EUROPEAN MEDICINES AGENCY

DARWIN EU

Real-World Evidence use in medicines regulation

OHDSI symposium 3 Jul 2023

- Presented by Andrej Segec
- European Medicines Agency, Data Analytics and Methods Taskforce – Real World Evidence

Disclaimer

The views expressed in this presentation are my personal views and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

The presenter does not have any conflict of interests.

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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 -

Enabling use & establishing the value of RWE

- Facilitating access
- Build business processes
- Set standards
- Validate methods
- Train/share knowledge
- Establish value across use cases
- International collaboration:
  - build on ICMRA → RWE statement: 4 collaboration areas
  - ICH RWE reflection paper 'International harmonisation of real-wor
    convergence of general principles regarding planning and reportin
    with a focus on effectiveness of medicines' →public consultation

PERSPECTIVES

PERSPECTIVE

Real-World Evidence in EU Medicines Regulation: Enabling Use and Establishing Value

Peter Arlett[1]*, Jesper Kjaer[2], Karl Broich[3] and Emer Cooke[1]

We outline our vision that 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. We are working to deliver this vision through collaboration where we leverage the best that different stakeholders can bring. This vision will support the development and use of better medicines for patients.

Real-world data (RWD) and real-world evidence (RWE) are already used in the regulation of development, authorisation, and supervision of medicines in the European Union. Their place in safety monitoring and disease epidemiology are well-established while their evidentiary value for additional use cases, notably for demonstrating efficacy, requires further evaluation.[1] During the coronavirus disease 2019 (COVID-19) pandemic, RWE rapidly provided impactful evidence on drug safety, vaccine safety, and effectiveness and we were reminded of the importance of robust study methods and transparency.[2] Our vision, anchored in the European Medicines Regulatory Network (EMRN) strategy to 2025, is that by 2025 the use of RWE will have been enabled and the value will have been established across the spectrum of regulatory use cases.[3] Delivering this vision will support the development and use of better medicines for patients.

In December 2018, the US Food and Drug Administration (FDA) published its framework for RWE underpinned by three pillars: whether RWD are fit for use, whether the study designs can provide adequate evidence, and whether the study conduct meets regulatory requirements.[4] In 2019 in the European Union, we published the OPTIMAL framework for RWE also consisting of three pillars: operational, technical, and methodological.[5] More recently, the EU approach places RWE in the wider context of big data and is guided by the priority recommendations of the Big Data Task Force. These recommendations are being implemented through the Big Data Steering Group and the second multi-annual work plan was published in August 2021.[6] Figure 1 represents the workplan with its 11 workstreams which will deliver our vision for RWE by 2025. The workplan places emphasis on collaboration across stakeholders and with international regulatory partners. This work also needs to be seen in the wider EU policy context, most notably the European Commission's plans for a European Health Data Space.[7]

Acknowledging different frameworks to conceptualize the challenges and opportunities of RWE, we believe the two main priorities for the European Union are to enable its use and establish its value for regulatory decision making. The EMRN is working to deliver on both priorities through a collaborative approach where we leverage the best that different stakeholders can bring, and where those stakeholders can complement the central role of industry in generating evidence.

ENABLING USE

To enable use, we are working on multiple fronts with our stakeholders, including patients, healthcare professionals, industry, regulatory and public health agencies, health technology assessment bodies, payers, and academia. We are initiating work to establish a data quality framework, not just for RWD but for all data used in regulatory decision making. We are striving to improve the discoverability (findability) of RWD through agreement of metadata for RWD and through a public catalogue of RWD sources[8] that builds on the early work of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). The ENCePP Guide on Methodological Standards in Pharmacoepidemiology,[9] extensively updated in 2021, is the core of our efforts to drive up the standards of study methods for RWE, and this is complemented by recently published guidance on conducting studies based on patient registries.[10]

The European Medicines Agency (EMA) and some national medicines agencies

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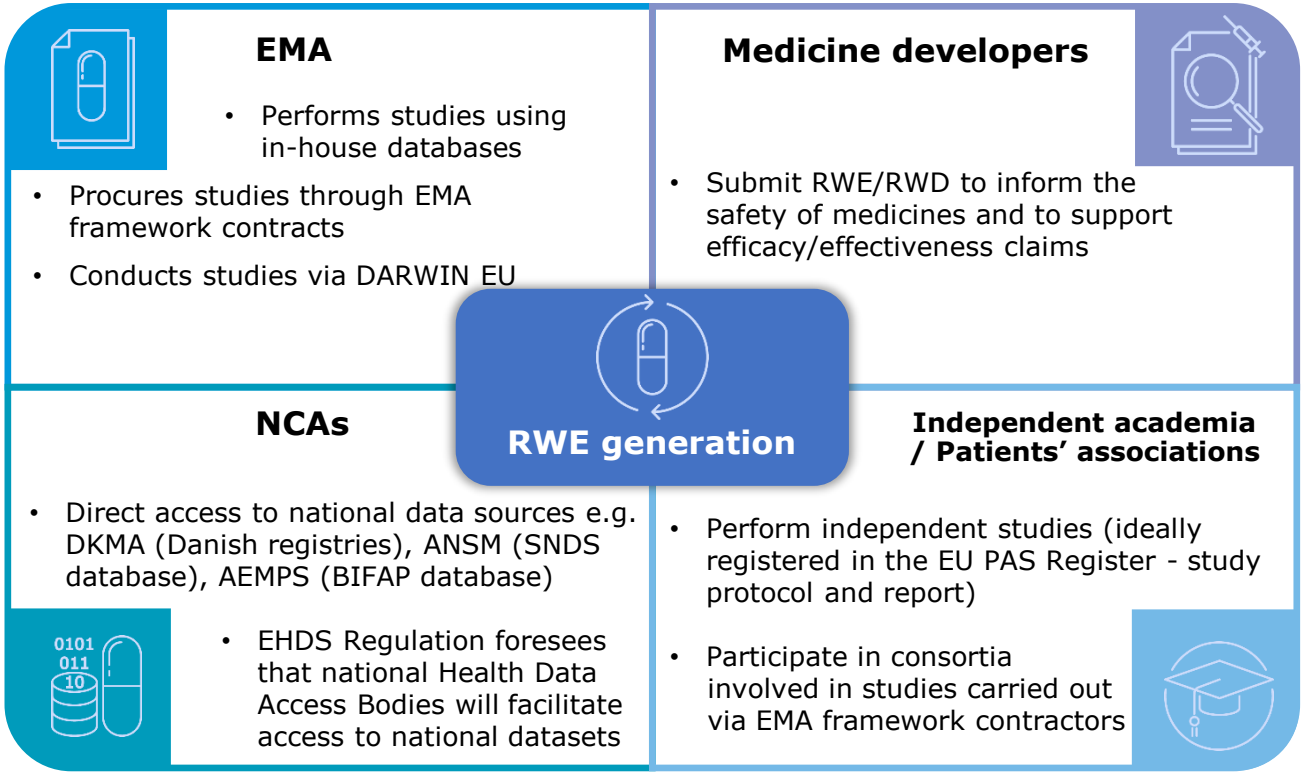
Supply: Real-world evidence



	Flynn et al. (2021) What was the Contribution of Real-World Evidence in EU?	Eskola et. al (2021) Use of Real-World Data and Evidence in Drug Development in EU	Purpura et al. (2021) The Role of Real-World Evidence in FDA
Number of products reviewed	158	111	136
Period	Jan 2018 – Dec 2019 (submitted marketing applications, including non-published information)	Jan 2018 – Dec 2019 (approved marketing applications, only published information)	Jan 2019 – June 2021 (approved marketing applications, only published information)
Number of products with RWE included	**63 (39.9%)**	**111 (100%)**	**116 (85.2%)**
Therapeutic area with higher use of RWE	Oncology and anti-infectives	Oncology, hematology and anti-infectives	Oncology and anti-infectives
Key messages	• Widespread use of RWE to support evaluation of marketing applications • RWE in pre-authorization (1/3) and post-authorization (2/3) • RWE included to support safety (87.3%) and efficacy (49.2%) • Most common data sources were registries (60.3%) followed by hospital data (31.7%)	The study confirms that RWD/RWE contribute to medicines development learning and regulatory decisions • in virtually all phases • across different therapeutic areas • product characteristics RWD/RWE particularly supports conditional marketing authorizations and approval of orphan medicines.	Successful use of RWE in regulatory approvals required: • fit-for-purpose data • good study design, appropriate data collection, and thoughtful data analysis • proactive communication with FDA

HMA / EMA Big Data Steering Group

The European Medicines Agency (EMA) and Heads of Medicines Agencies (HMA) set up a joint task force to describe the big data landscape from a regulatory perspective and identify practical steps for the **European Medicines Regulatory Network to make best use of big data in support of innovation and public health** in the European Union (EU). This led to the creation of the Joint HMA/EMA Big Data Steering Group and Big Data Steering Group Work Plan.

Jan. 2020

'Ten recommendations to unlock the potential of big data for public health in the EU'

May 2020

1st Big data steering group meeting in May 2020

Sep. 2020

Publication of the 1st BDSG workplan 2020/2021

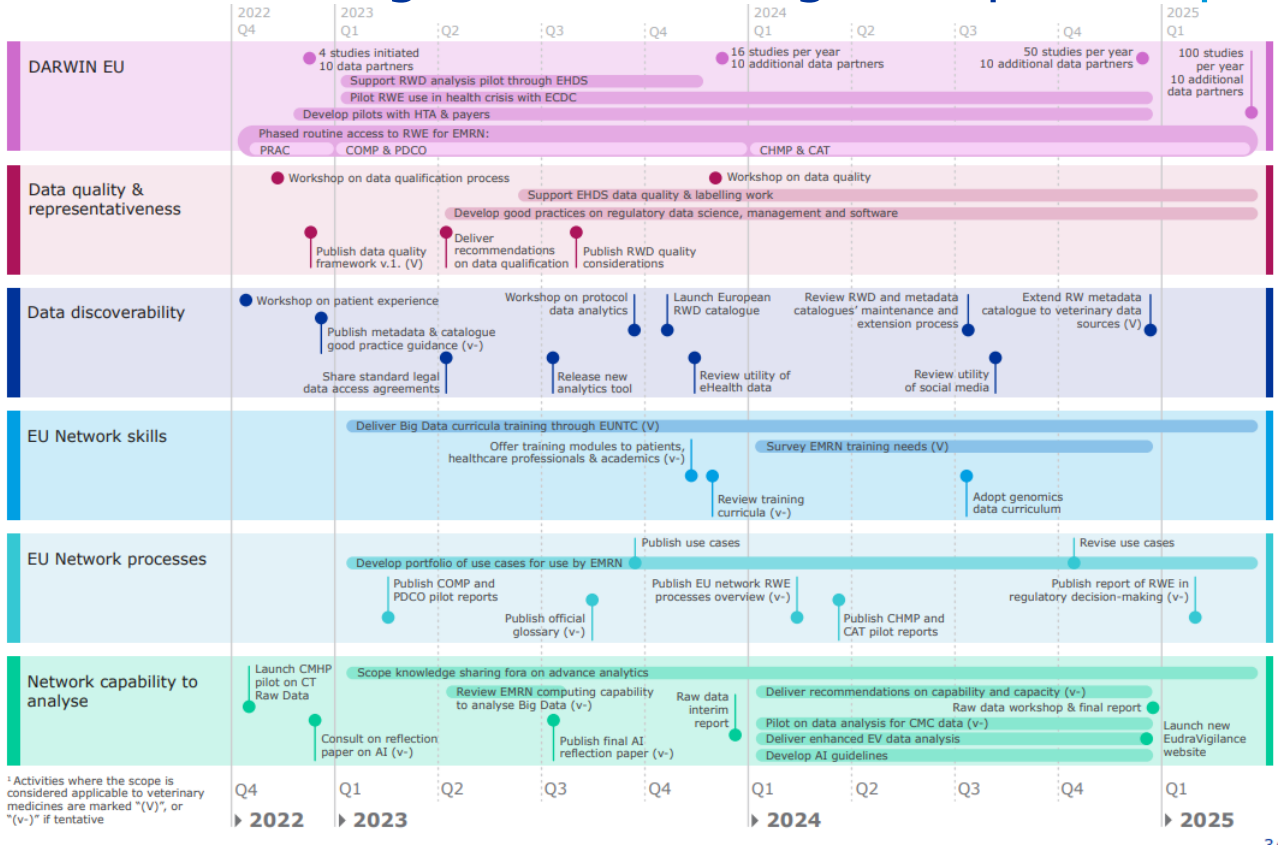
Aug. 2021

Publication of the 2nd BDSG workplan 2021/2023

Jul 2022

3rd BDSG workplan

HMA-EMA Joint Big Data Steering Group work plan



[1] Activities where the scope is considered applicable to veterinary medicines are marked "(V)", or "(v-)" if tentative

- Delivery of expert advice
- Governance framework
- International initiatives
- Stakeholder engagement
- Veterinary recommendations

Why can RWD analyses be useful for regulators?

Ultimate goal: better informed and more efficient regulatory decision-making

To help fill knowledge gaps

- Providing additional information needed for decision-making such as more recent data or additional sensitivity analyses, or access to more and different databases (e.g. those established and maintained by public health authorities)

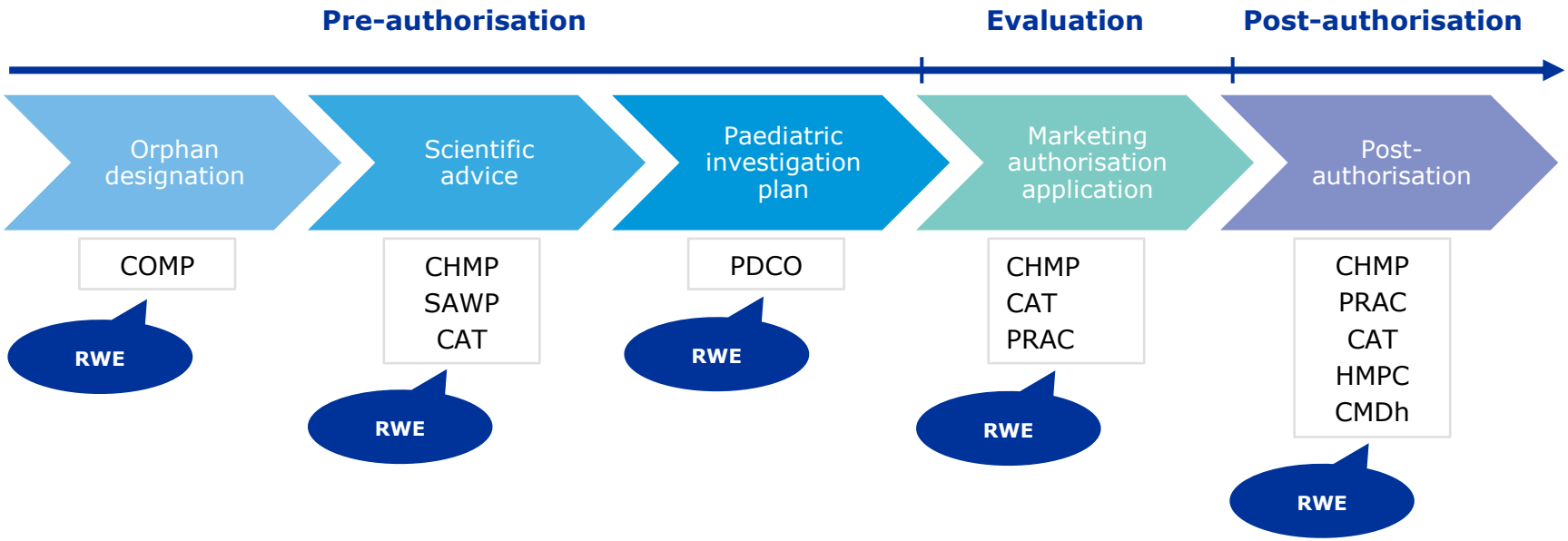
Transparent and tailored analyses

- Transparent and trusted sources of RWD
- Tailored to the Committee's questions, with involvement of the Committee/requester at every step

Faster evidence generation, avoiding the procedural steps for imposing and supervising MAH sponsored studies

Ability to study multiple substances of the same class avoiding unnecessary duplication and inefficiency that might be feature of studies done by industry

RWE use across the medicinal product lifecycle



Towards delivering the 2025 RWE vision

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.

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

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

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

Demand: Three main areas for which RWD analyses can support committees' decision-making

1 Support the planning and validity of applicant studies

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

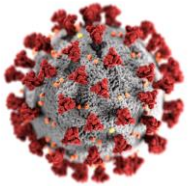
2 Understand the clinical context

- Disease epidemiology
- Clinical management
- Drug utilisation

3 Investigate associations and impact

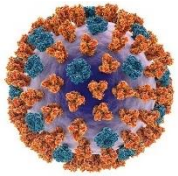
- Effectiveness and safety studies
- Impact of regulatory actions

DARWIN EU® as central pillar for health crisis planning & response



Possible use cases include

- Monitoring the use of medicines to predict demand and shortages
- Understanding the disease natural history to support development of vaccines and therapeutics
- Provide evidence for repurposing existing medicines
- Monitor the safety and effectiveness of vaccines and therapeutics post-authorisation



DARWIN EU® will support decision making on medicines and future crisis responses with an operational infrastructure for conducting RWE studies

RWE studies experience report published + infosheet

Take stock of the **experience with regulatory-led RWD studies** and evaluate the **opportunities and challenges in supporting regulatory decision making**

1. RWE needs

Understand:

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

2. Suitability of data sources

Understand:

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

3. Process for RWE studies

Review the process for:

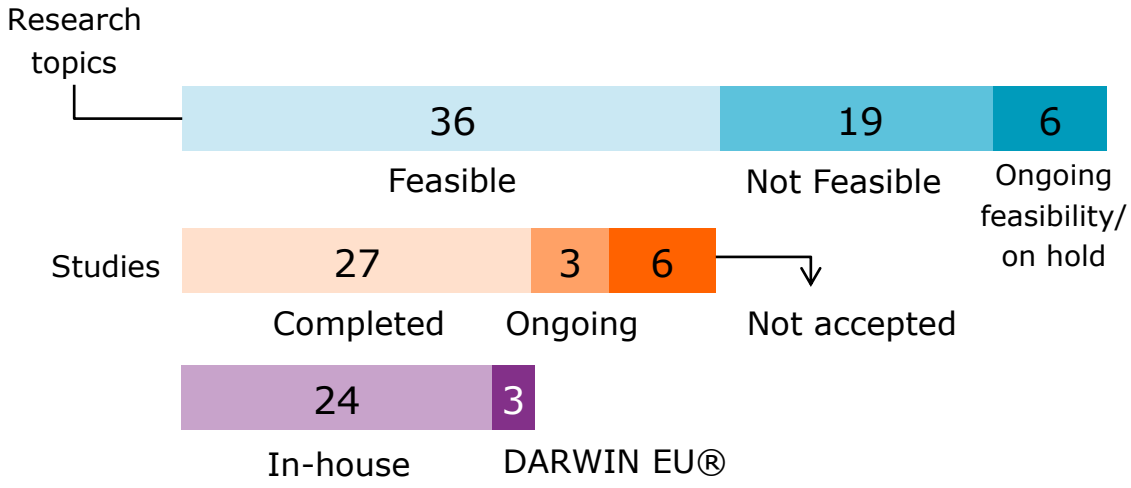
- receiving **study requests, proactively offering** and **conducting** RWE studies;
- identify **opportunities for improvements.**

September 2021 – February 2023

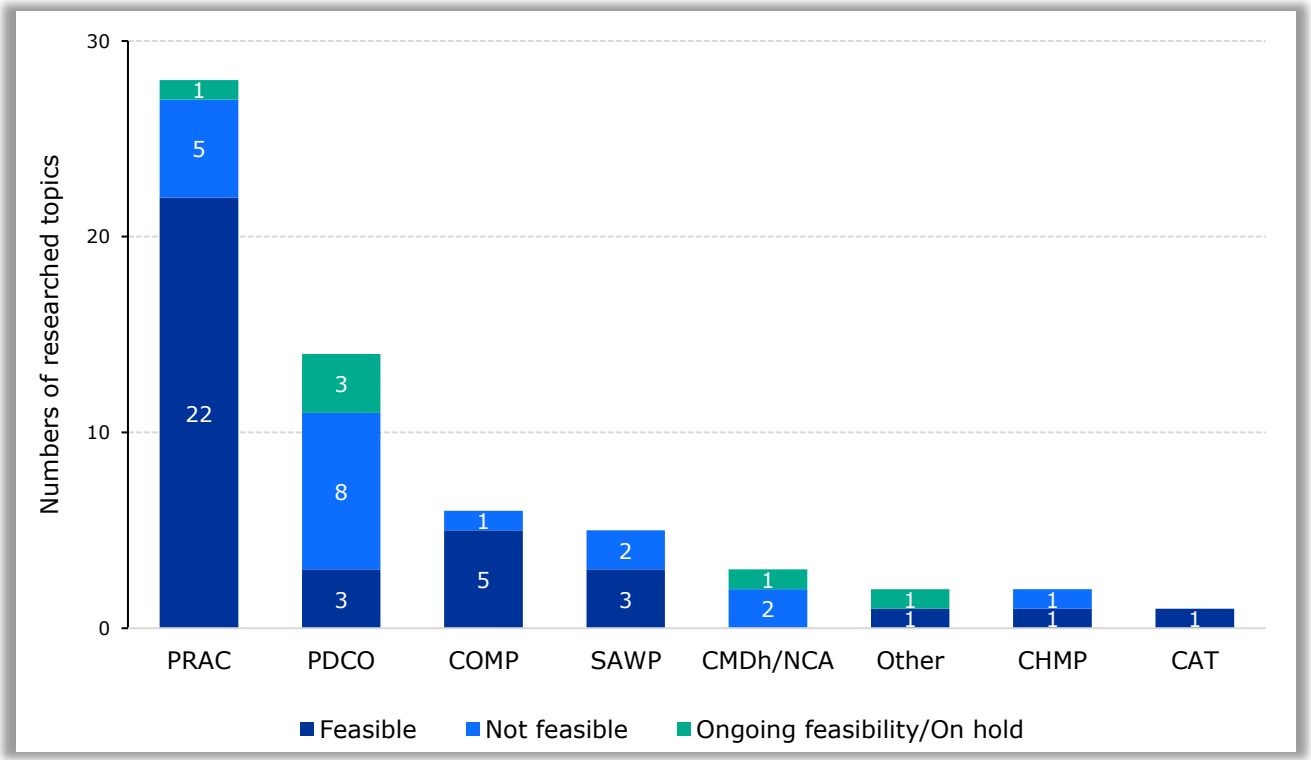
Main results – Overview of RWE studies

61
research topics

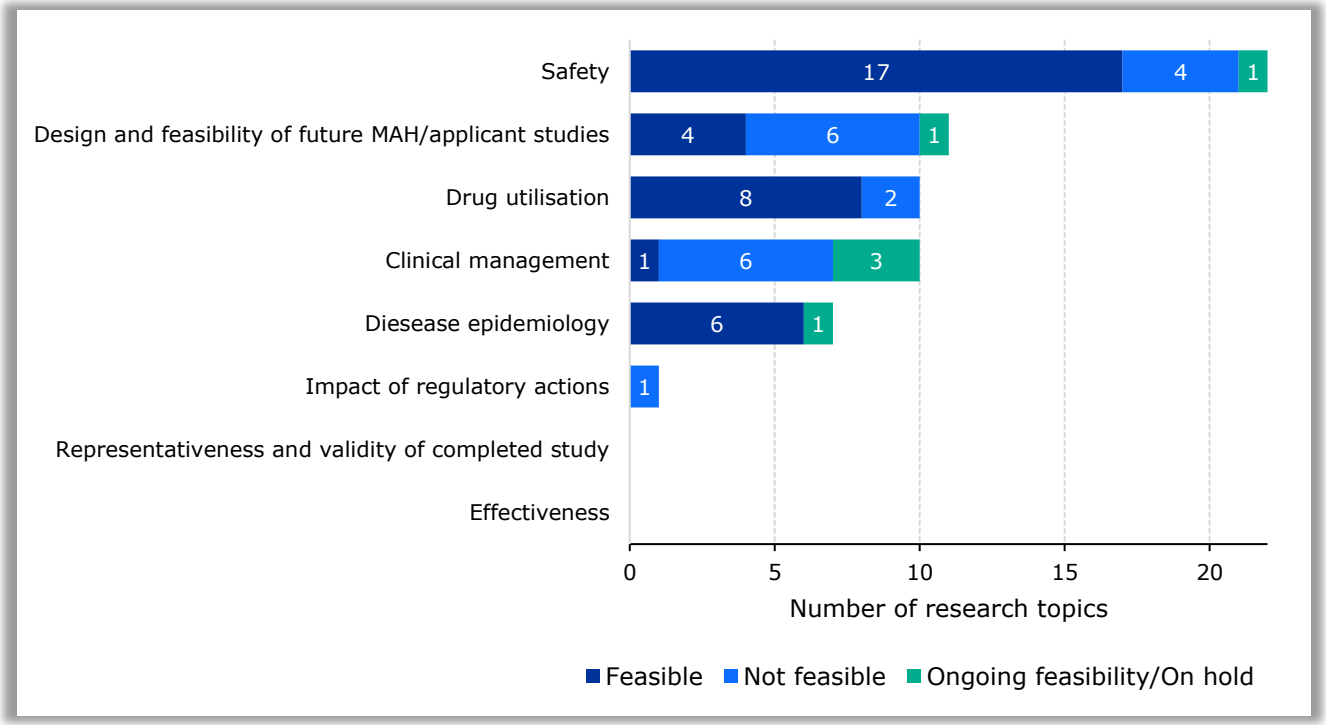
49	8	4
In-house	DARWIN EU	FWC



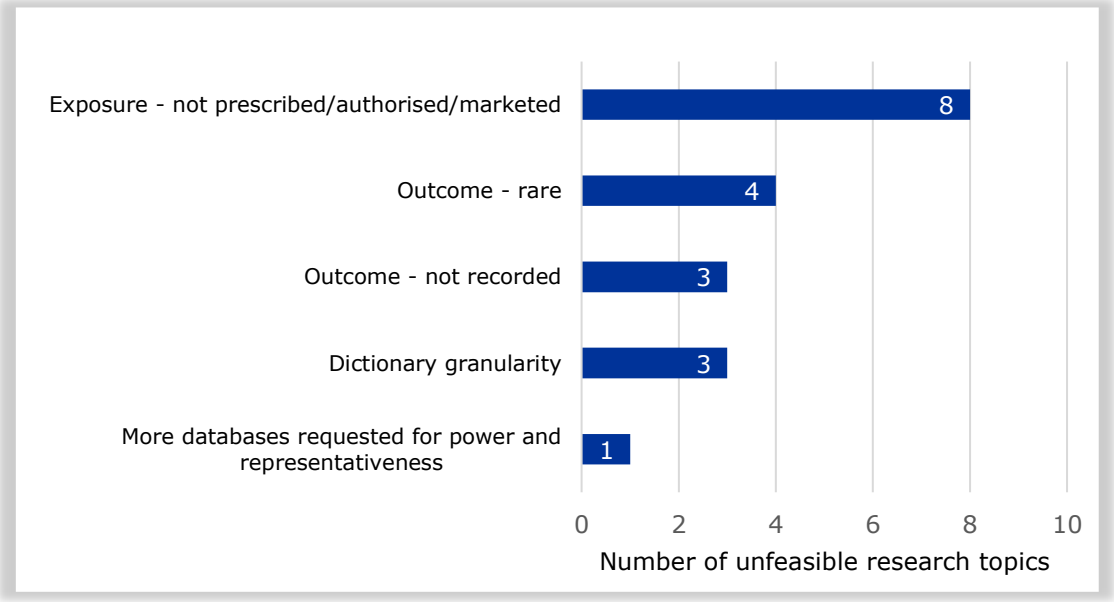
Research topics by committees/requester



Use case categories



Reasons for unfeasibility of studies (19)



*** Lack of granularity in the information contained in the databases** includes outcomes that are poorly captured by the coding system, or insufficient information on prescribing, dose, duration of use, and indication

Towards delivering the 2025 RWE vision

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.

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
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- Coordination Centre launched February 2022
- Onboarded first **10 data partners**
- **First studies** finalised
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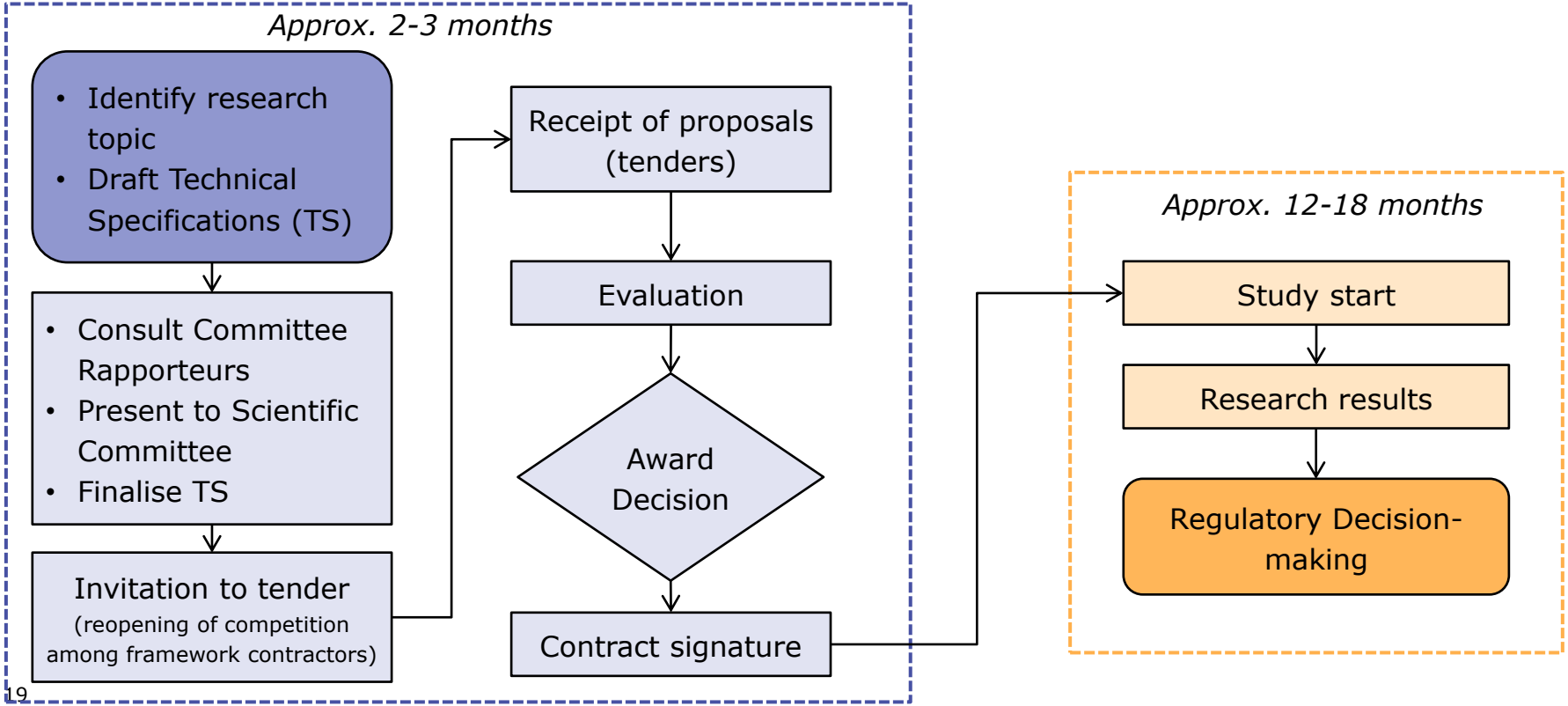
Regulatory authorities also have access to national databases e.g., Nordic registries, SNDS, BIFAP, …

EMA-funded (FWC) studies – the process



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

Towards delivering the 2025 RWE vision

A tale with three pathways…

EMA studies using in-house databases

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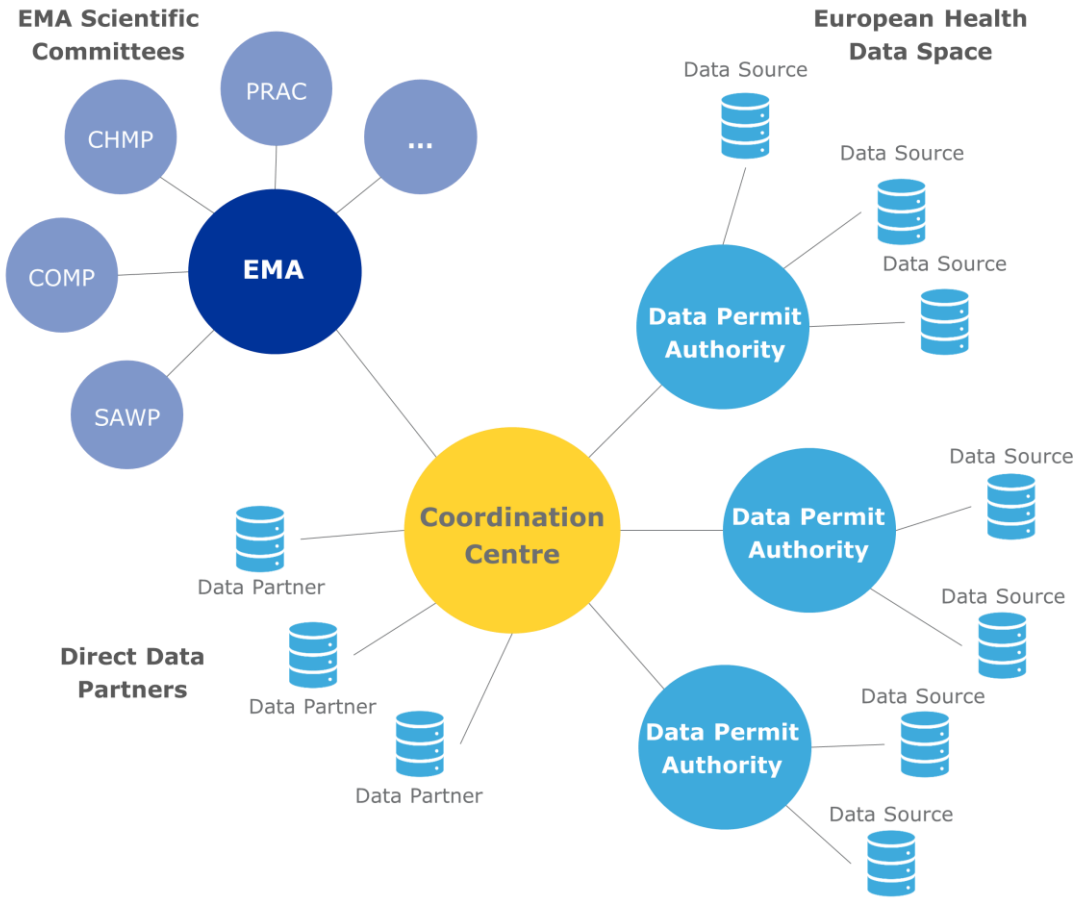
+ Regulatory authorities also have access to national databases e.g., Nordic registries, SNDS, BIFAP, …

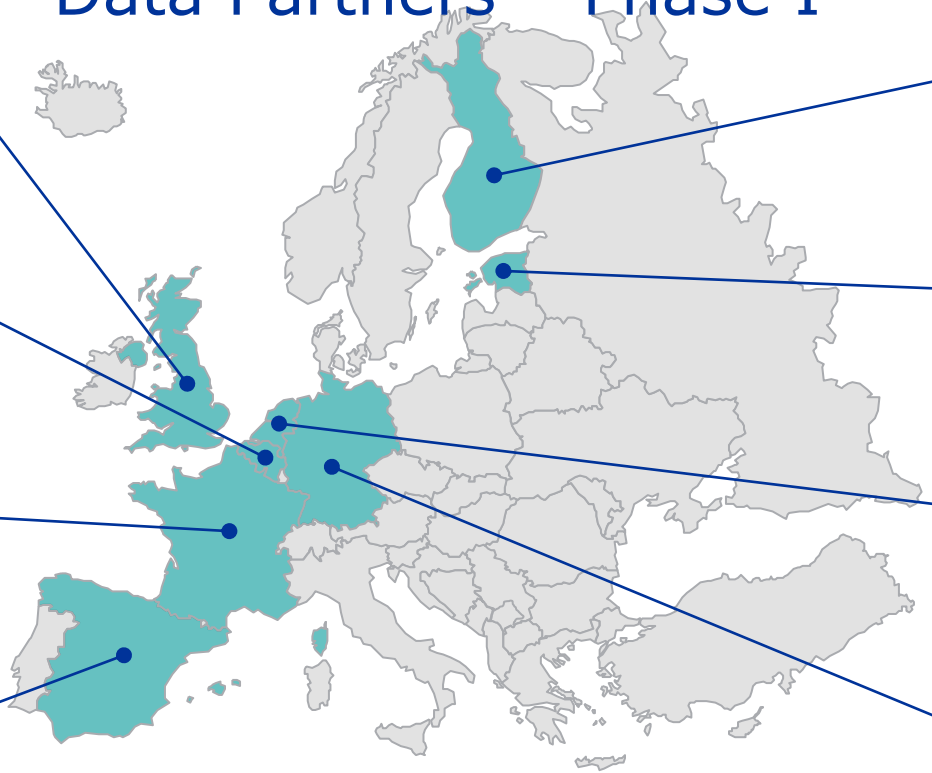
DARWIN EU® is a federated **network** of **data**, **expertise** and **services** that supports better decision-making throughout the product lifecycle by generating reliable **evidence from real world healthcare data**



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



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

Currently selecting Phase II DPs after open call for expression of interest

DARWIN EU establishment in 2023

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

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

Studies started in 2022 (year 1/ phase I)

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

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

Table of contents

DARWIN EU

Study Report for C1-003

Author(s): Katia Verhamme, Maria de Ridder, Talita Duarte Salles, Dani Prieto Alhambra, Miguel-Angel Mayer, Romain Griffier

Version: v3.1

Dissemination level: Public

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**

Ongoing studies

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

CHMP
Complex

EHDS coagulopathy of COVID-19

EC/EHDS
Complex

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

Erythomycin use as prokinetic

NCA
OTS

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

HTA/Payers
OTS

Naloxone use in treatment of opioid overdose.

CHMP
OTS

Drug utilisation study of prescription **opioids**.

PRAC
OTS

OTS = off-the-shelf study

Closing remarks

- RWE use is being enabled and established across regulatory use cases, informing regulatory decision making on medicines
- Three pathways of RWE generation
- DARWIN EU establishment focus on DPs, studies, pilot use cases and developing pipelines, leading to high study volume meeting the demand and shorter timelines in future years

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

Coordination Centre website: www.darwin-eu.org

For questions to the Coordination Centre, please contact: enquiries@darwin-eu.org

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Any questions?

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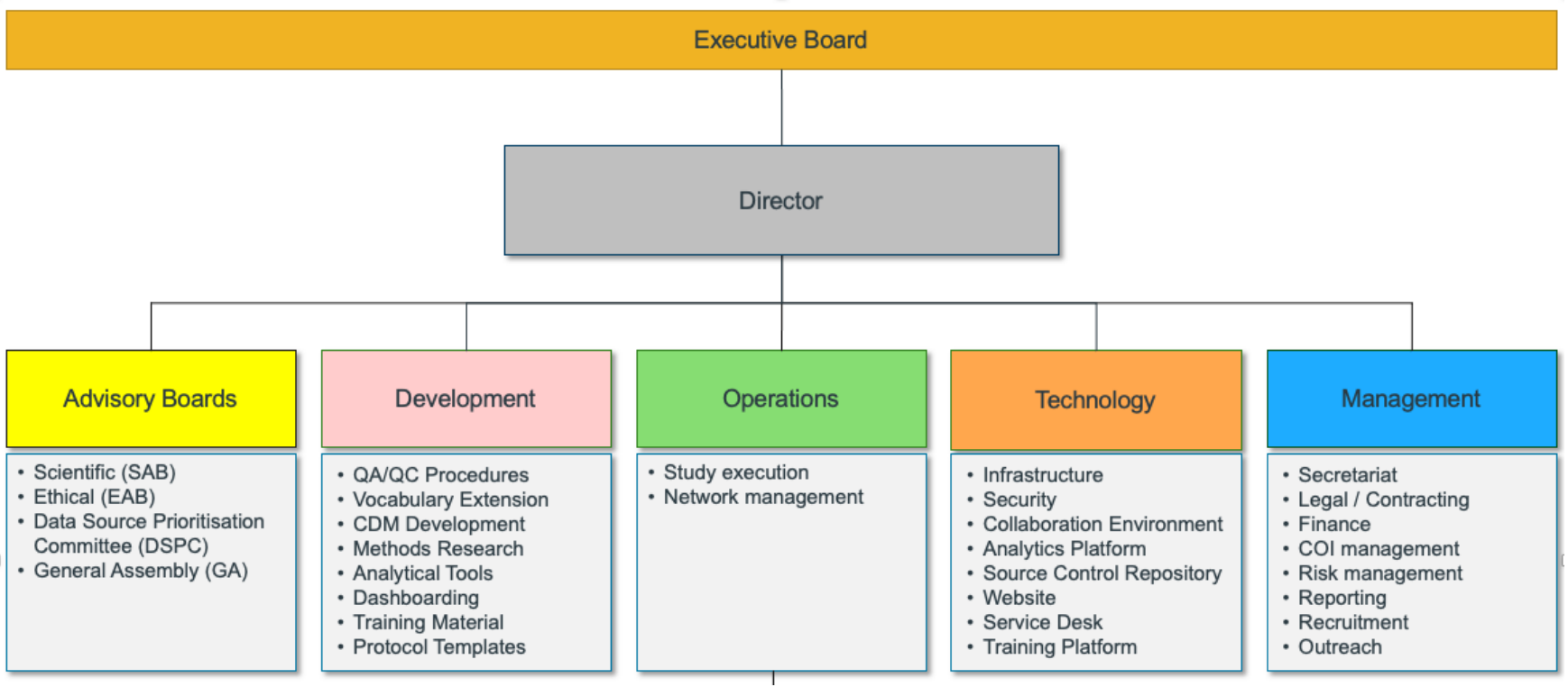
The Hyve

ODYSSEUS
DATA SERVICES INC

Structure of the DARWIN EU® Coordination Centre



DARWIN EU

Coordination Centre

Development

Ed Burn

Disclosure

This presentation represents the views of the DARWIN EU® Coordination Centre only and cannot be interpreted as reflecting those of the European Medicines Agency or the European Medicines Regulatory Network.

- Overview of development activities
- Example use of DARWIN EU® R packages

- Overview of development activities
- Example use of DARWIN EU® R packages

Catalogue of Standard Data Analyses

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.

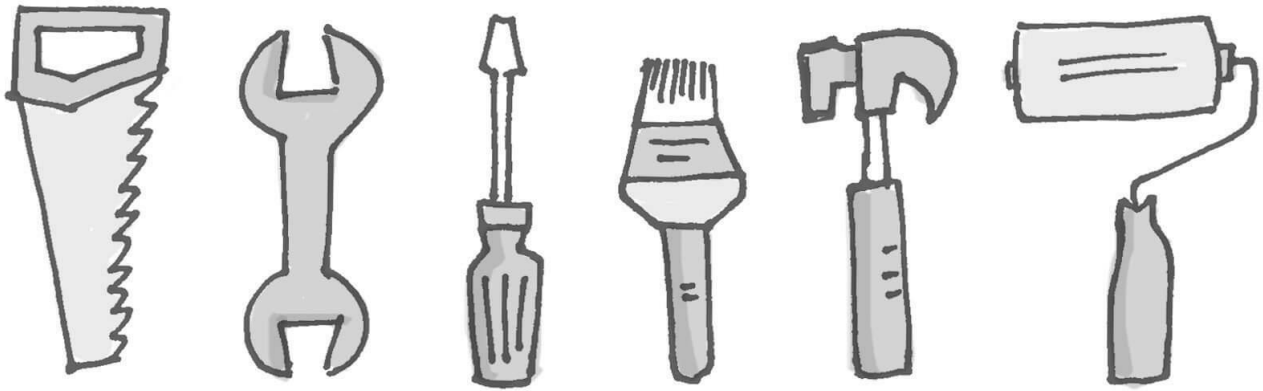
- Patient-level characterisation
- Patient-level DUS analyses
- Population-level DUS analyses
- Population-level descriptive epidemiology

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.

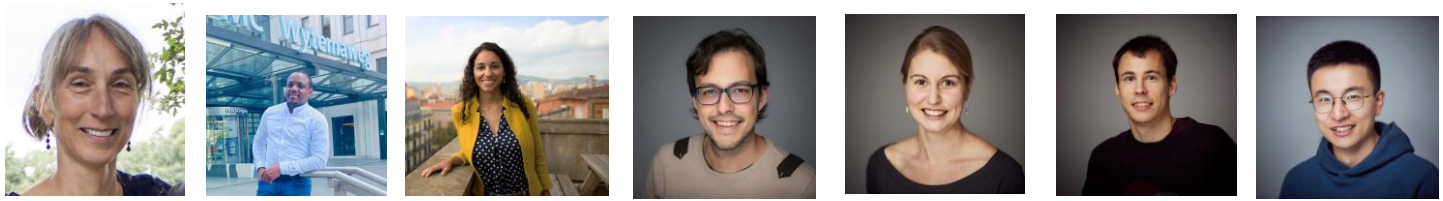
- Prevalent user active comparator cohort studies
- New user active comparator cohort
- Self-controlled case risk interval
- Self-controlled case series
- Time series analyses and Difference-in-difference studies
- RMM effectiveness

Building tools



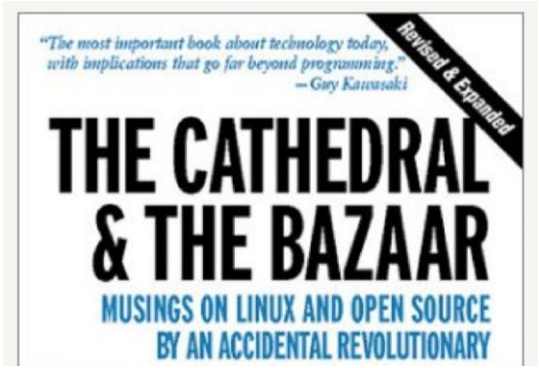
Primary focus of the development pillar is providing tools (mostly R packages) to help users to perform standard data analyses

User profiles



- Epidemiologists and data scientists
- Interact with our R packages directly, preparing analysis scripts that use them
- Value flexibility and extensibility in tools

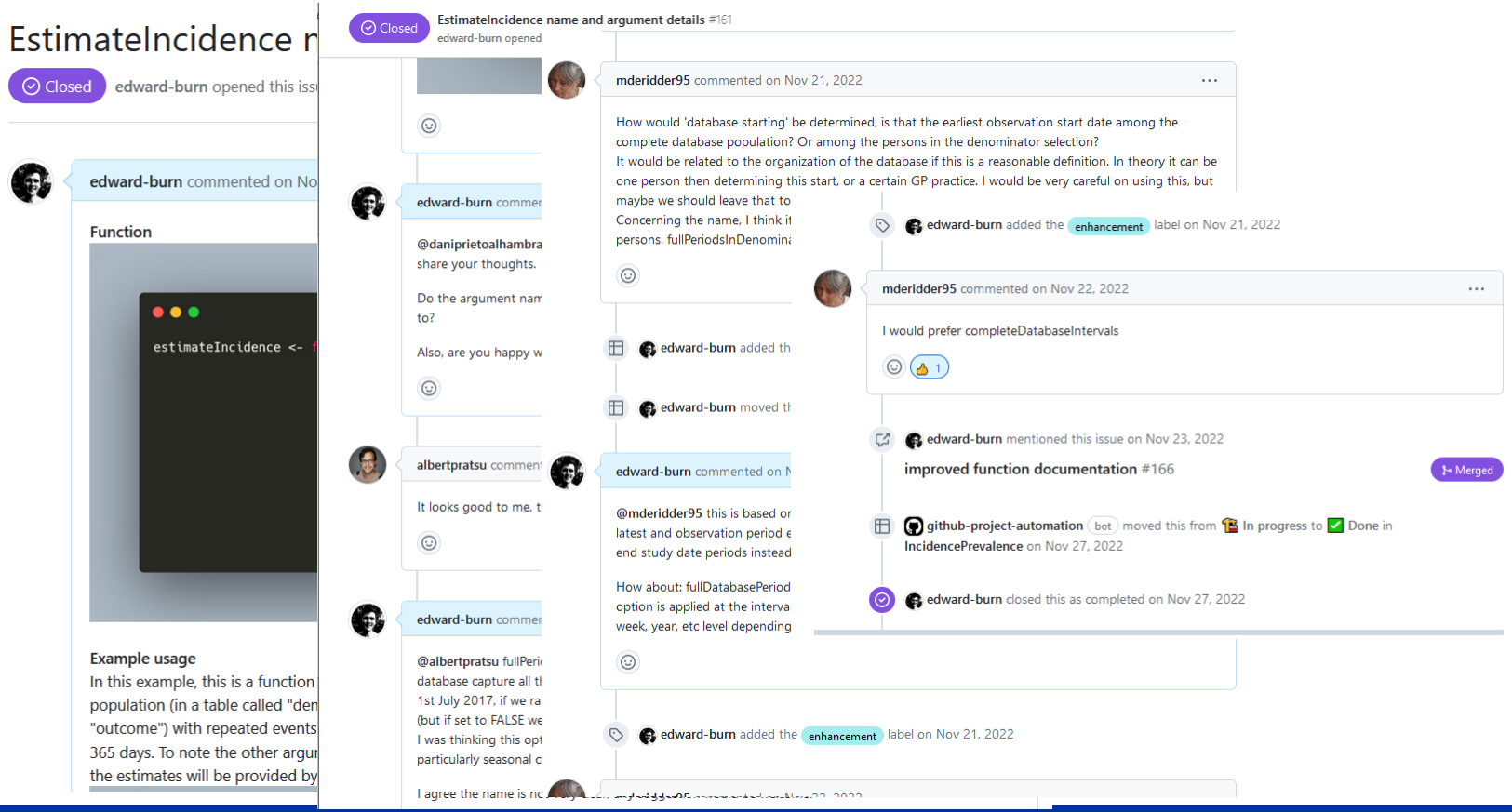
Users as co-developers



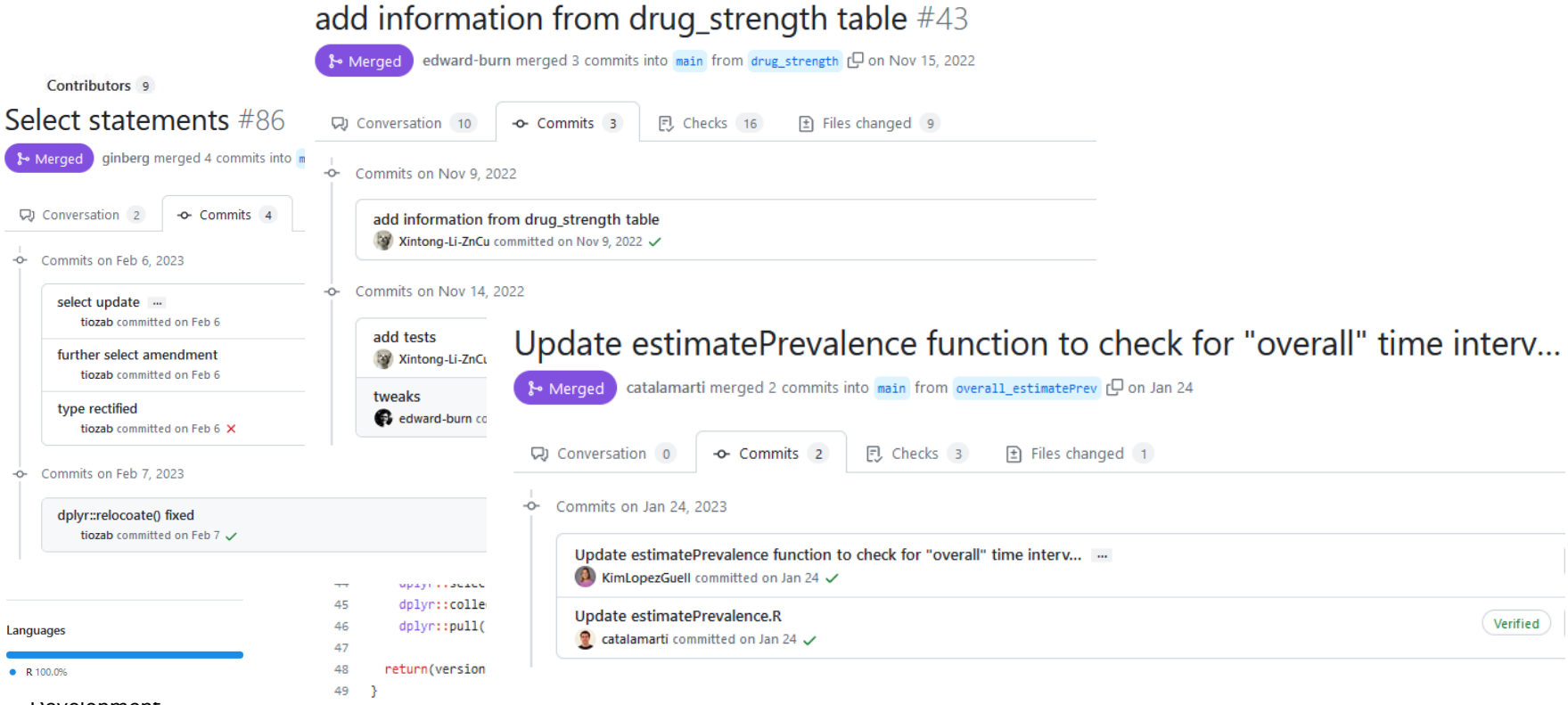
TREATING YOUR USERS AS CO-DEVELOPERS IS YOUR LEAST-HASSLE ROUTE TO RAPID CODE IMPROVEMENT AND EFFECTIVE DEBUGGING.

RELEASE EARLY. RELEASE OFTEN. AND LISTEN TO YOUR CUSTOMERS.

User-centered design



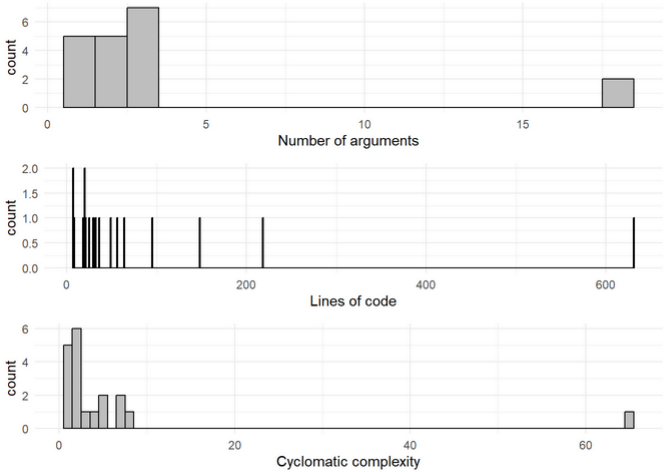
User contributions



Package Reviewer (PaRe)

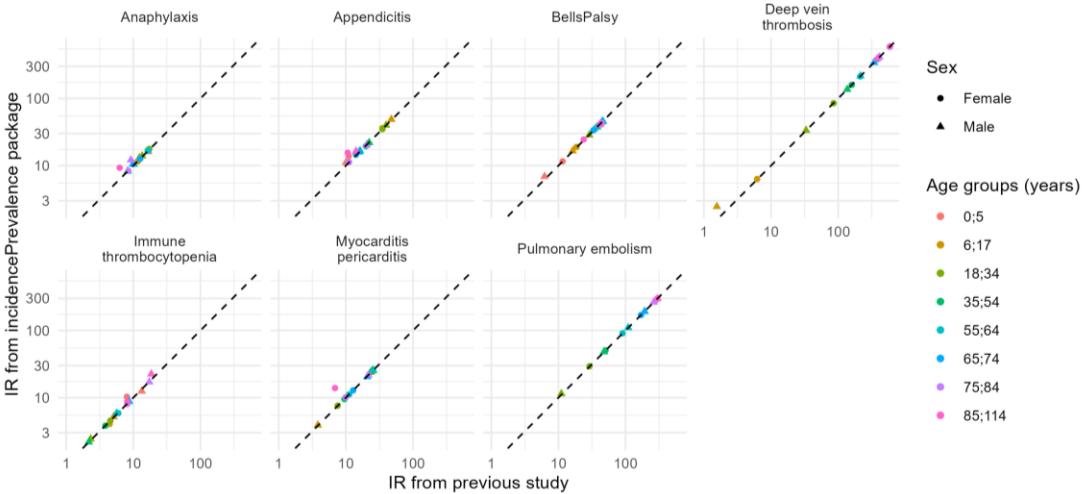
Summary of package functions

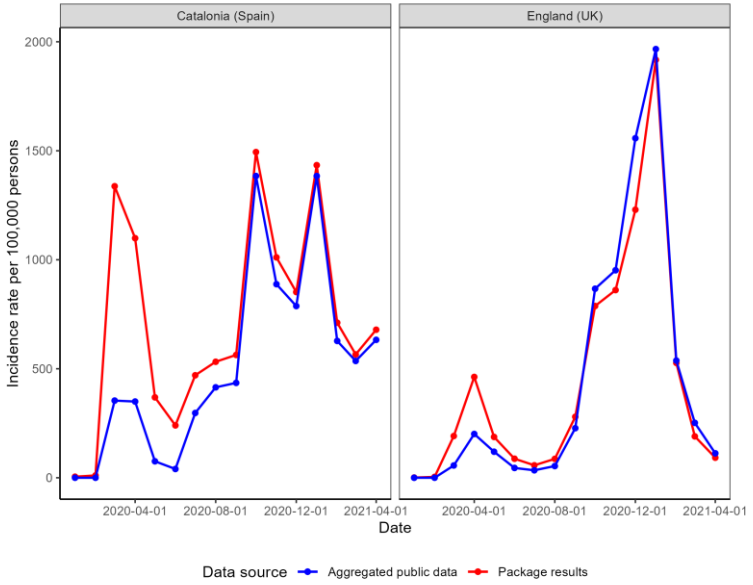
	min	median	max
Number of arguments	1	2	18
Lines of code	7	30	631
Cyclomatic complexity	1	2	65



Function	Number of arguments	Lines of code	Cyclomatic complexity	Location
runSearch	18	631	65	runSearch.R (from line: 34)
getCandidateCodes	18	148	8	getCandidateCodes.R (from line: 97)
mockVocabRef	1	218	7	mockVocabRef.R (from line: 28)
getMatches	2	32	7	runSearch.R (from line: 690)
getMappings	3	95	5	getMappings.R (from line: 46)
getFuzzyMatches	3	29	5	runSearch.R (from line: 736)
getConceptClassId	3	64	4	vocabUtilities.R (from line: 176)
getDomains	2	56	3	vocabUtilities.R (from line: 66)
checkDbType	3	7	2	utils.R (from line: 17)
checkTableExists	3	8	2	utils.R (from line: 26)

Software validation: IncidencePrevalence



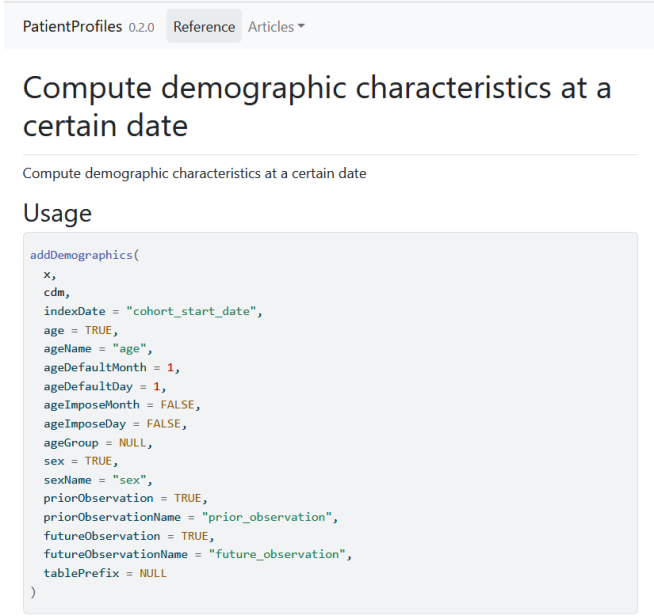


Software performance : IncidencePrevalence

Task	CPRD AURUM (n=39,999,011)	CPRD GOLD (n=15,662,217)	SIDIAP (n=8,265,343)	IPCI (n=2,612,850)
Generating denominator (8 cohorts)	19 mins	8 mins	3 mins	1 min
Yearly period prevalence	11 mins	5 mins	5 mins	1 min
Monthly period prevalence	17 mins	6 mins	8 mins	2 mins
Yearly incidence	8 mins	3 mins	4 mins	1 min
Monthly incidence	13 mins	5 mins	7 mins	1 min

- Overview of development activities
- Example use of DARWIN EU® R packages

CDMConnector and PatientProfiles



CodelistGenerator

Vocabulary based code list

CodelistGenerator 1.5.0 Reference Articles Changelog

Get descendant codes for drug ingredients

Get descendant codes for drug ingredients

Usage

```
getDrugIngredientCodes(cdm, name = NULL, doseForm = NULL)
```

Arguments

cdm
cdm_reference via CDMConnector

name
Names of ingredients of interest. For example, c("acetaminophen", "codeine"), would result in a list of length two with the descendant concepts for these two particular drug ingredients.

doseForm
Only descendants codes with the specified dose form will be returned. If NULL, descendant codes will be returned regardless of dose form.

Code list from systematic search

CodelistGenerator 1.5.0 Reference Articles Changelog

Generate candidate codelist for the OMOP CDM

This function generates a set of codes that can be considered for creating a phenotype using the OMOP CDM.

Usage

```
getCandidateCodes(
  cdm,
  keywords,
  exclude = NULL,
  domains = "Condition",
  conceptClassId = NULL,
  doseForm = NULL,
  vocabularyId = NULL,
  standardConcept = "Standard",
  exactMatch = FALSE,
  searchInSynonyms = FALSE,
  searchViaSynonyms = FALSE,
  searchNonStandard = FALSE,
  includeSequela = FALSE,
  includeDescendants = TRUE,
  includeAncestor = FALSE,
  fuzzyMatch = FALSE,
  maxDistanceCost = 0.1,
  verbose = FALSE
)
```

DrugExposureDiagnostics and DrugUtilisation

Population-level DUS analyses

DrugExposureDiagnostics 0.4.3 Reference Articles Changelog

Execute all checks on Drug Exposure.

Execute all checks on Drug Exposure.

Usage

```
executeChecks(
  cdm,
  ingredients = c(1125315),
  subsetToConceptId = NULL,
  checks = c("missing", "exposureDuration", "type", "route", "sourceConcept",
    "daysSupply", "verbatimEndDate", "dose", "sig", "quantity", "histogram"),
  minCellCount = 5,
  sample = 1e+06,
  tablePrefix = NULL,
  earliestStartDate = "2010-01-01",
  verbose = FALSE
)
```

DrugUtilisation 0.2.1 Reference

This function is used to summarise the dose table over multiple cohorts.

This function is used to summarise the dose table over multiple cohorts.

Usage

```
summariseDrugUse(
  cohort,
  cdm,
  strata = list(),
  drugUseVariables = drugUseColumns(cohort),
  drugUseEstimates = c("median", "q25", "q75"),
  minCellCount = 5
)
```

IncidencePrevalence

- Population-level DUS analyses
- Population-level descriptive epidemiology
- Time series analyses and Difference-in-difference studies
- RMM effectiveness

IncidencePrevalence 0.4.0 Reference Articles

Estimate period prevalence

Estimate period prevalence

Usage

```
estimatePeriodPrevalence(
  cdm,
  denominatorTable,
  outcomeTable,
  denominatorCohortId = NULL,
  outcomeCohortId = NULL,
  outcomeLookbackDays = 0,
  interval = "years",
  completeDatabaseIntervals = TRUE,
  fullContribution = FALSE,
  minCellCount = 5,
  temporary = TRUE,
  returnParticipants = FALSE
)
```

IncidencePrevalence 0.4.0 Reference Articles

Collect population incidence estimates

Collect population incidence estimates

Usage

```
estimateIncidence(
  cdm,
  denominatorTable,
  outcomeTable,
  denominatorCohortId = NULL,
  outcomeCohortId = NULL,
  interval = "years",
  completeDatabaseIntervals = TRUE,
  outcomeWashout = Inf,
  repeatedEvents = FALSE,
  minCellCount = 5,
  temporary = TRUE,
  returnParticipants = FALSE
)
```

Coordination Centre

STUDY OPERATIONS

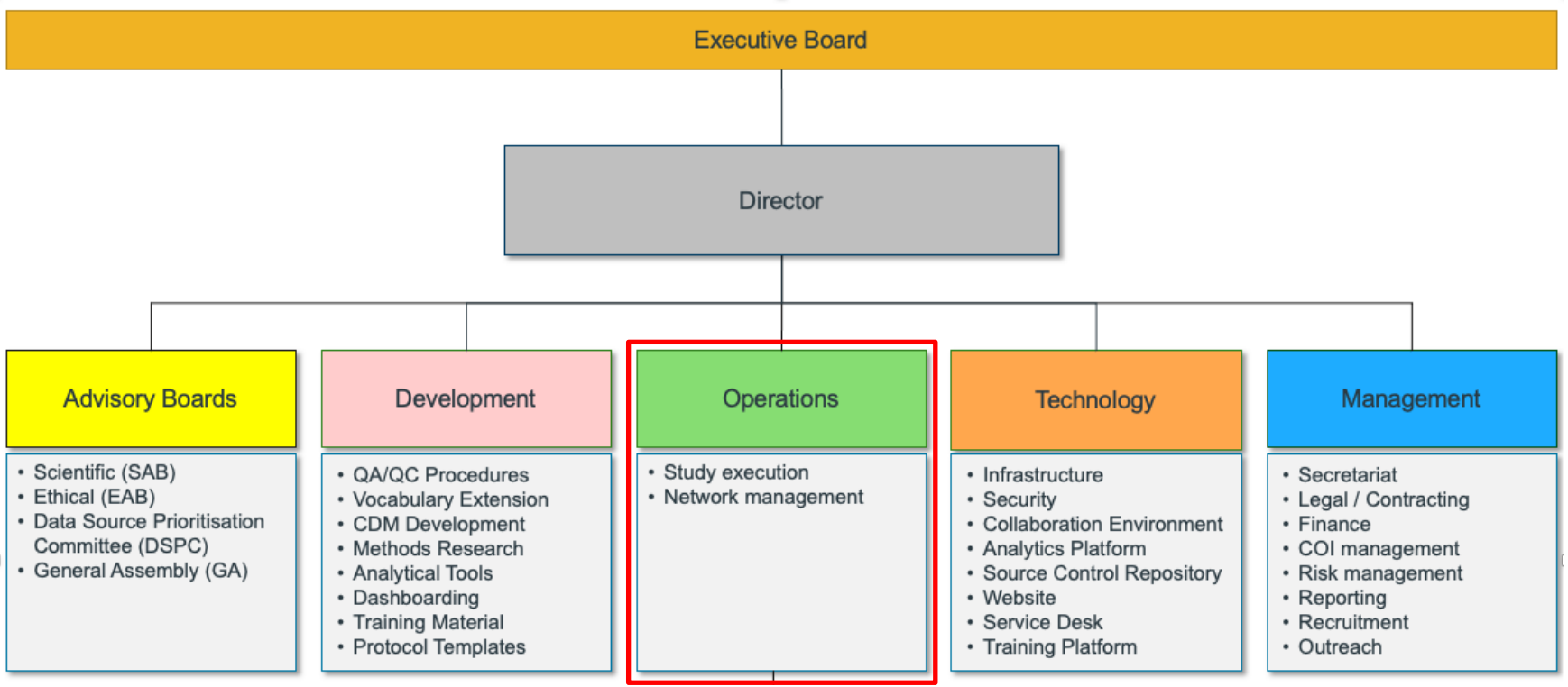
Katia Verhamme

OHDSI EUROPE SYMPOSIUM

Disclosure

This presentation represents the views of the DARWIN EU® Coordination Centre only and cannot be interpreted as reflecting those of the European Medicines Agency or the European Medicines Regulatory Network.

Establishment and Evolution of the Coordination Centre



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 • 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

Expected number of studies

PHASE I Establishment – 1st year → PHASE II Establishment – 2nd year → PHASE III Operation – 1st year → Operation 2nd year → Operation 3rd year

	Year 1	Year 2	Year 3	Year 4	Year 5
Phases	Phase I	Phase II	Phase III	Option 1	Option 2
Routine Repeated analysis	At least 1 study	6	30	60	60
Off the shelf studies	At least 2 studies	6	30	60	60
Complex Studies	1	4	12	24	24
Very Complex Studies	0	0	0	1	1

Expected number of studies

PHASE I Establishment – 1st year → PHASE II Establishment – 2nd year → PHASE III Operation – 1st year → Operation 2nd year → Operation 3rd year

	Year 1	Year 2	Year 3	Year 4	Year 5
Phases	Phase I	Phase II	Phase III	Option 1	Option 2
Routine Repeated analysis	At least 1 study	-	30	60	60
Off the shelf studies	At least 2 studies	6 + 8	30	60	60
Complex Studies	1	4	12	24	24
Very Complex Studies	0	0	0	1	1

1. Study Exploration	Study Feasibility- Study request by EMA: - Do we have the data? – Darwin Portal - Do we have the analytical pipelines? (OTS)	EMA
2. Study Initiation	- Work Order Form Data Partners - Creation of Study Team: PI/data analyst - Declaration of Interest	Database Partners
3. Study Implementation	- Study outline/Protocol – Upload to EUPAS register - IRB approval - Kick-off meeting - Phenotyping – Cohort Diagnostics - Study Package – Test Run	Darwin CC: - Network Pillar - Development Pillar - Technology Pillar - Management Pillar
4. Study Execution	- Data Partners run Study Package - Data QC by Data Partners - Results uploaded to DRE - Results reviewed by PI	
5. Study Dissemination	- Generation of Study Report (ENCePP template) - Upload to EUPAS register - Manuscript generation - Study archiving	

STUDIES YEAR 1

Study Title	Committees	Study Type	Type of analysis	Data bases	Status
DARWIN EU® - **Prevalence of rare blood cancers in Europe**	COMP	OTS	Disease Epidemiology	IPCI (Nl) SIDIAP (Spain) CPRD Gold (UK) IQVIA LPD (Be) IQVIA DA (Ge)	Completed
DARWIN EU® - **Drug utilisation of valproate**-containing medicinal products in women of childbearing potential	Following safety referral	OTS	Drug Utilisation Study	IPCI (Nl) SIDIAP (Spain) CPRD Gold (UK) IQVIA LPD (Be) IQVIA DA (Ge) HDSF (Fi)	Completed
DARWIN EU® - **DUS of Antibiotics** in the 'Watch' category of the WHO AWaRe classification of antibiotics for evaluation and monitoring of use	PRAC/CHMP	OTS	Drug Utilisation Study	IPCI (Nl) CHUBX (France) SIDIAP (Spain) IMASIS (Spain) IQVIA DA (Ge) CPRD Gold (UK)	Completed
DARWIN EU® - **Background rates** of serious adverse events to contextualise safety assessments in clinical trials and non-interventional studies in adolescent and adult patients with **severe asthma**.	CHMP	Complex (complex phenotype)	Disease Epidemiology	IPCI (Nl) SIDIAP (Spain) IMASIS (Spain) CPRD Gold (UK) Estonian Biobank	Ongoing

STUDIES YEAR 2 (1)

Study Title	Committees	Study Type	Type of analysis	Data bases	Status
DARWIN EU® - **Multiple myeloma**: patient characterisation, treatments and survival in the period 2012-2022	HTA/Payers	OTS	Disease Epidemiology and Treatment Pattern analysis	IQVIA DA (Ge) SIDIAP (Spain) IMASIS (Spain) Estonian Biobank ACI Varha (Fi) CHUBX (France) IKNL (Nl)	Ongoing
DARWIN EU® **Drug Utilisation Study** of **prescription opioids**.	PRAC	OTS	Drug Utilisation Study	Estonian Biobank IPCI (Nl) SIDIAP (Spain) CHUBX (France) IQVIA LPD (Be) IQVIA DA (Ge) ACI Varha (Fi)	Ongoing
DARWIN EU® – **EHDS Use Case**: **Natural history** of **coagulopathy in COVID-19 patients** and persons **vaccinated** against SARS-CoV-2 in the context of the OMICRON variant	EC/EHDS	Complex	SIR	IPCI (NL) SIDIAP (Spain) IQVIA DA (Ge) Estonian Biobank CPRD GOLD (UK)	Ongoing
DARWIN EU® - Co-prescribing of endothelin receptor antagonists (ERAs) and phosphodiesterate-5 inhibitors (PDE-5is) in **pulmonary arterial hypertension** (PAH)	CHMP	OTS	Disease Epidemiology and Treatment Pattern analysis	CHUBX (France) CPRD GOLD (UK) Estonian Biobank IQVIA DA (Ge)	Ongoing

STUDIES YEAR 2 (2)

Study Title	Committees	Study Type	Type of analysis	Data bases	Status
DARWIN EU® - **Use of take-home naloxone** for opioid overdose treatment	CHMP	OTS	Drug Utilisation Study	IQVIA DA (Ge) IQVIA DA (Be) CPRD Gold (UK) SIDIAP	Ongoing
DARWIN EU® **DUS of medicines with prokinetic properties** in children and adults diagnosed with gastroparesis	NCA	OTS	Drug Utilisation Study	IPCI (NI) CHUBX (France) SIDIAP (Spain) IMASIS (Spain) IQVIA DA (Ge) IQVIA LPD (Be) CPRD Gold (UK)	Ongoing

Study Feasibility:

As of to date: **13 feasibility requests** in year 2:

- 6 studies received green light
- 4 studies suggested to put on hold ➔ different reasons: lack of data or need of more recent data
- 3 Feasibility assessments either just received or under review by EMA

Expected number of studies

PHASE I Establishment – 1st year → PHASE II Establishment – 2nd year → PHASE III Operation – 1st year → Operation 2nd year → Operation 3rd year

	Year 1	Year 2	Year 3	Year 4	Year 5
Phases	Phase I	Phase II	Phase III	Option 1	Option 2
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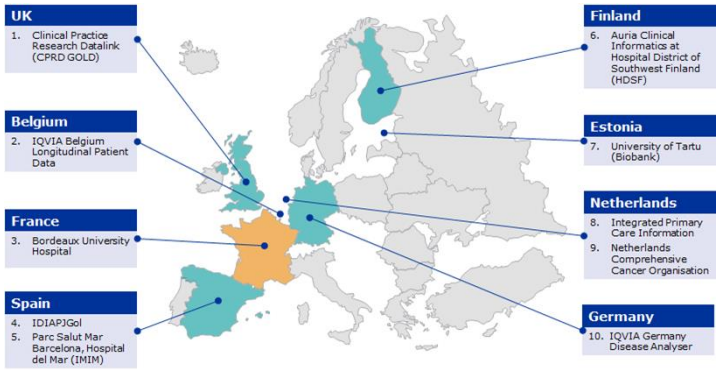
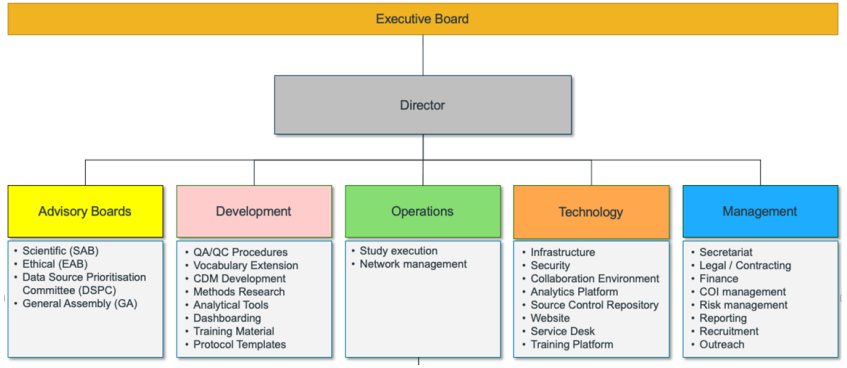
Off the shelf studies	At least 2 studies	6 + 8	30	60	60
Complex Studies	1	4	12	24	24
Very Complex Studies	0	0	0	1	1





EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA Colleagues:
RWE group

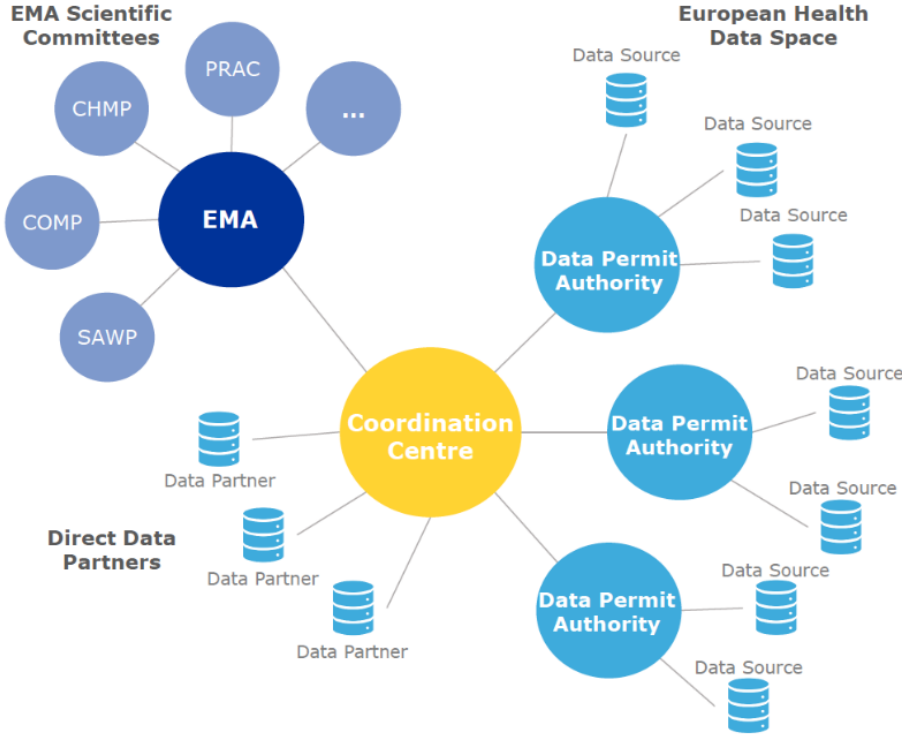
The SIDIAP experience as Data Partner in DARWIN EU

Talita Duarte-Salles
Real World Epidemiology Research Group
IDIAPJGol, Barcelona-Spain
tduarte@idiapjgol.org

IDIAP JORDI GOL

DARWIN EU Network

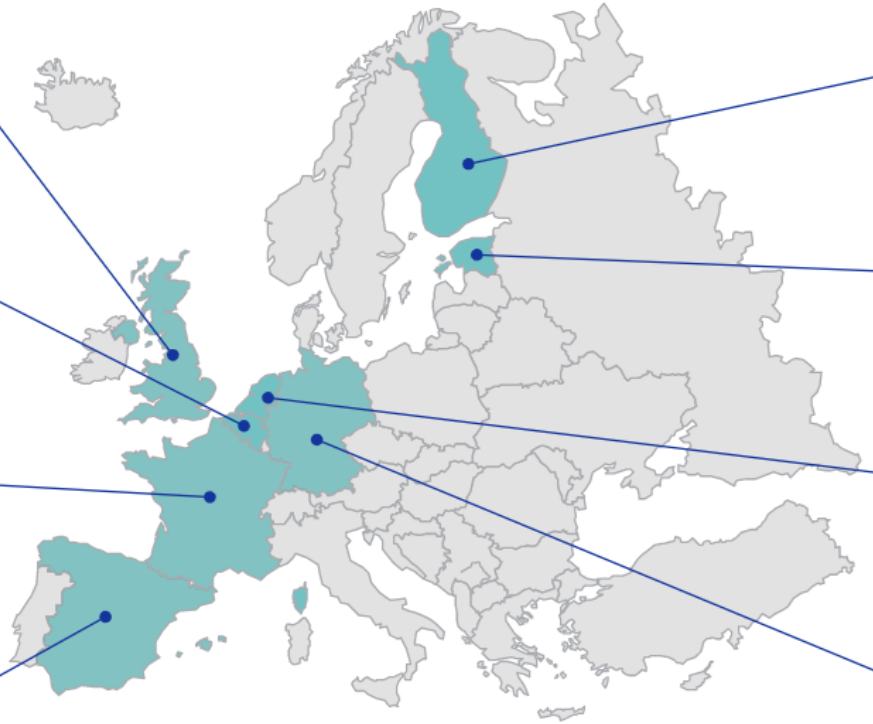
DARWIN EU® is a federated **network** of **data**, **expertise**, and **services** that supports better decision-making throughout the product lifecycle by generating reliable **evidence from real world healthcare data**



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

DARWIN EU Data Partners in 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

IDIAP Jordi Gol and SIDIAP

IDIAP Jordi Gol and SIDIAP

www.sidiap.org

- The Information System for Research in Primary Care (SIDIAP)
- Outpatient linked to inpatient care
- >8 million people (5.8 million active)
- Data available from 2006 and updated on a 6-monthly basis
- Mean follow-up time 15.5 years

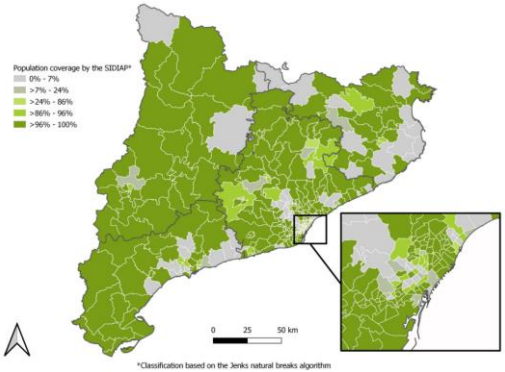
IDIAP Jordi Gol and SIDIAP

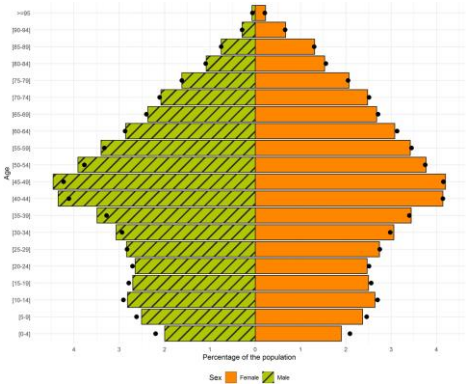
IDIAP JORDI GOL

SIDIAP

www.sidiap.org

- The Information System for Research in Primary Care (SIDIAP)
- Outpatient linked to inpatient care
- >8 million people (5.8 million active)
- Data available from 2006 and updated on a 6-monthly basis
- Mean follow-up time 15.5 years
- Representative of the general population living in Catalonia

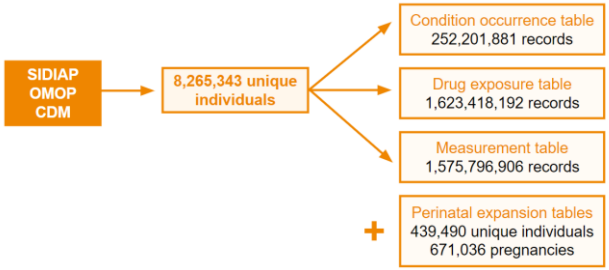




Recalde M et al. Data Resource Profile: The Information System for Research in Primary Care (SIDIAP). Int J Epidemiol, December 2022, Pages e324–e336, https://doi.org/10.1093/ije/dyac068

SIDIAP OMOP-CDM

- EMIF (2015) → EHDEN (2019 and 2020)



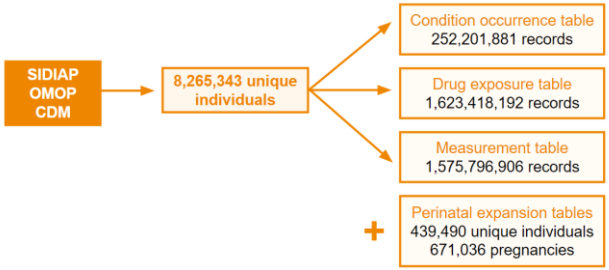
SIDIAP OMOP-CDM

OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

- EMIF (2015) → EHDEN (2019 and 2020)

EMIF

EHDEN
EUROPEAN HEALTH DATA & EVIDENCE NETWORK



- Evidence generating in local and network studies

nature communications

Article

https://doi.org/10.1038/s41467-022-34669-9

Thrombosis and thrombocytopenia after vaccination against and infection with SARS-CoV-2 in Catalonia, Spain

Edward Burn[1,2,5], Elena Roel[1,3,5], Andrea Pistillo[1], Sergio Fernández-Bertolin[1], Maria Aragón[1], Berta Raventós[1,3], Carlen Reyes[1], Katia Verhamme[4], Peter Rijnbeek[4], Xintong Li[2], Victoria Y. Strauss[2], Daniel Prieto-Alhambra[2,4,6] & Talita Duarte-Salles[1,6]

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-020-18849-z OPEN

Deep phenotyping of 34,128 adult patients hospitalised with COVID-19 in an international network study

Edward Burn et al.#

Open access Original research

BMJ Open

Impact of the COVID-19 pandemic on diagnoses of common mental health disorders in adults in Catalonia, Spain: a population-based cohort study

Berta Raventós,[1,2] Andrea Pistillo,[1] Carlen Reyes,[1] Sergio Fernández-Bertolin,[1] Maria Aragón,[1] Anna Berenguera,[1,2] Constanza Jacques-Aviñó,[1,2] Laura Medina-Perucha,[1,2] Edward Burn,[1,2] Talita Duarte-Salles[1]

RESEARCH

Association between covid-19 vaccination, SARS-CoV-2 infection, and risk of immune mediated neurological events: population based cohort and self-controlled case series analysis

Xintong Li,[1] Berta Raventós,[2,3] Elena Roel,[2,3] Andrea Pistillo,[2] Eugenia Martinez-Hernandez,[4] Antonella Delmestri,[1] Carlen Reyes,[2] Victoria Strauss,[1] Daniel Prieto-Alhambra,[1,5] Edward Burn,[1,2] Talita Duarte-Salles[2]

BMJ: first published as 1

IDIAP JORDI GOL

DARWIN EU studies - SIDIAP

SIDIAP has been invited to participate in **the first four studies** of the DARWIN EU® network:

- **Prevalence** of **rare blood cancers** in Europe
- **Drug utilisation** of **valproate**-containing medicinal products in **women** of childbearing potential
- **Drug utilisation** study of **antibiotics** in the **‘Watch’** category of the WHO AWaRe classification of antibiotics for evaluation and monitoring of antibiotic use
- Background rates of **serious adverse events** to contextualise safety assessments in clinical trials and non-interventional studies i**n adolescent and adult patients with severe asthma**

SIDIAP has also participated in many **feasibility assessments**

IDIAP JORDI GOL

Challenges as DPs

Technical issues

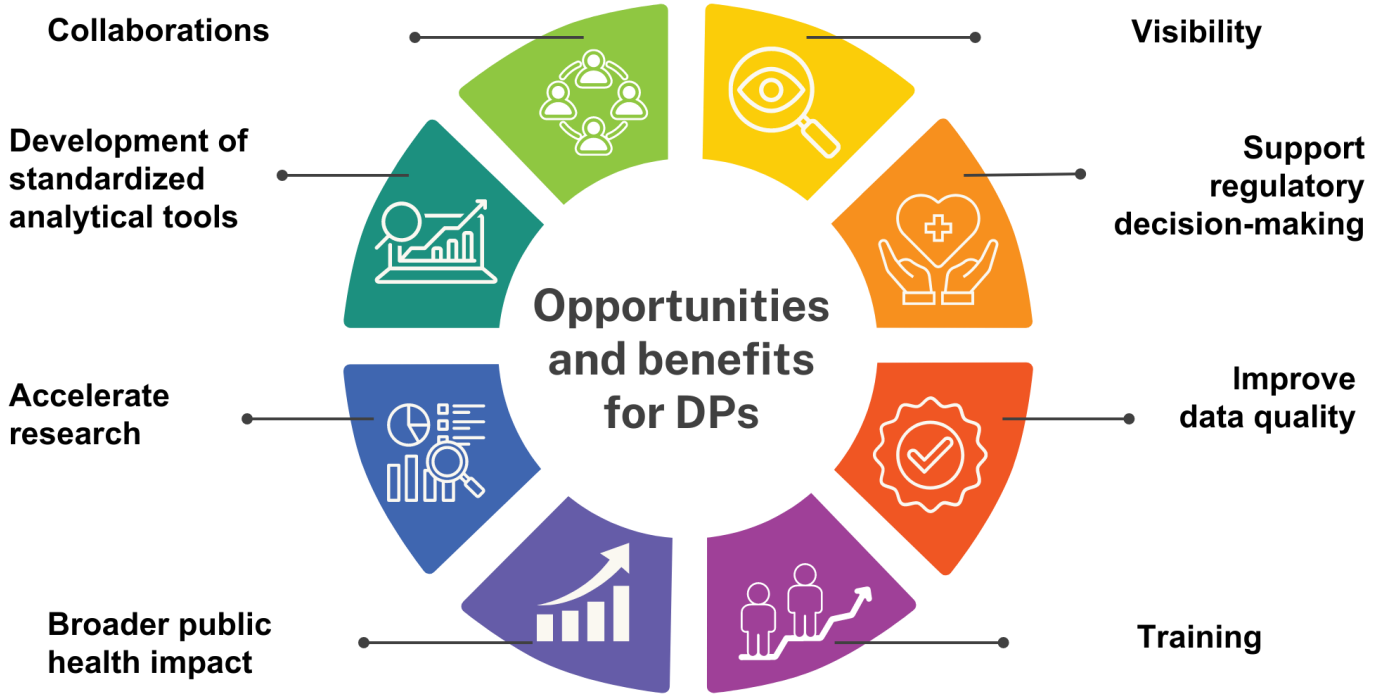
Time

- For approvals
- Study exectution
- Review results

Funding

IDIAP
JORDI GOL

Opportunities and Benefits for DPs



IDIAP
JORDI GOL

Final remarks

- ✓ Challenges that lead to opportunities
- ✓ Endless opportunities
  - To improve internal processes
  - To participate in the development of standardized methodologies and analytics that will shape the future of regulatory research
  - To contribute to the generation of real-world evidence to support regulatory decision-making
- ✓ Potential for improving healthcare outcomes through data-driven research

IDIAP
JORDI GOL

Acknowledgements

- Healthcare professionals and patients

- Real World Epidemiology (RWEpi) research group

Alicia Abellán
Postdoctoral researcher

Carlen Reyes
Postdoctoral researcher

Andrea Pistillo
Statistician and PhD researcher

Berta Raventós
PhD researcher

Laura Pérez
Postdoctoral researcher

Núria Mercadé
Data scientist

- SIDIAP Team

María Aragón
Data scientist

Sergio Fernández
Data scientist

Clara Rodríguez
Statistician

IDIAP JORDI GOL

Acknowledgements

Thank you!

Talita Duarte-Salles
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IDIAPJGol, Barcelona-Spain
TDuarte_Salles
tduarte@idiapjgol.org

DARWIN EU

Coordination Centre

Drug utilisation of valproate-containing medicinal products in women of childbearing age: a network study part of DARWIN EU®

Albert Prats-Uribe, Martí Català, Katia M Verhamme, Maria de Ridder, Carlen Reyes, Talita Duarte-Salles, Peter Rijnbeek, Edward Burn, Daniel Prieto-Alhambra, Annika M. Jödicke

OHDSI EU 2023

Disclosure

This presentation represents the views of the DARWIN EU® Coordination Centre only and cannot be interpreted as reflecting those of the European Medicines Agency or the European Medicines Regulatory Network.

Report – ENCEPP 84554

https://www.encepp.eu/encepp/viewResource.htm?id=84554

Shiny App

https://data-dev.darwin-eu.org/EUPAS50789/

Background

Valproic acid/valproate-containing medicine (VPA)

Indicated for **Epilepsy, Bipolar disorder, Migraine** prevention.

Teratogen – risk of neurodevelopmental impairment and **congenital malformations**

Use in **women of childbearing age** is restricted :

EMA has issued risk minimisation measures in 2014 and 2018

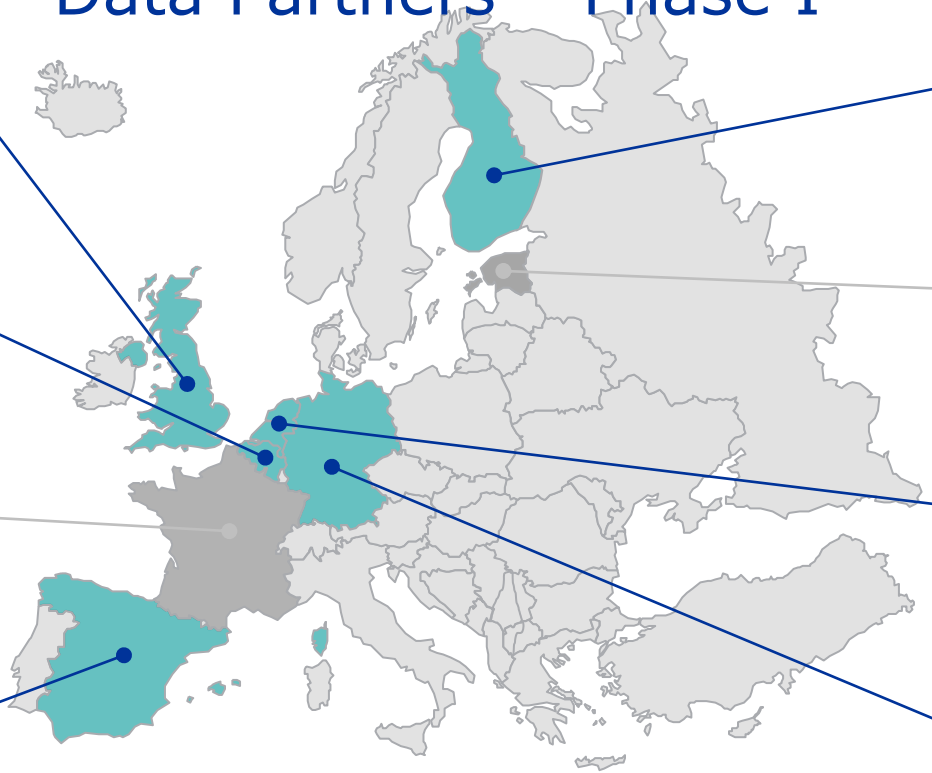
Objectives

The objectives of this study are

1.To characterise the **prevalence and incidence** of use of VPA and alternative antiepileptic therapies among **women** aged **12 to 55 years** of age. Analyses will be stratified by calendar year and age.

2.To characterise the **use of VPA** among women aged 12 to 55 years of age. Analyses will be stratified by indication (i.e. epilepsy, bipolar disorder and migraine prevention), calendar year and age.

Data Partners – Phase I



UK

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Netherlands

Integrated Primary Care Information

Netherlands Comprehensive Cancer Organisation

Germany

IQVIA Germany Disease Analyser

Variables

Exposure/s

Drug of interest: VPA Valproic acid, Sodium valproate, Magnesium valproate, Valproate semisodium and Valpromide

Alternative treatments

Covariates for stratification in population-level drug utilisation study:
Age: 5-year age bands will be used: 12-14, 15-19, 20-24, … , 50-54, 55.

Covariates for patient-level drug utilisation study:
Indication: Epilepsy , Bipolar disorder , Migraine

Co-morbidities and co-medication for **large-scale patient characterisation**

STUDY TYPE	STUDY CLASSIFICATION	TYPE OF ANALYSIS
Population Level DUS	Off-the-shelf (C1)	- Population-based incidence rates - Population-based prevalence
Patient Level DUS	Off-the-shelf (C1)	- Characterisation of patient-level features for new VPA users - Frequency and % of indication/s - Estimation of minimum, p25, median, p75, and maximum initially prescribed or dispensed dose/strength of VPA - Estimation of minimum, p25, median, p75, and maximum treatment duration VPA

For all analyses a minimum cell count of 5 will be used when reporting results, with any smaller counts obscured.

Timelines

Feasibility – 15th July

Approval Feasibility – 26th July

Protocol Submission – 1st September

Protocol Approval - 24th October

KO meeting - 17th November

Study package execution – November - January

Final Results – 6th January

Final Report – 17th January

From request to report:
6 months

Protocol writing:
1 Month

Protocol Approval to report:
2-2.5 Months

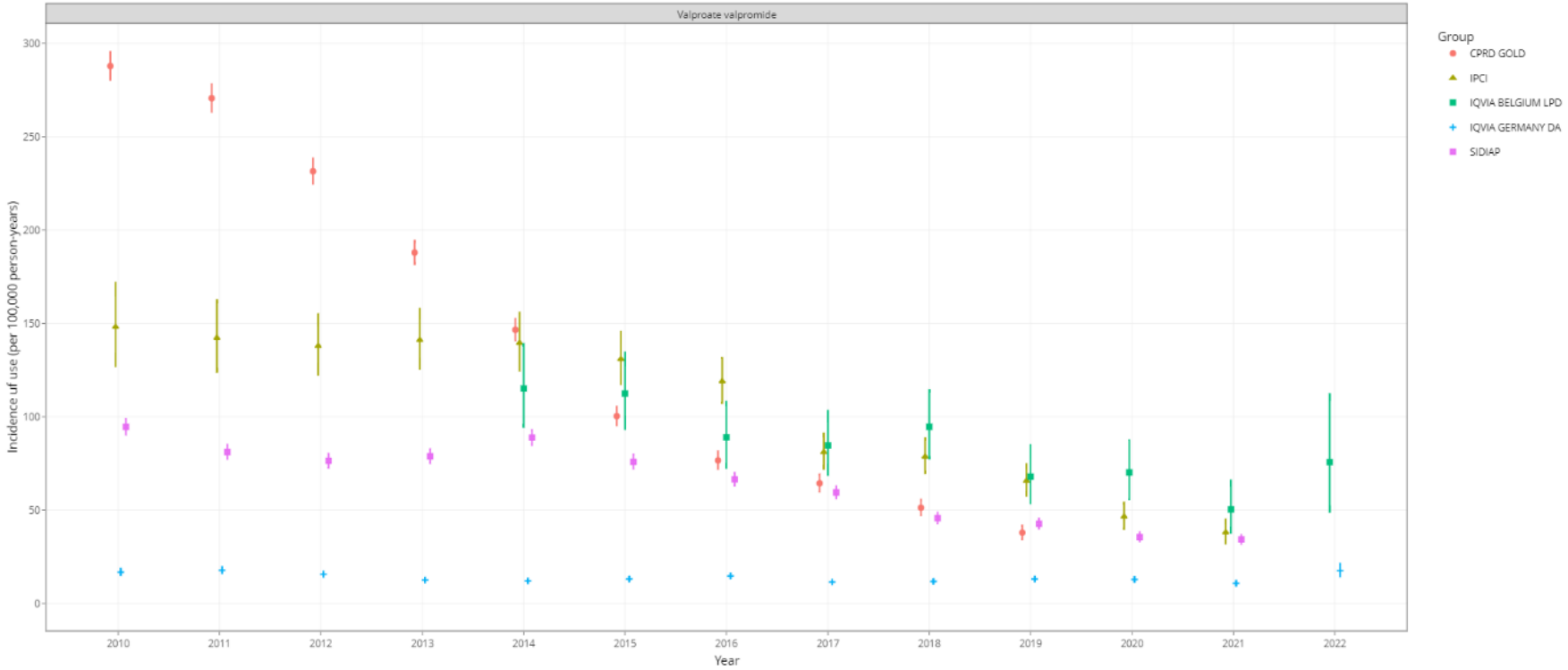
Results Population Level

The **incidence** of new use and **prevalence** of VPA amongst women 12 to 55 years **decreased** over the period 2010-2021

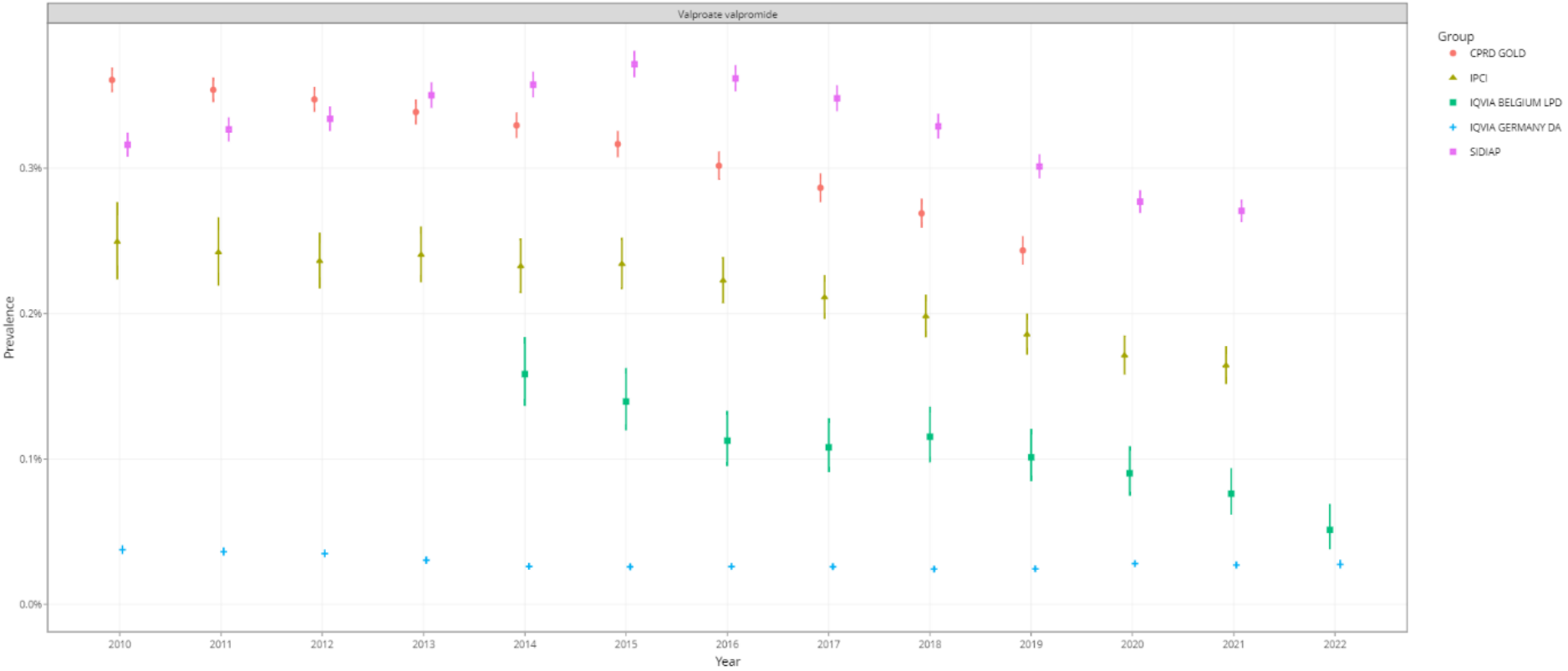
The **older age groups** (>= 45) had **higher prevalence** remained **stable** or increased during the study period. Younger age groups (<45) had a lower prevalence, which decreased over time.

Incidence of use of VPA showed a decreasing pattern for all age groups in all databases.

Incidence rates of VPA use in women 12 to 55



Prevalence of VPA use in women 12 to 55



Results Patient Level

Database	CPRD GOLD	IPCI	SIDIAP	IQVIA Belgium LPD	IQVIA Germany DA
Number subjects	6416	1241	10398	945	4002
Sex, N (%)					
Female	6416 (100%)	1241 (100%)	10398 (100%)	945 (100%)	4002 (100%)
Age					
median [p25 - p75]	40 [29 - 47]	43 [32 - 49]	40 [30 - 48]	41 [31 - 49]	43 [31 - 50]

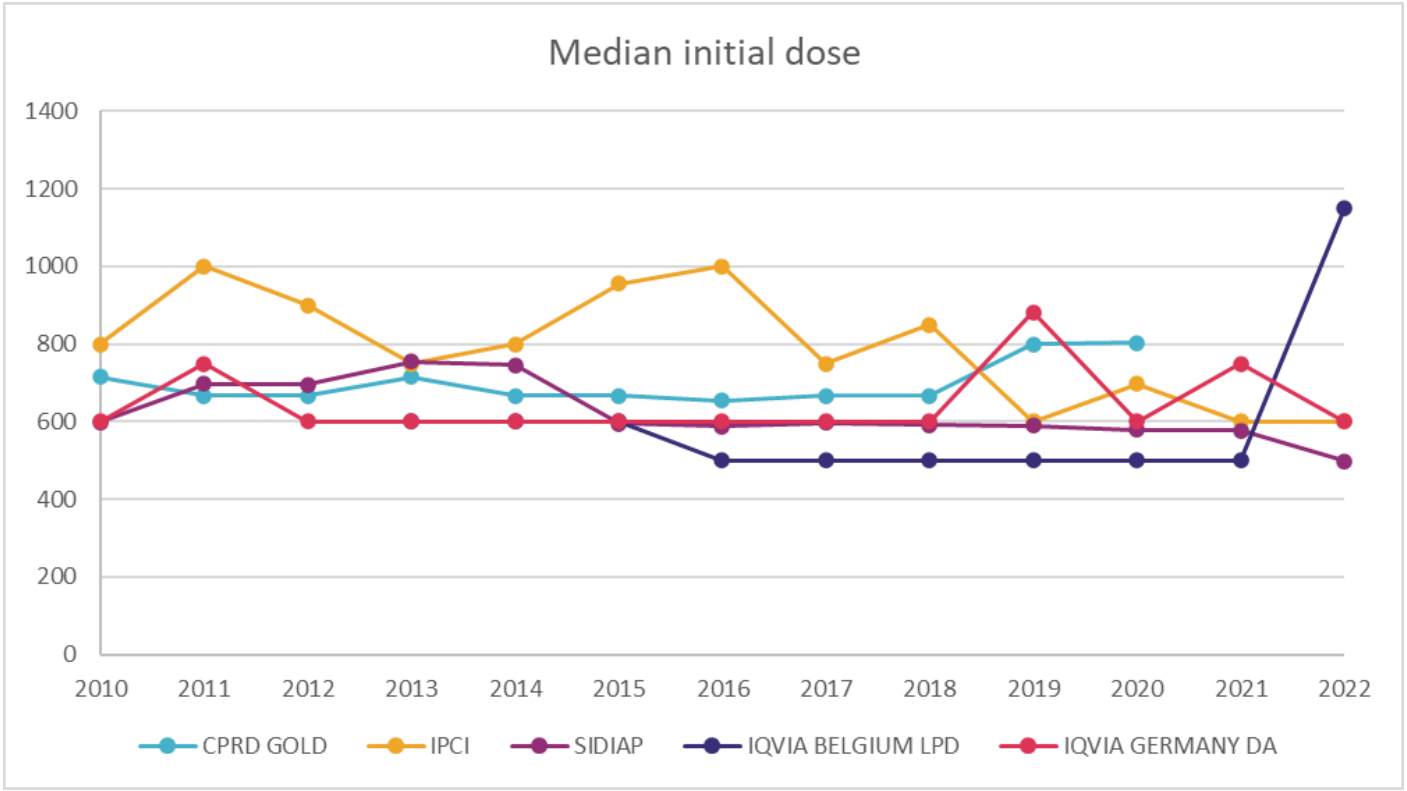
Results Patient Level

Database	CPRD GOLD	IPCI	SIDIAP	IQVIA Belgium LPD	IQVIA Germany DA
Anxiety	2260 (35.2%)	392 (31.6%)	4099 (39.4%)	307 (32.5%)	806 (20.1%)
Asthma	1017 (15.9%)	102 (8.2%)	545 (5.2%)	143 (15.1%)	234 (5.8%)
Chronic Kidney Disease	146 (2.3%)	<5	128 (1.2%)	<5	63 (1.6%)
Chronic Liver Disease	20 (0.3%)	<5	103 (1%)	NA	16 (0.4%)
COPD	82 (1.3%)	21 (1.7%)	96 (0.9%)	113 (12%)	135 (3.4%)
Dementia	23 (0.4%)	<5	37 (0.4%)	<5	64 (1.6%)
Depressive disorder	2460 (38.3%)	194 (15.6%)	2610 (25.1%)	414 (43.8%)	1420 (35.5%)
Diabetes	252 (3.9%)	57 (4.6%)	366 (3.5%)	59 (6.2%)	208 (5.2%)
GERD	174 (2.7%)	19 (1.5%)	262 (2.5%)	172 (18.2%)	84 (2.1%)
Heart failure	13 (0.2%)	6 (0.5%)	18 (0.2%)	<5	43 (1.1%)
HIV	6 (0.1%)	NA	53 (0.5%)	<5	5 (0.1%)
Hypertension	333 (5.2%)	96 (7.7%)	601 (5.8%)	166 (17.6%)	431 (10.8%)
Hypothyroidism	366 (5.7%)	56 (4.5%)	896 (8.6%)	104 (11%)	313 (7.8%)
Infertility	63 (1%)	NA	144 (1.4%)	<5	<5
Inflammatory Bowel Disease	40 (0.6%)	6 (0.5%)	36 (0.3%)	7 (0.7%)	30 (0.7%)
Malignant neoplastic disease	199 (3.1%)	59 (4.8%)	332 (3.2%)	27 (2.9%)	137 (3.4%)
Myocardial Infarction	10 (0.2%)	<5	16 (0.2%)	<5	13 (0.3%)
Osteoporosis	44 (0.7%)	7 (0.6%)	84 (0.8%)	22 (2.3%)	32 (0.8%)
Pneumonia	89 (1.4%)	51 (4.1%)	369 (3.5%)	29 (3.1%)	115 (2.9%)
Rheumatoid Arthritis	25 (0.4%)	9 (0.7%)	24 (0.2%)	5 (0.5%)	32 (0.8%)
Stroke	81 (1.3%)	37 (3%)	142 (1.4%)	14 (1.5%)	81 (2%)
Venous Thromboembolism	88 (1.4%)	25 (2%)	59 (0.6%)	28 (3%)	65 (1.6%)

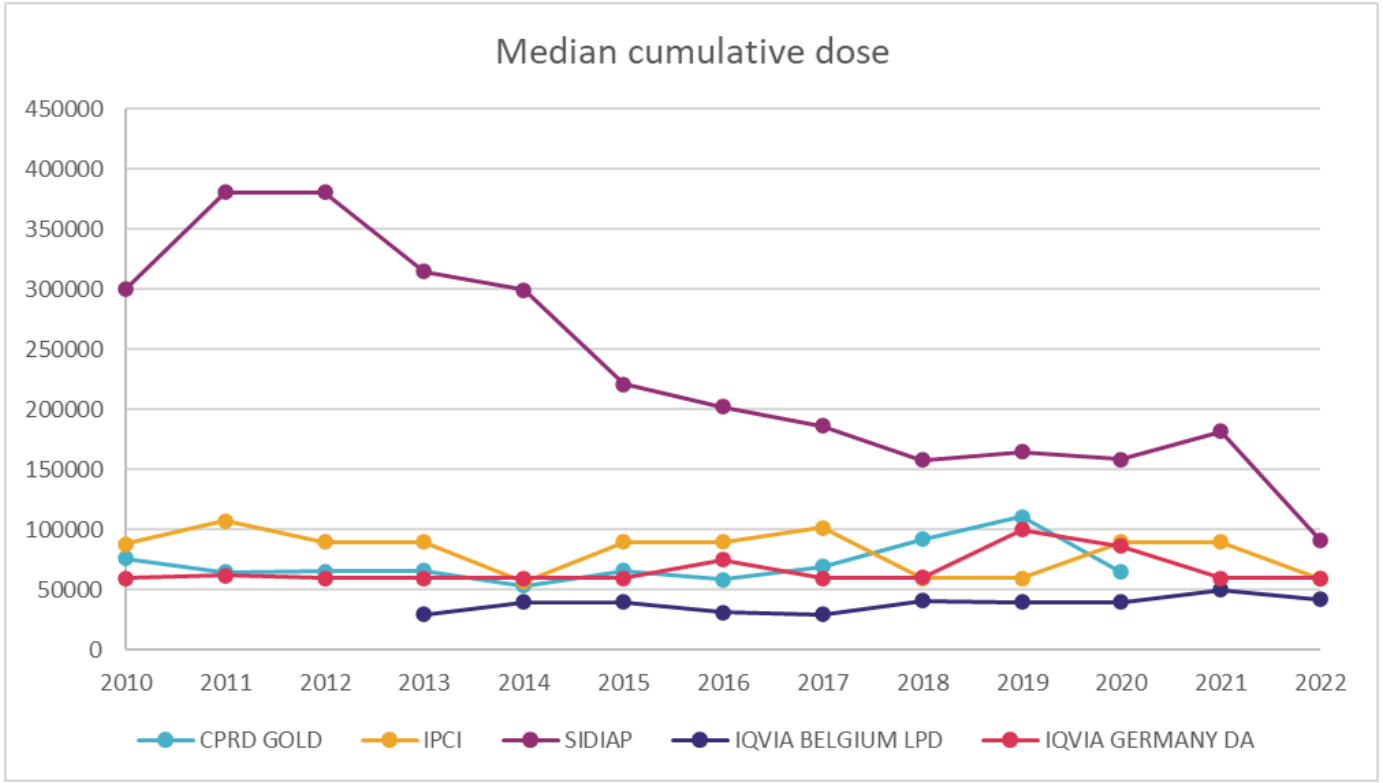
Results Patient Level

Database	CPRD GOLD	IPCI	SIDIAP	IQVIA Belgium LPD	IQVIA Germany DA
Agents acting on Renin Angiotensin System	366 (5.7%)	132 (10.6%)	618 (5.9%)	59 (6.2%)	228 (5.7%)
Antibacterials (systemic)	3043 (47.4%)	395 (31.8%)	3668 (35.3%)	308 (32.6%)	441 (11%)
Antidepressants	3774 (58.8%)	381 (30.7%)	6243 (60%)	365 (38.6%)	1102 (27.5%)
Antiinflammatory and Antirheumatic Agents	2233 (34.8%)	460 (37.1%)	5357 (51.5%)	368 (38.9%)	627 (15.7%)
Antineoplastic agents	<5	18 (1.5%)	100 (1%)	11 (1.2%)	18 (0.4%)
Antithrombotics	448 (7%)	78 (6.3%)	263 (2.5%)	27 (2.9%)	101 (2.5%)
Beta Blocking Agents	1079 (16.8%)	242 (19.5%)	695 (6.7%)	167 (17.7%)	270 (6.7%)
Calcium Channel Blockers	220 (3.4%)	50 (4%)	219 (2.1%)	30 (3.2%)	86 (2.1%)
Diuretics	314 (4.9%)	56 (4.5%)	348 (3.3%)	30 (3.2%)	172 (4.3%)
Drugs for Acid related disorder	1861 (29%)	382 (30.8%)	3519 (33.8%)	258 (27.3%)	507 (12.7%)
Drugs for obstructive airway diseases	1242 (19.4%)	315 (25.4%)	1858 (17.9%)	207 (21.9%)	197 (4.9%)
Drugs used in diabetes	262 (4.1%)	45 (3.6%)	283 (2.7%)	47 (5%)	102 (2.5%)
Hormonal contraceptives (systemic)	1291 (20.1%)	136 (11%)	415 (4%)	150 (15.9%)	59 (1.5%)
Immunosuppressants	48 (0.7%)	12 (1%)	76 (0.7%)	<5	18 (0.4%)
Lipid modifying agents	414 (6.5%)	82 (6.6%)	736 (7.1%)	63 (6.7%)	97 (2.4%)
Opioids	2140				

Median initial dose (mg/day) by year and database



Median cumulative annual dose (mg) by year and database



Conclusion

The **incidence and prevalence of use of VPA among women of childbearing age have declined** in BE, DE, ES, NL, and the UK. Specially in younger women.

Although **initial dose did not change over time**, cumulative annual use decreased in ES (but not in any of the other countries).

Quick analytics -> ~ 2m from protocol approval to report with winter holidays

Report

https://www.encepp.eu/encepp/viewResource.htm?id=84554

Shiny App

https://data-dev.darwin-eu.org/EUPAS50789/

DARWIN EU

Coordination Centre

Drug utilisation of antibiotics in the 'Watch' category of the WHO AWaRe classification of antibiotics for evaluation and monitoring of use: a network study part of DARWIN EU®

Johnmary T. Arinze, Maria de Ridder, Talita Duarte-Salles, Marti Catala-Sabate, Antonella Delmestri, Hezekiah Omulo, James Brash, Hanne van Ballegooijen, Juan Manuel Ramírez-Anguita, Angela Leis, Miguel-Angel Mayer, Romain Griffier, Peter Rijnbeek, Dani Prieto Alhambra, Katia MC Verhamme

OHDSI EU 2023

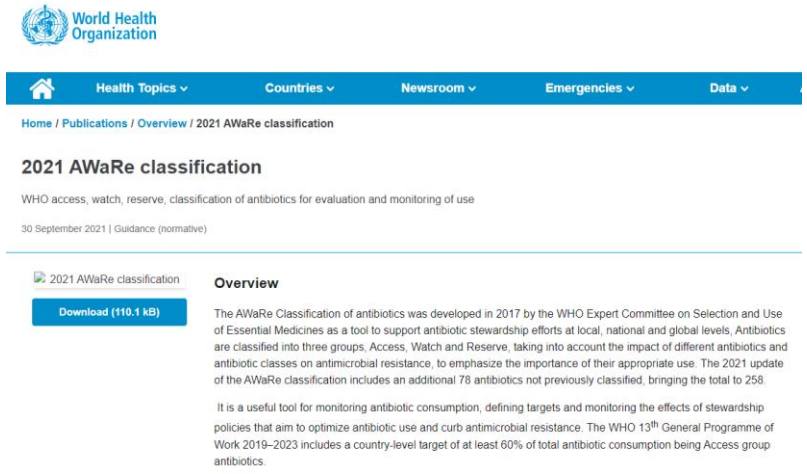
Disclosure

This presentation represents the views of the DARWIN EU® Coordination Centre only and cannot be interpreted as reflecting those of the European Medicines Agency or the European Medicines Regulatory Network.

Background

The WHO 2021 AWaRe classification (who.int) of antibiotics for evaluation and monitoring of use classifies 258 antibiotics into 3 categories (**Access/Watch/Reserve**) according to their impact on antimicrobial resistance.

The Watch list includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine and/or antibiotics that are at relatively high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of stewardship programs and monitoring.



Objectives

1. To investigate **the incidence rate and prevalence of use** of antibiotics (from the WHO Watch list) stratified by calendar year, age, sex and country/database during the study period 2012-2021.

2. To explore **duration of antibiotic use** as well as **indication for antibiotic prescribing/dispensing**.

Methods (1)

- Retrospective cohort study
- Data sources: All mapped to **OMOP CDM**

Country	Name of Database	Health Care setting (e.g. primary care, specialist care, hospital care)	Type of Data (EHR, claims, registries)	Number of subjects in database	End of calendar period covered
NL	IPCI	Primary care	EHR	2.7 million	30/6/2022
FR	CHUBX	Secondary care (in and outpatients)	EHR	2.2 million	18/12/2022
ES	SIDIAP	Primary care	EHR	8.3 million	30/6/2022
ES	IMASIS	Secondary care (in and outpatients)	EHR	1.0 million	9/7/2022
DE	IQVIA Germany	Primary care and outpatient specialist care	EHR	8.5 million	30/6/2022
UK	CPRD GOLD	Primary care	EHR	15.7 million	30/6/2020

- Study period: 2012 - 2021

Methods (2)

- ***Population-level utilisation of antibiotics:***
  - **Annual incidence** - the number of new users after 30 days of no use per 100,000 person-years of the population at risk of getting exposed during the period for each calendar year
  - **Prevalence** - total number of individuals who use the drug of interest during a given year divided by the population at risk of getting exposed during that year

- ***Patient-level utilisation of antibiotics:***
  - **Duration of use** - two drug eras were merged into one continuous drug era if the distance in days between end of the first era and start of the second era was ≤ 7 days.

Results (1)

The Watch list from the WHO consists of 141 antibiotics (137 individual antibiotics with some additional entries for oral or parenteral use).

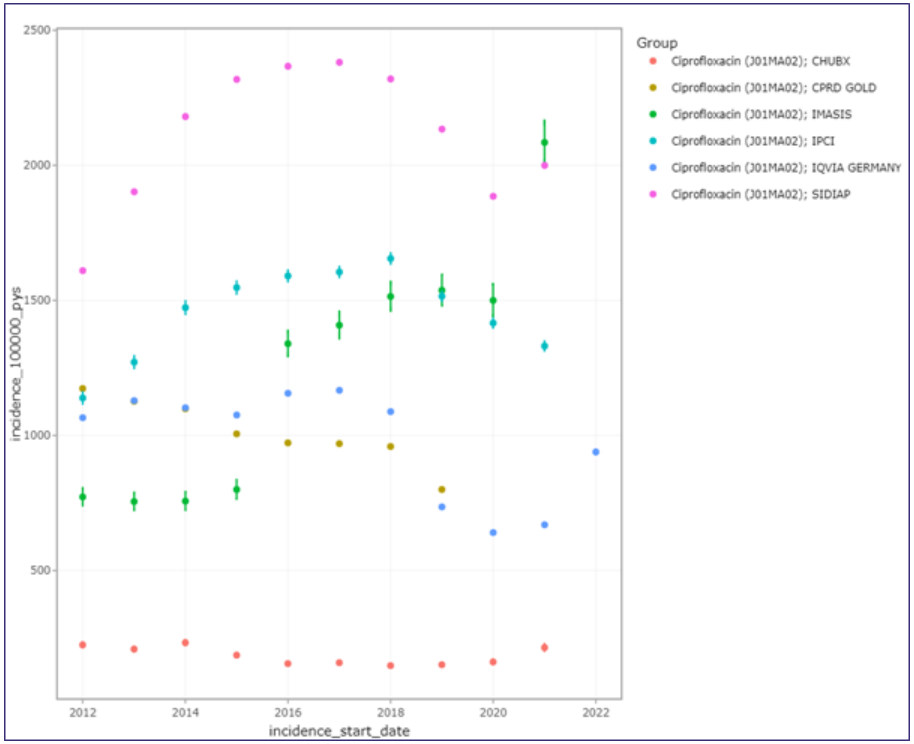
Of these antibiotics, only 78 appeared as used/prescribed in at least one of the data sources during the study period

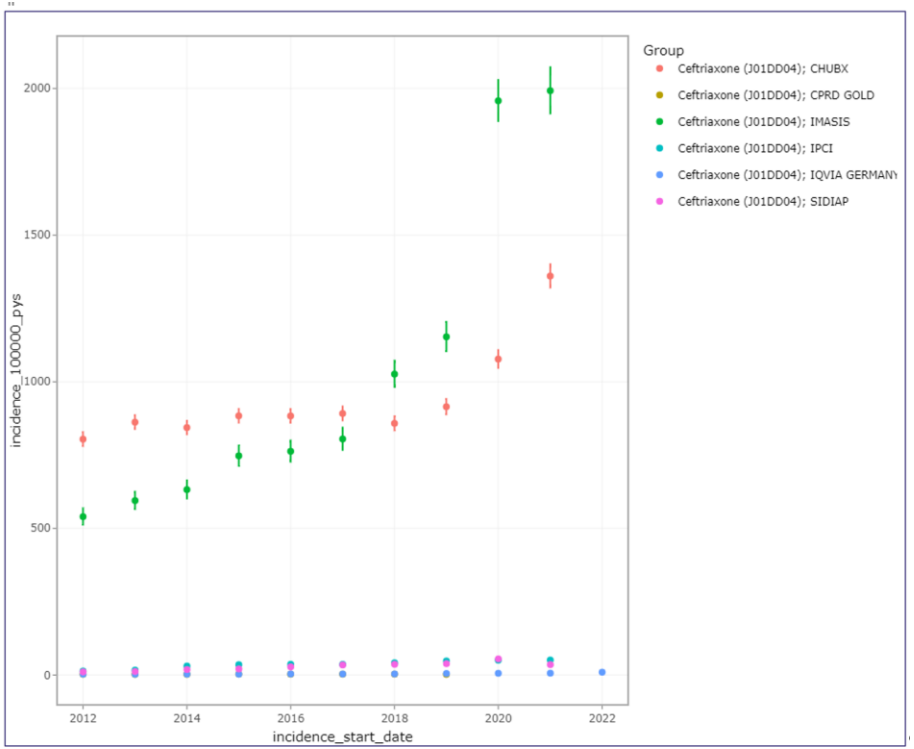
Results (2) – Incidence of antibiotic use

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

Number of new users/100,000 PY

Results (3) – Incidence of ciprofloxacin & ceftriaxone use





Results (4) – Duration of antibiotic use

CPRD GOLD	IPCI	SIDIAP	IMASIS	CHUBX	IQVIA Germany
Antibiotic	Duration (median, p25-p75)	Duration (median, p25-p75)	Duration (median, p25-p75)	Duration (median, p25-p75)	Duration (median, p25-p75)
Azithromycin	3 (1 - 3)	4 (4 - 4)	3 (3 - 3)	3 (3 - 3	1 (1 - 1)
Cefaclor	7 (5 - 7)	9 (8 - 9)	7 (6 - 7)	5 (1 – 7)	1 (1 - 1)
Ceftriaxone	7 (4 - 7)	5 (2 - 5)	30 (1 - 30)	7 (2 - 10	2 (1 - 2)
Cefuroxime	7 (7 - 7)	8 (6 - 8)	7 (7 - 7)	6 (6 - 7)	1 (1 - 1)
Ciprofloxacin	5 (5 - 5)	8 (8 - 8)	7 (7 - 7)	5 (5 - 10)	2 (1 - 2)
Clarithromycin	7 (7 - 7)	8 (8 - 8)	7 (7 - 7)	7 (5 - 7)	1 (1 - 1)
Erythromycin	7 (5 - 7)	9 (8 - 9)	7 (7 - 7)	30 (8 - 30)	1 (1 - 1)
Fosfomycin	1 (1 - 1)	3 (3 - 3)	1 (1 - 1)	1 (1 - 1)	1 (1 - 1)
Levofloxacin	10 (7 - 10)	8 (8 - 8)	14 (7 - 14)	7 (5 - 10)	1 (1 - 1)
Lymecycline	56 (28 - 56)	NA	NA	NA	NA
Ofloxacin	14 (14 - 14)	11 (8 - 11)	14 (7 - 14)	30 (5 - 30)	NA
Oxytetracycline	28 (7 - 28)	8 (4 - 8)	17 (12 - 17)	5 (5 - 7)	1 (1 - 1)
Pheneticillin	NA	NA	7 (7 - 7)	NA	NA
Piperacillin_tazobactam	28 (28 - 28)	NA	37 (18 - 37)	30 (30 - 30)	6 (3 - 6)
Vancomycin	10 (10 - 10)	11 (6 - 11)	10 (7 - 10)	7 (5 - 10)	4 (2 - 4)
Azithromycin	3 (1 - 3)	4 (4 - 4)	3 (3 - 3)	3 (3 - 3	1 (1 - 1)

Conclusions

- Incidence rate were mainly below 100/100.000 PY except for use of ciprofloxacin, clarithromycin, fosfomycin and azithromycin in most of the database.
- The incidence rates of use remained stable or decreased over time for all antibiotics …
- … except for ceftriaxone, cefuroxime, piperacilline-tazobactam and vancomycin, that increased in use over time, mainly due to secondary care use
- For the majority of investigated antibiotics, the incidence increased with age and was comparable by sex.
- The median duration of use was usually around one week but shorter in secondary care

Data Analysis and Real World Interrogation Network (DARWIN EU®)

Questions and Answers Session

Closing Remarks

Peter R. Rijnbeek
Professor of Medical Informatics
Department of Medical Informatics
Erasmus MC, The Netherlands

A great journey ahead!

- Further growth of the Data Network
- Multiple new European projects
- National Nodes Expansion
- Many research studies on more data sources
- Many publications on methods
- Further expansion of training curriculum driven by the European Health Data and Evidence Network (EHDEN)
- DARWIN EU® going into its Operational Phase with a strong increase in number of studies to support regulatory decision making.

Join the Community

Join Our Workgroup Efforts!

Join A Workgroup | **Weekly Workgroup Meeting Schedule**

Get To Know The OHDSI Workgroups

Workgroups present updates on the weekly OHDSI community calls at least one time per year. The most recent update is posted below, as well as their announced objectives and key results for 2023, and the latest number of workgroup members and leads. Please get to know the exciting research happening around the community and join any workgroups that interest you.

Asia-Pacific (APAC)
Current Participants: 297
Lead: Mui Van Zandt
2023 OKRs

ATLAS/WebAPI
Current Participants: 253
Lead: Anthony Sena
2023 OKRs

Clinical Trials
Current Participants: 295
Leads: Mike Hamidi, Lin Zhen
2023 OKRs

Common Data Model
Current Participants: 686
Lead: Clair Blacketer
2023 OKRs

CDM Vocabulary Subgroup
Current Participants: 686
Lead: Michael Kallfelz
2023 OKRs

Data Network Quality
Current Participants: 298
Lead: Clair Blacketer
2023 OKRs

Dentistry
Current Participants: 8
Lead: Robert Koski
2023 OKRs

Early-Stage Researchers
Current Participants: 243
Leads: Faaizah Arshad, Ross Williams
2023 OKRs

There are 32 Workgroups!

July Community Calls

Date	Topic
July 4	No Meeting
July 11	European Symposium Review
July 18	Vulcan: An HL7 FHIR Accelerator Transforming Clinical & Translational Research
July 25	Around The Asia-Pacific Region

EHDEN Academy
EUROPEAN HEALTH DATA & EVIDENCE NETWORK

OHDSI Global Symposium
October 20-22 East Brunswick, New Jersey
Hilton Hotel & Conference Center

Group Photo

But first something else…

How to close this symposium..

2018

2019

Join the OHDSI Band!










Whe ou're dow nd troubled
And you need so ve and care

Getting to the OHDSI Symposium this year was quite a ride for Patrick and Peter

Thank You Erasmus MC Team!

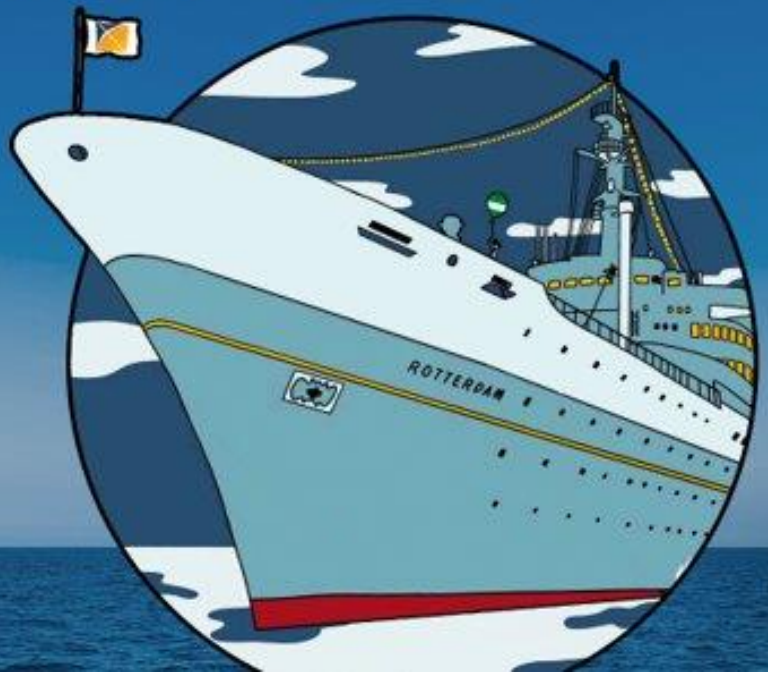
EUROPEAN OHDSI SYMPOSIUM

EUROPE

July 3rd 2023 Rotterdam

Tutorials: July 1st and 2nd

"Full Steam Ahead!!"



Organised by:

Erasmus MC
University Medical Center Rotterdam

Health Data Science