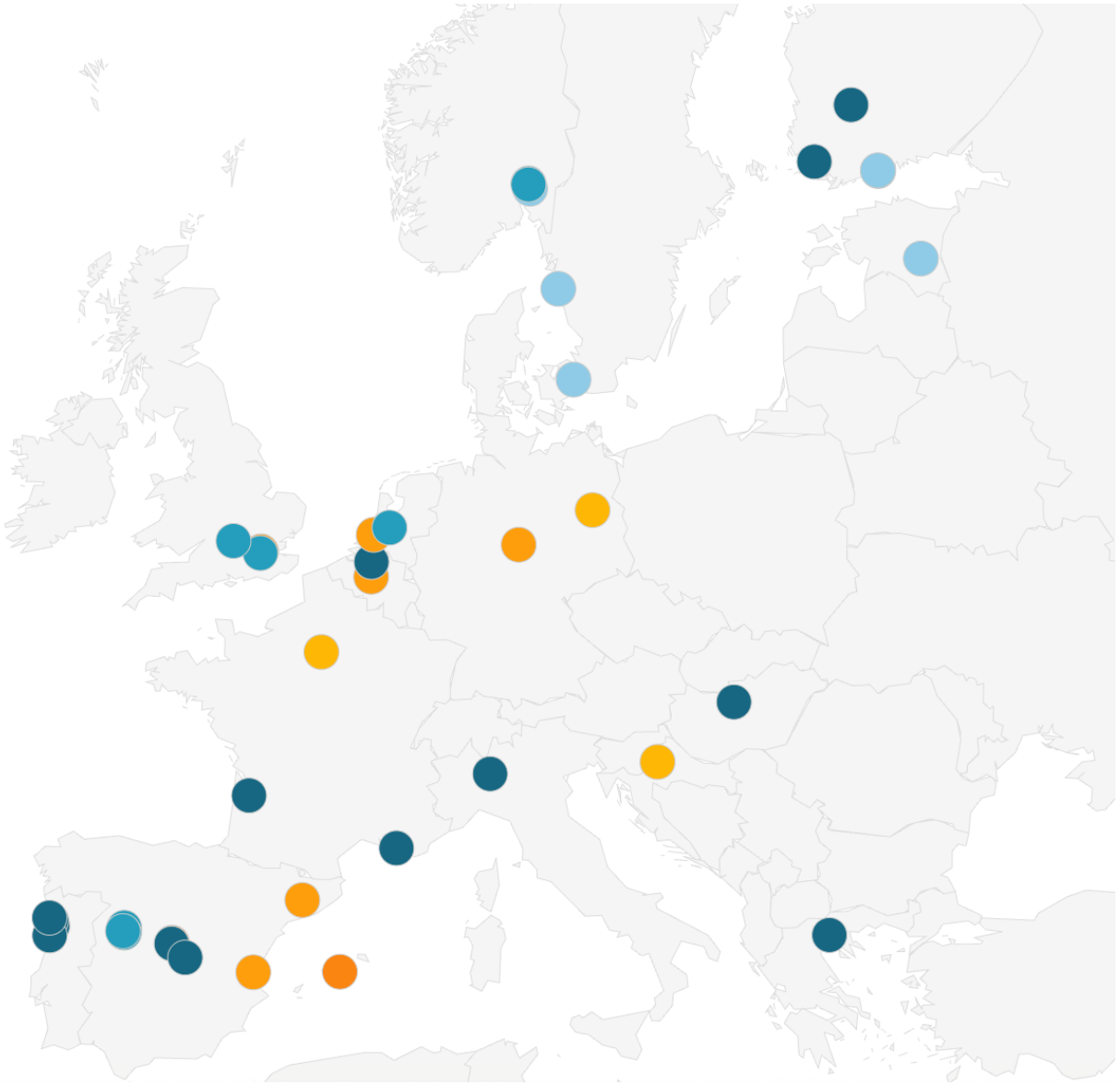
Croatia
National Public Health Information System

Greece
Papageorgiou General Hospital

Italy
POLIMI

The network by data type

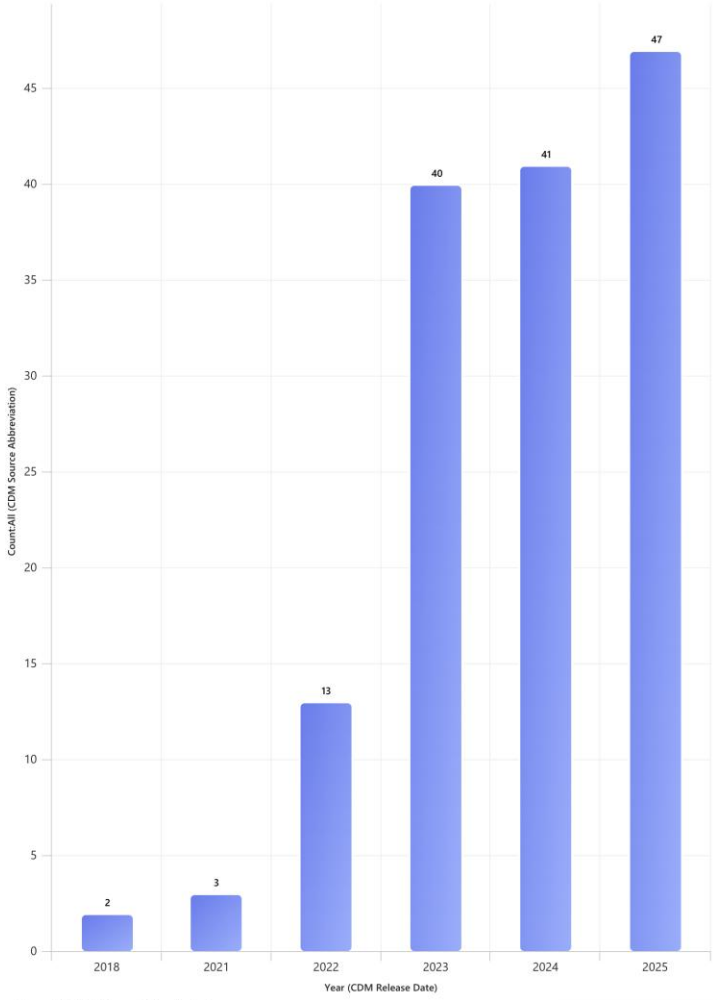
Type	N
Biobank	2
Population Registry	5
Hospital + GP	2
GP	6
Claims	3
Hospital	15
Disease Registry	8



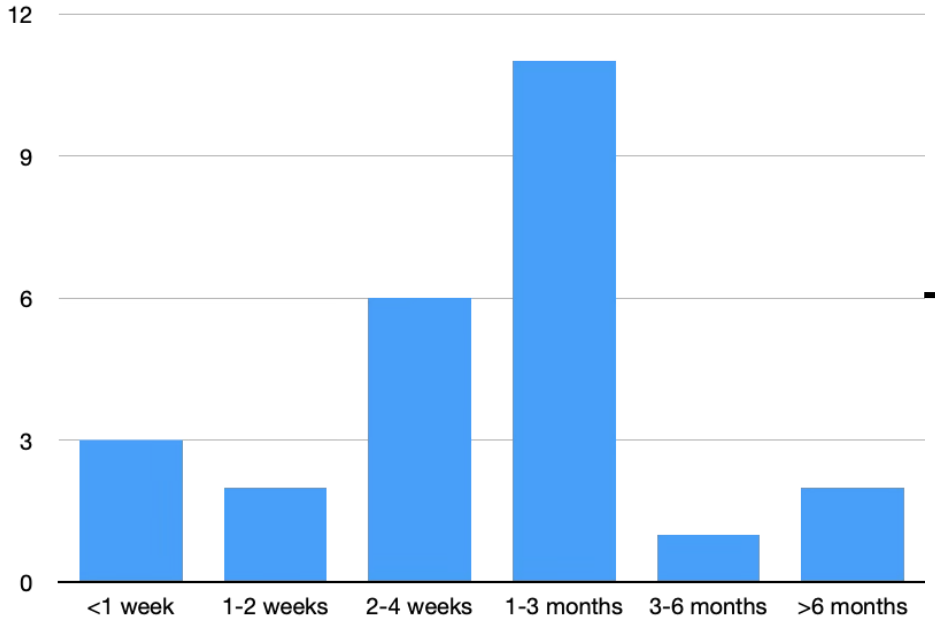
Data quality is continuously improved

- DPs target releasing the data twice a year
- System for issue tracking & fixing
- Examples of studies that lead to enhanced data quality; herbal medicines & ICU drug utilisation.
- Some foundational studies (pregnancy & oncology) are performed to increase mappings and preparedness of the network for future studies.

CDM releases reviewed p.a.

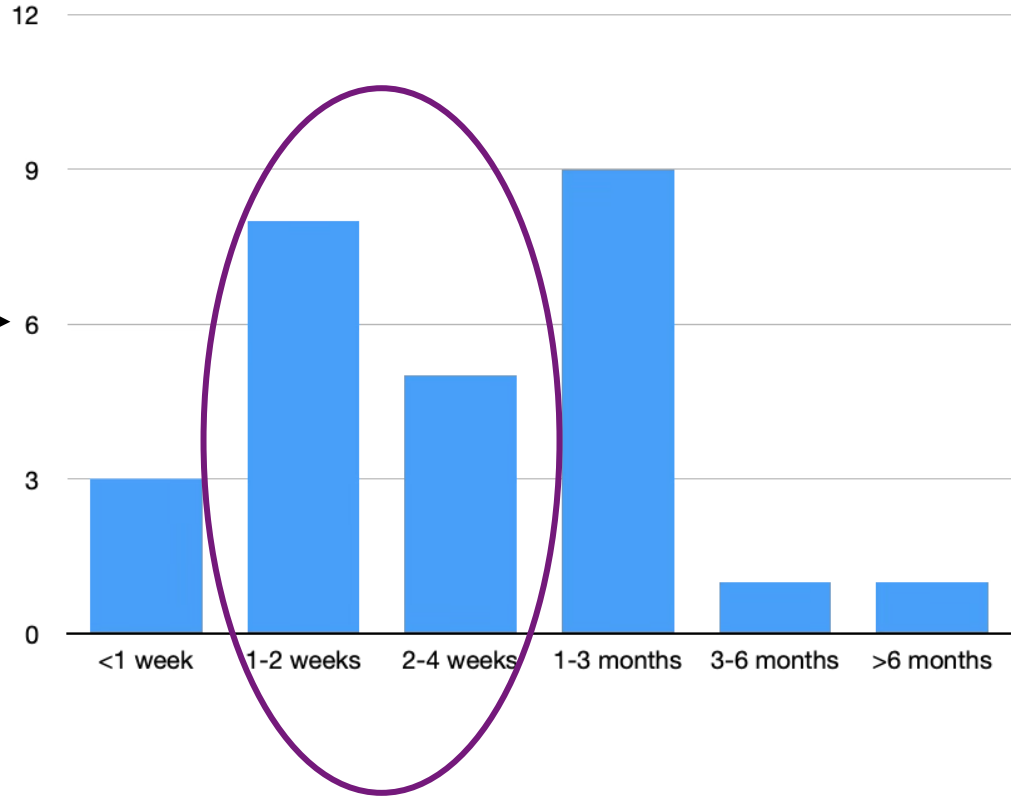


IRB Timelines



Blanket protocols

Use of EMA letter of Intent



EHDS

European Commission

EUROPEAN HEALTH DATA SPACE

#EUDigitalHealth

MAY 2024

OBJECTIVES

Official Journal
of the European Union

EN
L series

2025/327

5.3.2025

REGULATION (EU) 2025/327 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 11 February 2025

on the European Health Data Space and amending Directive 2011/24/EU and Regulation (EU) 2024/2847

(Text with EEA relevance)

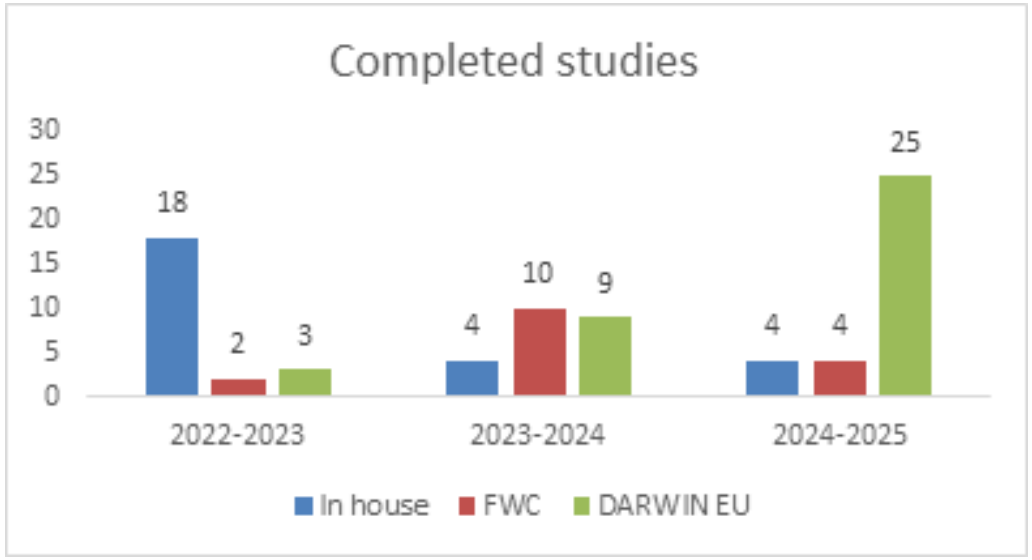
THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

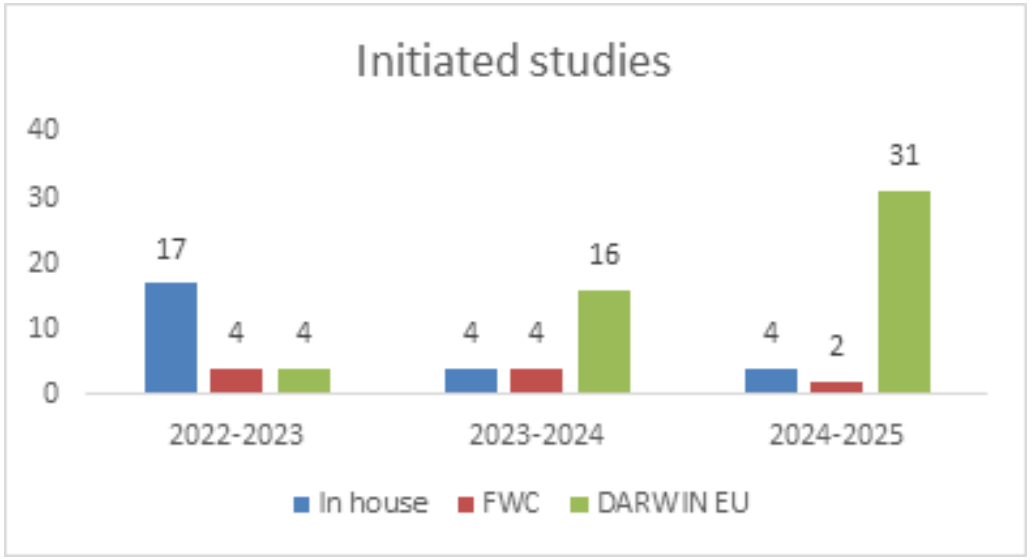
ealth data;

th data for research, innovation

EMA

DARWIN EU became the main RWE generation pathway





>100 studies in total via DARWIN EU to date

54 completed studies

48 ongoing studies

Duration of studies

- 3.8 months for studies conducted though DARWIN EU (improved from 4.4 months in 2022-2023)
- A decreased duration compared to 2022, maintained also despite increased volume of studies
- Already a very good duration for epidemiological studies in general, enabled by CDM and rapid analytics.

… and a broader positive impact on the EU research landscape

- Increased **collective knowledge and expertise** for EMRN, **keeping regulators at the forefront** of this fast-evolving evidence-driven healthcare landscape

- **Identify needs for further guidelines** and contribute to **guidance development** in the field of pharmacoepidemiology and RWE

- Several additional benefits for EU research institutions and stakeholders involved in the studies (**methodological expertise, enhanced infrastructures, increased rigor and transparency**), increasing the EU's competitiveness in clinical research.

Learnings and feedback on DARWIN EU

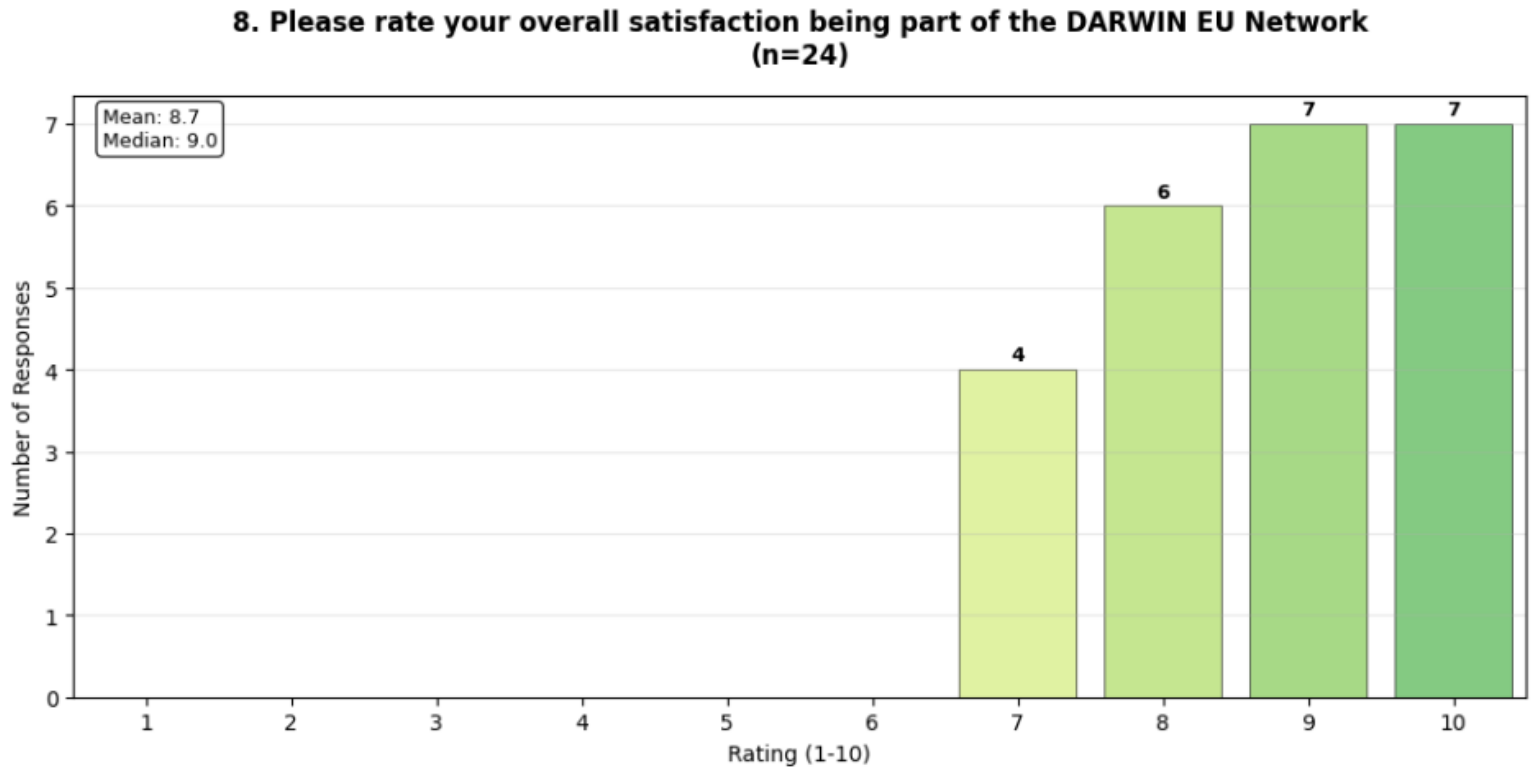
Benefits

- **Federated network concept proven**
- **Delivery of studies at unprecedented speed and number**
- **Proactive** (rather than reactive) generation
- **Impactful** evidence
- **Fill knowledge gaps** across products' **lifecycle**
- Increased demand from **stakeholders**
- High volume of **data partners**
- Directly impacting **RWD source landscape in Europe**
- Use of CDM has improved **understanding of data**
- Understanding and development of **methods**

Limitations

- **Delays in delivering results** as expected
  - Delays with DPs IRB approval
  - Code execution issues and delays at DPs
- **Lack of granularity** of data for some research topics
- **Limited number of DPs** to answer some of the objectives
- **Fewer (or too few) outcomes or exposures** than anticipated after feasibility assessment
- **Too many stratification (sub-groups)** with limited information per group due to data protection rules
- **Optimise** protocol and/or report writing
- Lack of **interpretation and/or assessment of impact of limitations on results**

Impact analysis – DP satisfaction of being in the DARWIN EU network



Analysis of DARWIN EU studies' impact (8 Feb. 2024 to 7 Feb. 2025)

Benefit / use	N (% total*)
Translated into **regulatory decisions**: • Supporting labelling changes (or no need for change) • Informing product review and scientific advice • Informing feasibility of additional studies (requested by committees)	8 (32%)
Helped in **preparedness** (PHE, PhV, shortages)	5 (20%)
Not used for decision making in an active procedure, but helped to improve knowledge (workplan, methods, context, delay, etc.)	12 (48%)

As a benchmark, over the period 2022-2024, 86 studies were conducted by the FDA through the Sentinel Network. 29 were considered as “impactful” (34%).

*Total completed studies during the period = 25 studies

Case studies illustrating impact

Background incidence rates of selected vaccine adverse events of special interest (AESIs) in Europe

Need for the study

- Rapid regulatory **response** to vaccine safety concerns crucial to maintain public **confidence**
- Background incidence rates (BGRs) of adverse events of special interest (AESIs) used in observed-to-expected analyses as an essential initial step in the continuum of **safety signal management**

How was the study conducted?

- AESI list developed based on knowledge of most representative **AESIs for several vaccines** (incl. COVID-19) and consultation with EMA and PRAC experts
- Population-level **cohort** study in **5 European databases**
- **Phenotyping** all conditions again, with regulatory and clinical input
- BGRs/100,000 person-years estimated, stratified by calendar month, year, age group and sex within each database

Why is this important?

- **Preparatory work** to support **faster response** and **contextualisation** of vaccine safety signals
- While multiple studies have generated BGRs, estimates are heterogeneous across data sources, with variable **granularity** in terms of population groups and factors such as seasonality
- Regularly updated evidence important to support **preparedness** and regulatory decision-making

43 AESIs, phenotyped again with regulatory input

Immune-mediated diseases
Guillain Barré syndrome
Kawasaki disease
Narcolepsy
Immune Thrombocytopenia
Type 1 diabetes
Autoimmune thyroiditis
Facial nerve palsy/Bells' palsy
Blood disorders
Thrombocytopenia
Thrombotic thrombocytopenia syndrome
Disorders of the cardiovascular system
Coronary artery disease
Heart failure
Single organ cutaneous vasculitis
Arrhythmia
Thrombotic microangiopathy
Cardiomyopathy
Myocarditis
Pericarditis

ENCePP plenary 1 Dec 2025

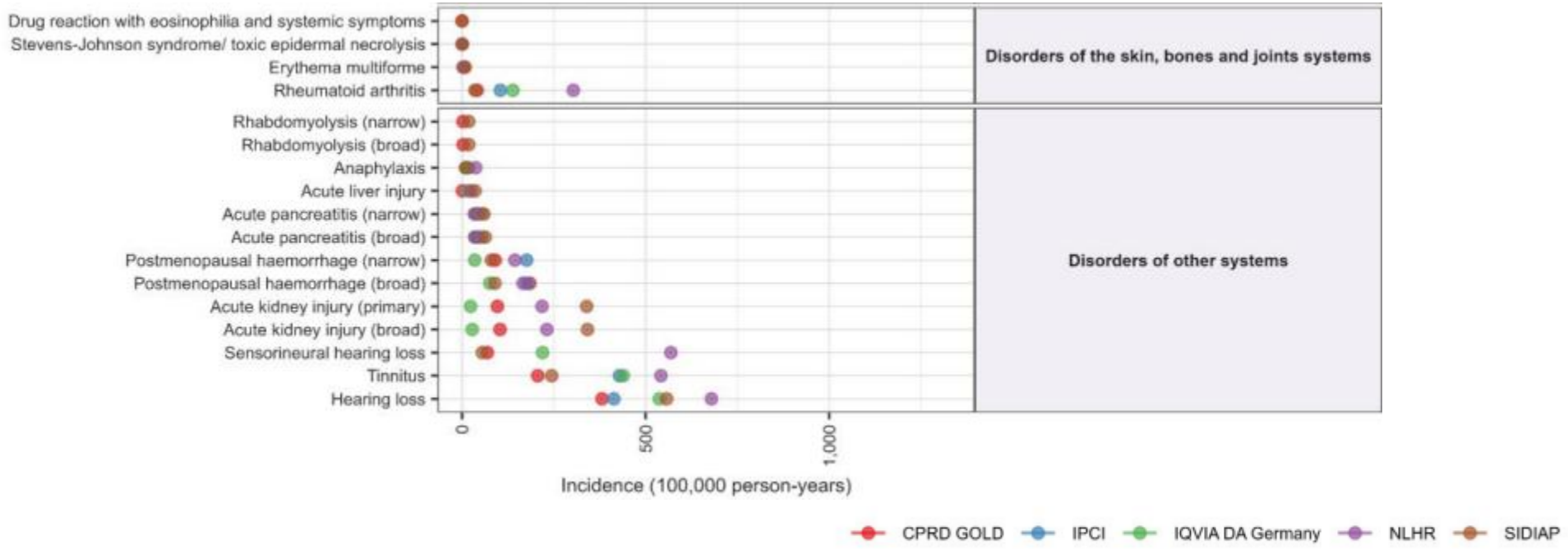
Coagulation disorders
Cerebral venous thrombosis
Deep vein thrombosis
Disseminated intravascular coagulation
Ischaemic stroke
Haemorrhagic stroke
Pulmonary embolism

Disorders of the nervous system
Epileptic convulsions/seizures
Non-epileptic convulsions/seizures
Febrile seizure
Multiple sclerosis
Acute Aseptic Meningitis
Myelitis including transverse myelitis
Encephalitis, which includes encephalomyelitis and ADEM
Neuritis including optic neuritis
Erythema multiforme

Disorders of the skin, bones and joints systems
Rheumatoid arthritis
Drug reaction with eosinophilia and systemic symptoms
Stevens-Johnson syndrome/ Toxic epidermal necrolysis
Disorders of other systems
Acute kidney injury
Acute liver injury
Anaphylaxis
Pancreatitis (Acute)
Rhabdomyolysis
Sensorineural hearing loss
Tinnitus
Postmenopausal haemorrhage

EMA

Standardised incidence rates per outcome



Use of higher-risk antibiotics from the WHO Watch list, including azithromycin

CHMP
ECDC

Need for the study

The antibiotic **azithromycin** has been used for decades to treat various infections in children and adults. It is listed by the WHO as an essential medicine.

The medicine is also classified in the WHO's Watch category due to its higher risk of antimicrobial resistance (AMR). Data show that resistance against this antibiotic has increased in recent years.

How was the study conducted?

Commissioned by EMA, the study looked at how the 141 antibiotics on the WHO's 'Watch' list, including azithromycin, are prescribed and for how long.

The study used data from routine clinical care in 5 European countries.

The results show a broad use of azithromycin across Europe, both in adults and children, with the medicine ranking among the top 5 to 10 in most databases.

How were the results used?

The study provided data on the use of the antibiotic across Europe.

CHMP used the results when it re-evaluated the benefits and risks of azithromycin medicines given by mouth or infusion (drip) into a vein. The aim was to promote a more rational medicine use to preserve its effectiveness.

The results help track the use of antibiotics that need to be closely monitored due to potential risks – like fluoroquinolones.

Why this matters?

Based on its assessment, CHMP recommended several changes to the way azithromycin is used in the EU, including the removal of certain indications.

Using this common antibiotic more wisely will help the EU monitor antibiotic use and support global fight against AMR.

Use of higher-risk antibiotics from the WHO Watch list, including azithromycin

Table 12.1.4-1: Incidence rate (per 100,00 PY, with 95% confidence intervals) of antibiotics from the WHO Watch list – top 20.

CPRD GOLD		IPCI		SIDIAP		IMASIS		CHUBX		IQVIA Germany	
Incidence	**Antibiotic**	**Incidence**	**Antibiotic**	**Incidence**	**Antibiotic**	**Incidence**	**Antibiotic**	**Incidence**	**Antibiotic**	**Incidence**	**Antibiotic**
3,577 (3,571; 3,583)	Clarithromycin	1,862 (1,853; 1,870)	Azithromycin	3,165 (3,160; 3,169)	Fosfomycin	1,218 (1,202; 1,234)	Levofloxacin	961 (952; 970)	Ceftriaxone	1353 (1350; 1355)	Cefuroxime
2,073 (2,068; 2,078)	Erythromycin	1,462 (1,455; 1,470)	Ciprofloxacin	2,567 (2,563; 2,571)	Azithromycin	1,213 (1,197; 1,229)	Ciprofloxacin	493 (487; 499)	Piperacillin_ tazobactam	985 (983;987)	Ciprofloxacin
1,023 (1,020; 1,026)	Ciprofloxacin	1,190 (1,184; 1,197)	Fosfomycin	2,098 (2,094; 2,101)	Ciprofloxacin	980 (966; 994)	Ceftriaxone	204 (200; 208)	Ofloxacin	981 (979; 984)	Azithromycin
868 (865; 871)	Lymecycline	828 (822; 834)	Clarithromycin	1,485 (1,482; 1,488)	Levofloxacin	831 (818; 844)	Azithromycin	191 (187; 195)	Ciprofloxacin	587 (585; 589)	Fosfomycin
518 (515; 520)	Oxytetracycline	517 (512; 521)	Pheneticillin	959 (956; 961)	Cefuroxime	830 (817; 843)	Fosfomycin	133 (129; 136)	Vancomycin	537 (535; 539)	Cefaclor
361 (359; 363)	Azithromycin	206 (204; 209)	Minocycline	813 (810; 815)	Clarithromycin	351 (343; 360)	Cefotaxime	131 (128; 134)	Levofloxacin	479 (477; 480)	Clarithromycin
73 (72; 73)	Ofloxacin	156 (153; 158)	Norfloxacin	623 (621; 625)	Norfloxacin	277 (270; 285)	Meropenem	125 (122; 128)	Spiramycin	377 (375; 378)	Roxithromycin
48 (48; 49)	Minocycline	142 (139; 144)	Oxytetracycline	345 (344; 347)	Cefixime	194 (188; 200)	Cefixime	89 (86; 92)	Tobramycin	326 (324; 327)	Levofloxacin
43 (43; 44)	Cefaclor	102 (100; 104)	Erythromycin	188 (187; 189)	Moxifloxacin	170 (164; 176)	Vancomycin	79 (77; 82)	Rifampicin	285 (284; 287)	Cefpodoxime-proxetil
31 (30; 31)	Fosfomycin	79 (78; 81)	Levofloxacin	173 (172; 174)	Rifaximin	161 (155; 167)	Ceftazidime	75 (73; 78)	Azithromycin	252 (251; 254)	Ofloxacin

Watch list antibiotics (continued)

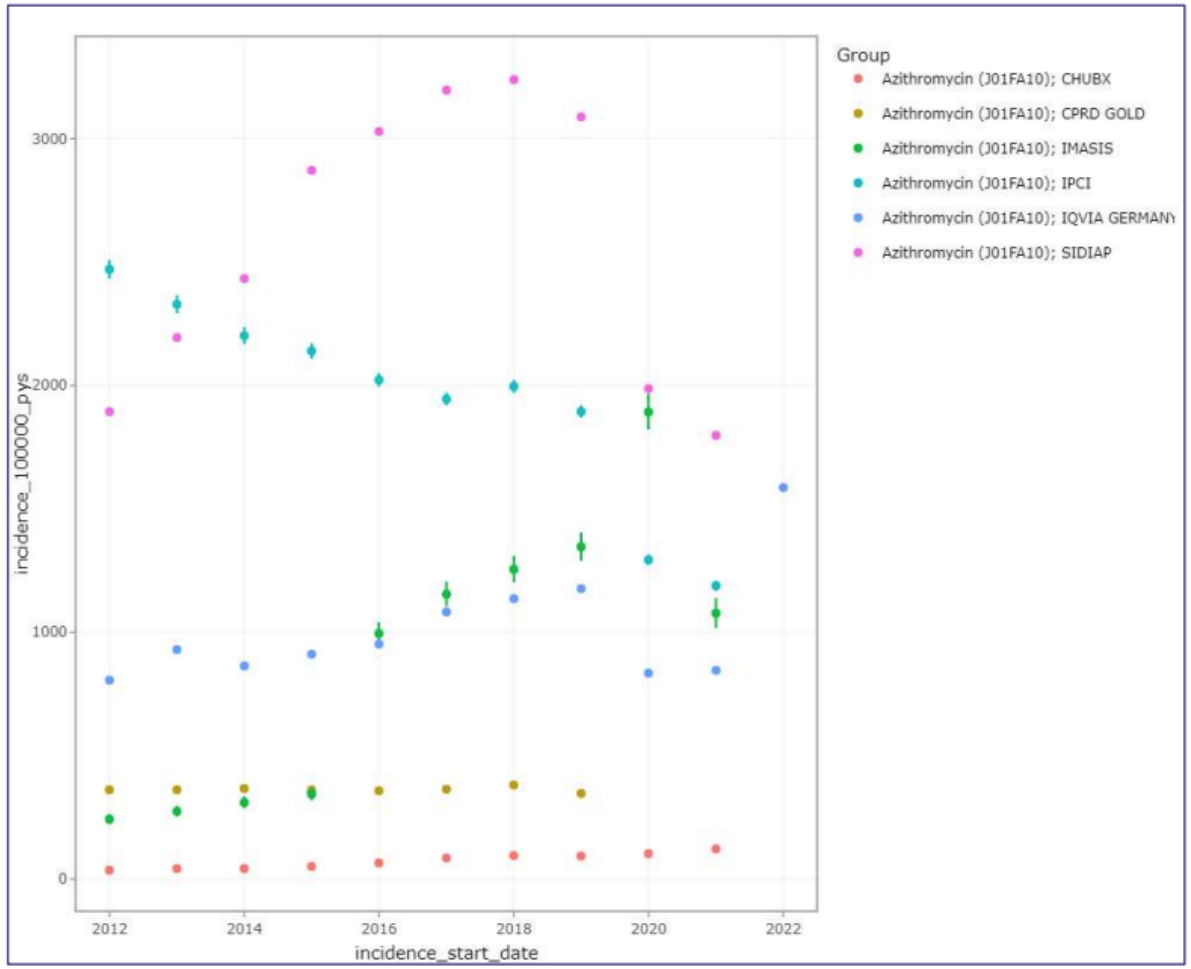


Figure 12.4.1-1: Incidence rates of azithromycin.

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Changes to the use of antibiotic azithromycin

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23 May 2025

Recommendations aim to optimise use and minimise development of antimicrobial resistance

News | Human | Referrals

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Related medicine information

EMA's human medicines committee (CHMP) has recommended several changes to the way the antibiotic azithromycin is used in the EU, including the removal of certain indications. These recommendations aim to optimise the use of this common antibiotic and minimise the development of antimicrobial resistance – the ability of microorganisms to become resistant to antimicrobials.

Azithromycin has been used for decades to treat a wide range of infectious diseases, both in children and adults. It is included in the World Health Organization (WHO) list of essential medicines, which highlights its importance for public health.

However, azithromycin is also classified by WHO as an antibiotic that carries a higher risk of antimicrobial resistance and is included in WHO's Watch category (AWaRe classification). Data show that antimicrobial resistance against this antibiotic has increased in recent years.

Medicines in WHO's Watch category should be prioritised as key targets for prudent use and monitoring. However, consumption data indicate an increased use of azithromycin medicines in recent years. A recent EMA-commissioned study, performed by DARWIN EU, showed a broad use of this antibiotic across the EU, both in adults and children.

And, updated data is hot off the press

- Working with ECDC, the ATB DUS was repeated
- covering **all WHO (2023) AWaRe antibiotics** per classification lists – Access, Watch, Reserve
- = 258 antibiotics and data from 11 countries

→Incidence of use

→ User characteristics

→ Indication for use, incl changes over the study period

Risk of suicidality after taking the antibiotic doxycycline

PRAC

Need for the study

Doxycycline is a broad-spectrum antibiotic, widely used to treat bacterial infections. It can be used for treatment of moderate or severe acne.

Based on spontaneous case reports, recent concerns have been raised about its side effects, particularly suicidality, but the data have been limited.

How was the study conducted?

The study generated more information to understand if the medicine is linked to suicidality. It looked at people who started taking doxycycline and compared their risk to people taking other medicines for treating acne or infections. It also considered the different health conditions the medicine is used to treat.

Data from 3 European countries were analysed.

How were the results used?

The study helped PRAC assess whether doxycycline might be linked to suicidal thoughts or behaviour. The committee concluded that the current evidence is not sufficient to establish a causal relationship between doxycycline and the risk of suicidality.

A separate DARWIN EU study showed the risk of suicidality is higher in patients with skin disorders, including acne.

Why this matters?

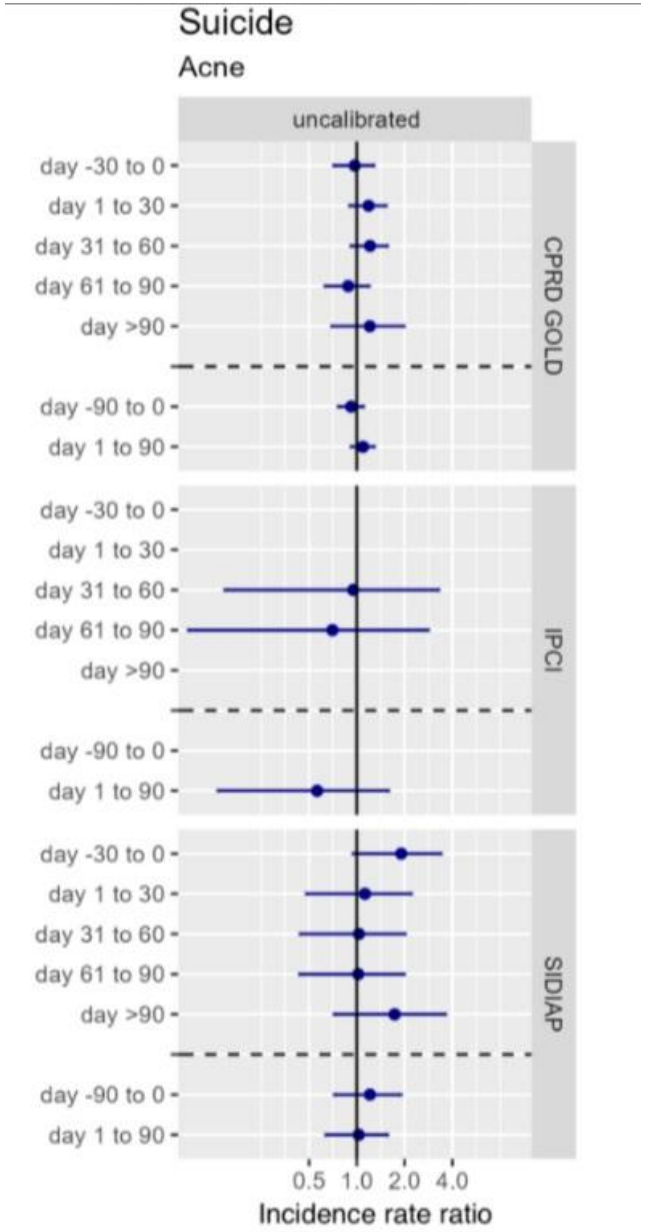
The study helped alleviate safety concerns and reassured patients using the medicine. This is important as the medicine is commonly used to treat acne, urinary tract and respiratory infections.

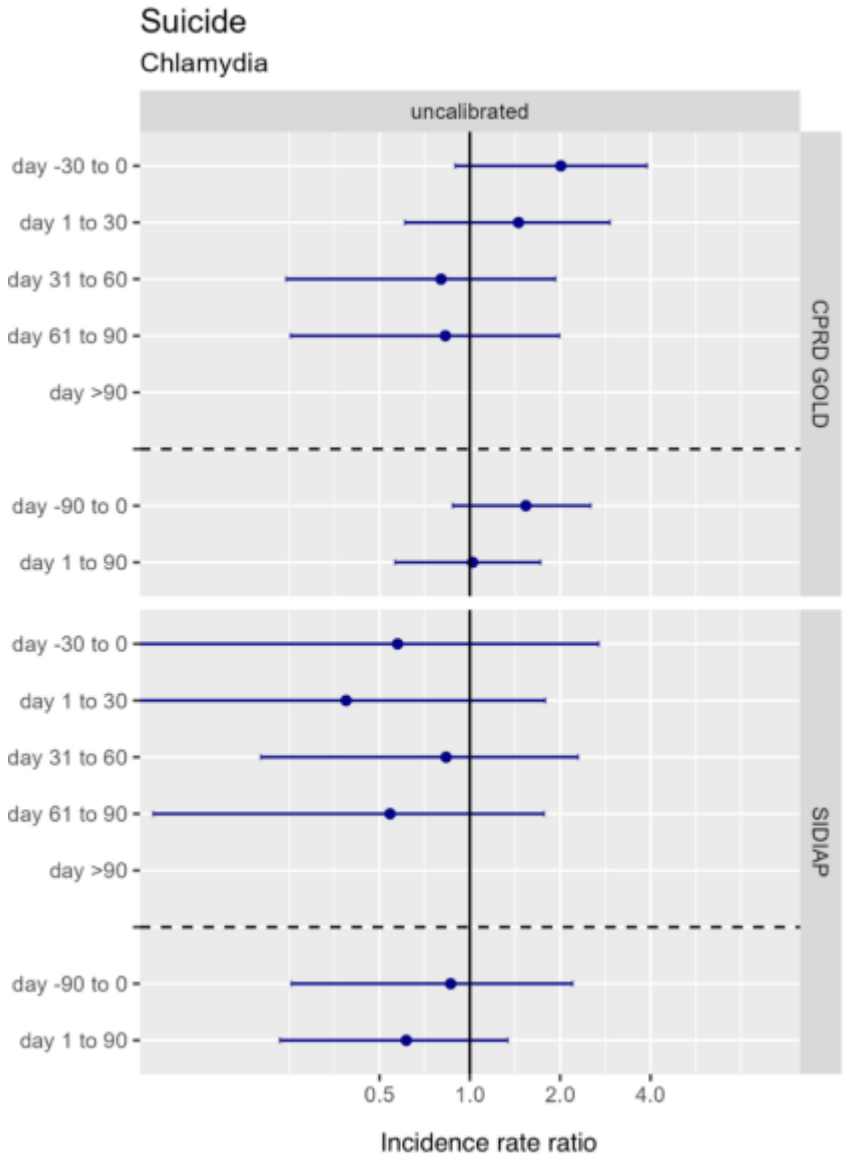
EMA

2 analytical approaches:

1. **New user cohort** with **active comparators** chosen per indication (not shown) – risk differences per indication are likely

2. **Self-controlled case series** where each user serves as their own control – comparing risk in risk windows during/before/after use (results shown)
➔ Better control for fixed confounders





Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 25-28 November 2024

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Doxycycline: currently available evidence not supporting link with risk of suicidality

EMA's safety committee (PRAC) has concluded that the currently available evidence is not sufficient to establish a causal relationship between the use of the antibiotic doxycycline and the risk of suicidality.

Doxycycline is a broad-spectrum antibiotic, widely used to treat a wide range of infections caused by bacteria such as acne, urinary and lower respiratory tract infections, dental infections, and skin infections. It is also used to prevent the development of certain infections, such as malaria.

A safety signal on the risk of suicidality, suicidal thoughts or actions with doxycycline was raised based on cases reported to the Finnish national competent authority, as well as further cases reported to EudraVigilance, the centralised European database of suspected side effects reports, and the medical literature.

The PRAC started its review in November 2023 and requested the marketing authorisation holders for doxycycline to perform a cumulative review of the data from all relevant sources.

The PRAC also requested a study based on real-world evidence, which includes data from electronic health records and disease registries, through DARWIN EU to facilitate the assessment of the signal. After reviewing all available evidence from spontaneous reports, the literature, the discussion on possible mechanisms and the study performed via DARWIN EU, the PRAC considered that the evidence is not sufficient to establish a causal relationship and that no update to the product information of doxycycline is warranted.

Suicide-related events in relation to doxycycline will be closely monitored and any new evidence will be discussed in the Periodic Safety Update Reports (PSURs).

Overall survival in patients with non-small cell lung cancer treated with selected immunotherapies as first treatment

HTA bodies and payers

Need for the study

Health technology assessment (HTA) bodies and payers requested the study in pursuit of evidence to better understand the effectiveness of immunotherapies compared to chemotherapies used to treat **non-small cell lung cancer (NSCLC)** in real-world settings.

This pilot study helped EMA understand evidence gaps by HTA bodies/payers and how to generate RWE for them.

How was the study conducted?

A comparative study to assess the overall survival of patients with locally advanced or metastatic NSCLC who start treatment with immunotherapies and how it compares to the survival of patients who get chemotherapies as first treatment.

The study used data from 3 EU countries, including cancer registry data.

How were the results used?

The results show that people with NSCLC tend to live longer when treated with immunotherapy, (particularly the most used pembrolizumab), compared to chemotherapy when used as first treatment.

This was after considering other factors that affect survival, such as age, sex, year of starting the treatment, tumour stage and patients' general wellbeing.

Why this matters

The first oncology study by DARWIN EU provides valuable insights into the effectiveness of immunotherapies versus chemotherapies in a real-world setting.

Better understanding of lung cancer treatments is important because these therapies are expensive and increasingly used as the population ages and more people are diagnosed with lung cancer.

Results

Estimated overall survival by treatment in Netherlands Cancer Registry

Treatment	N patients	N deaths	Median survival (95% CI) (months)	RMST at 4 years (95% CI) (months)	1-year survival (95% CI)	2-year survival (95% CI)	3-year survival (95% CI)
Chemotherapy	5,425	4,134	9.96 (9.56, 10.41)	17.25 (16.79, 17.71)	44.06 (42.72, 45.44)	27.04 (25.82, 28.33)	20.19 (19.04, 21.40)
Pembrolizumab	7,992	4,906	13.11 (12.58, 13.63)	20.14 (19.71, 20.60)	52.15 (51.01, 53.32)	34.77 (33.59, 35.99)	26.95 (25.74, 28.22)
Nivolumab	213	147	12.19 (9.43, 14.59)	16.92 (14.49, 19.32)	50.00 (43.26, 57.81)	25.04 (19.07, 32.89)	17.56 (12.26, 25.16)
Nivolumab + ipilimumab	62	27	16.16 (11.53, 35.74)	20.86 (15.21, 26.55)	62.04 (48.20, 79.86)	28.50 (15.63, 51.96)	22.80 (10.84, 47.95)

Objective 2

Results

Comparison of overall survival of patients with locally advanced or metastatic NSCLC under pembrolizumab to that of exclusive chemotherapy as first-line treatment in NCR after propensity score matching

Cohort	Treatment	Patients (n)	Events (n)	Hazard Ratio	95% CI
Target	Pembrolizumab	3,003	1,966	0.66	0.62-0.70
Compartor	Chemotherapy	3,003	2,332	1.00	--

Propensity score matching was conducting including the following covariates: **age, sex, index year, stage of tumour, and WHO performance status (WHO-PS)**.

Objective 3