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ISPOR Special Interest Group

Data Analysis and Real-World Interrogation Network – European Union (DARWIN EU) – Where Are We Now and What Is in Store for the Future?

Monday, 18 November 2024 | 15:15 – 16:15

Topics--

	Topic	Presenter(s)
1	Panelists' Introductions & Federated Data Networks	Dr. Phani Veeranki
2	RWE for Regulatory Decision Making -DARWIN EU	Dr. Patrice Verpillat
3	DARWIN-EU Co-Ordination Center	Dr. Dani Prieto-Alhambra
4	Opportunities for Multi-stakeholder Collaboration (Industry perspective)	Dr. Shuvayu Sen
5	Q&A	

1

Panelist Introductions

Today's Panelists

Moderator: Phani Veeranki, MD, DrPH

Panelist: Patrice Verpillat, MD, MPH, PhD

Panelist: Daniel Prieto-Alhambra, MD, PhD

Panelist: Shuvayu Sen, PhD

Phani Veeranki, MD, DrPH

Dr. Veeranki is a Senior Director & Principal Consultant at Optum Value & Evidence Solutions Teams.

He is a physician-scientist and has significant expertise and experience in clinical epidemiology, policy analysis and economic valuations to demonstrate the value of healthcare interventions. He has served as an advisor and investigator for numerous clinical trials, several cohort studies and cross-sectional surveys along with hospital-based quality improvement projects.

He is a thought leader in conducting interventional and observational research using real-world data and offers innovative clinical solutions, decentralized clinical trial solutions, research approaches and strategies to clients and internal partners. He has deep knowledge and expertise in methodological approaches to address clients' needs in multiple therapeutic areas including oncology, cardiovascular, respiratory, neurology, and rare/genetic diseases.

His work has been published in leading journals including *JAMA, CHEST, BMJ and AJPH.* Prior to joining Optum, he worked in various research capacities in both academia and industry. He holds a MD and DrPH in epidemiology and completed a fellowship in health outcomes research from Vanderbilt University Medical Center.

He serves as moderator on the panel.

Patrice Verpillat, MD, MPH, PhD

Dr. Verpillat is the Head of the Real-World Evidence (RWE) Workstream at the European Medicines Agency (EMA).

He is a medical doctor by training and also an epidemiologist. Before joining the EMA, he has worked ~20 years in the pharmaceutical industry where he had held positions in several international companies, always dealing with real world data (RWD) and non-interventional studies (NIS) in order to bring RWE into research, access and life-cycle product management.

He has published over 70 articles in Medline referenced journals. He has been involved in many organizations such as ENCePP, ICH M14 working group, European pharma association (efpia) and ISPE.

Dani Prieto Alhambra, MD, MSc, PhD

Professor Dani Prieto-Alhambra (MD, MSc (Oxon), PhD) is a clinician scientist with a long track record in pharmaco- and device epidemiology and real-world evidence research.

He led several initiatives and played a significant role in accelerating and improving the quality of real-world evidence internationally.

He leads the Health Data Sciences team at the Botnar Research Centre (University of Oxford) and recently took the role of deputy director for the EMA-funded DARWIN EU® initiative from the Medical Informatics department, Erasmus MC, Rotterdam.

He leads the Development pillar for the generation and/or validation of analytical tools to generate real world evidence for regulatory use.

Shuvayu Sen, PhD

Dr. Sen is Pharmaceutical executive with extensive leadership and experience in real world evidence, pricing, market access, reimbursement, big data, outcomes research, healthcare policy and management and digital technologies at major pharmaceutical companies.

His expertise lies in providing unique insights in improving business & scientific impact through the utilization of big data, real world evidence, innovative trials, health programs, and health economics and outcomes research. He made significant contributions to developing and delivering novel evidence to obtain positive access/formulary decisions in the US, EU, and Emerging Markets.

He has broad experience with both big and small molecules, and vaccines in various therapeutic areas including Osteoporosis, Respiratory, Endocrinology, Urology, Pain, infectious disease, Oncology, Neuroscience, Immunology, Women's Health and Virology.

He is currently a Vice President and Head of Oncology, V&I Outcomes Research at Merck.

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Disclosure

I have no conflicts of interest to declare

I am an employee of Optum LifeSciences. The views expressed in this presentation are personal views only and may not be understood or quoted as being made on behalf of, or reflecting the position of Optum or United Health Group

Federated Data Health Networks

- RWD/RWE are critical for healthcare decision-making (regulators, HTA bodies, payers & prescribers).
- RWD are healthcare data collected from observations of routine clinical practice and *not* in conventional RCTs.
- A single RWD or centralized approach has limitations- low sample size (molecules for Rare diseases), longer f/u, low statistical power to built robust prediction models
- COVID-19 pandemic has further demonstrated need for a distributed/decentralized federated data health networks (FDHN).
- **DARWIN-EU is a federated network enabling *informed regulatory decision making* in EU.**

2

RWE for Regulatory Decision-Making DARWIN-EU

Real-World-Evidence for Regulatory Decision-making
DARWIN EU®

Promises, Limitations and Challenges

European Regulatory perspectives

ISPOR Europe 2024

Presented by Patrice Verpillat on 18 November 2024
Data Analytics and Methods Taskforce, Real World Evidence Workstream

An agency of the European Union

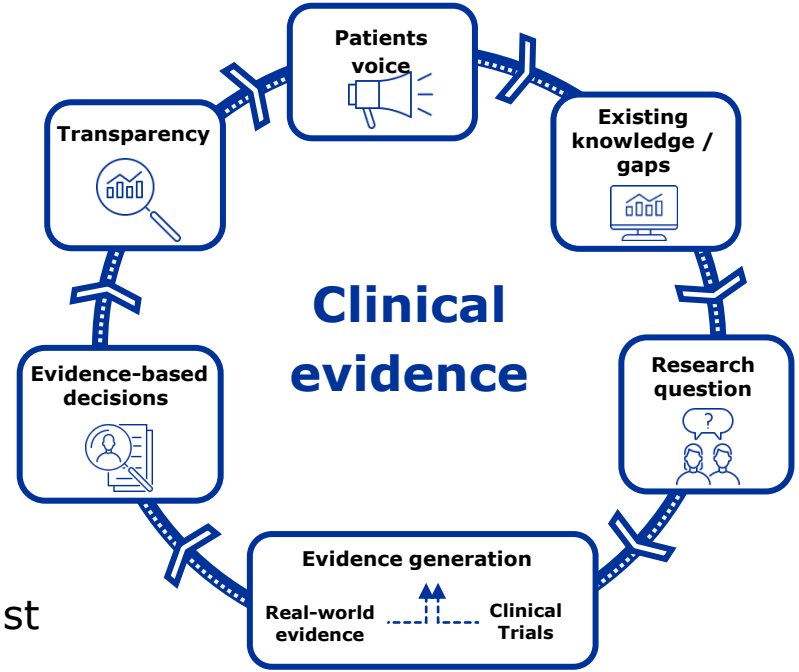
Disclaimer

The presenter does not have any conflict of interest.

The views expressed in this presentation are 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.

EU Regulatory Perspective on "Clinical Evidence"

- Patient voice guides every step of the way
- Evidence generation is planned and guided by **purpose**, data, knowledge and expertise
- Research question drives evidence choice and embraces spectrum of data and methods
- **Clinical trials remain core but are smarter, better and faster**
- **Real world evidence is enabled, and its value is established**
- High transparency level underpins societal trust



3 main pathways to use RWD for generating RWE @EMA

EMA studies using in-house databases

- **Primary and secondary care** health records from **France**, **Germany and UK**

Studies procured through EMA FWCs

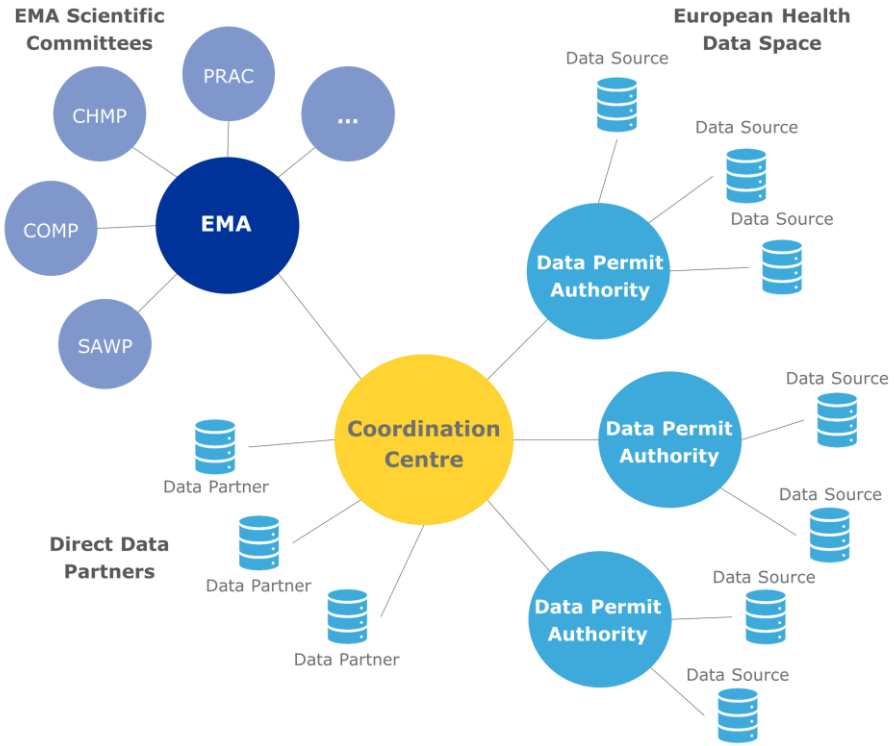
- Framework contract (FWC) since September 2021: services of **8 research organisations** and academic institutions
- Access to **wide network of data sources**: 59 data sources from 21 EU countries
- Ability to leverage external **scientific expertise**

DARWIN EU®

- Coordination Centre launched February 2022
- Onboarded **20 data partners** during the first 2 years
- **20+ studies** finalised
- Additional 10 data partners are foreseen to **be added each year** for 2024 and 2025

Data Analysis and Real-World Interrogation Network
DARWIN EU®

Federated **network** of **data**, **expertise** and **services** that supports better decision-making throughout the product lifecycle by generating **valid and reliable evidence from real-world healthcare data**

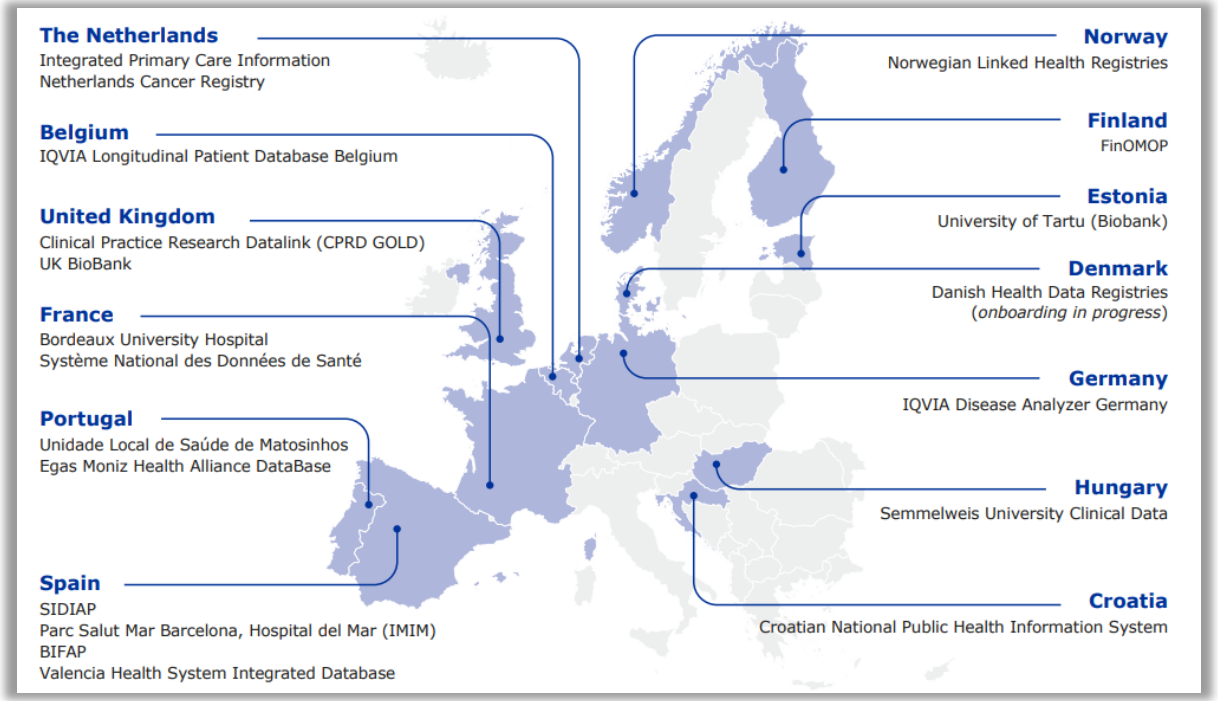


FEDERATED NETWORK PRINCIPLES

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

Data Partners

Access to data from ~130 million patients in 2024



How RWE can support regulatory decision-making?

1 Understand the clinical context

- Disease epidemiology
- Clinical management
- Drug utilisation

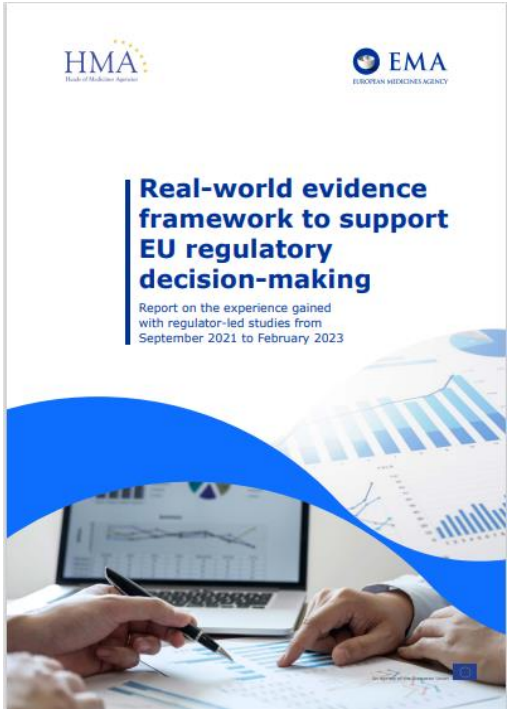
2 Support the planning and validity

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

3 Investigate associations and impact

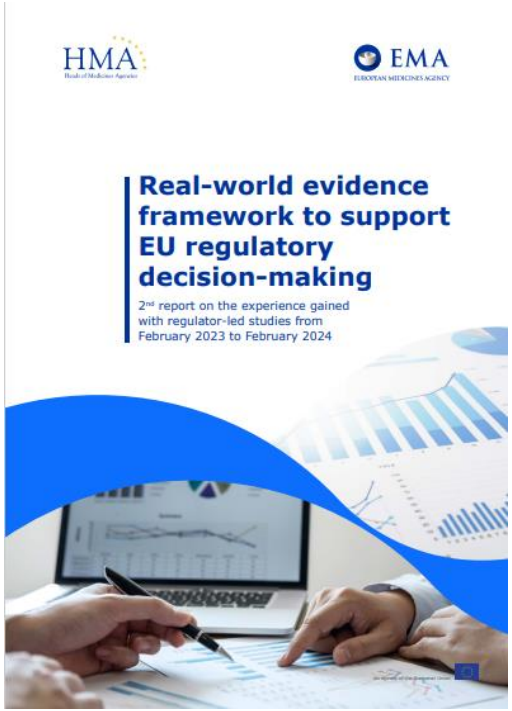
- (Comparative) Effectiveness and safety studies
- Impact of regulatory actions

Reports on RWE experience



Published in June 2023

Period covered: **Sep 2021 to Feb 2023**



Published in July 2024

Period covered: **Feb 2023 to Feb 2024**

Focus on 2nd report

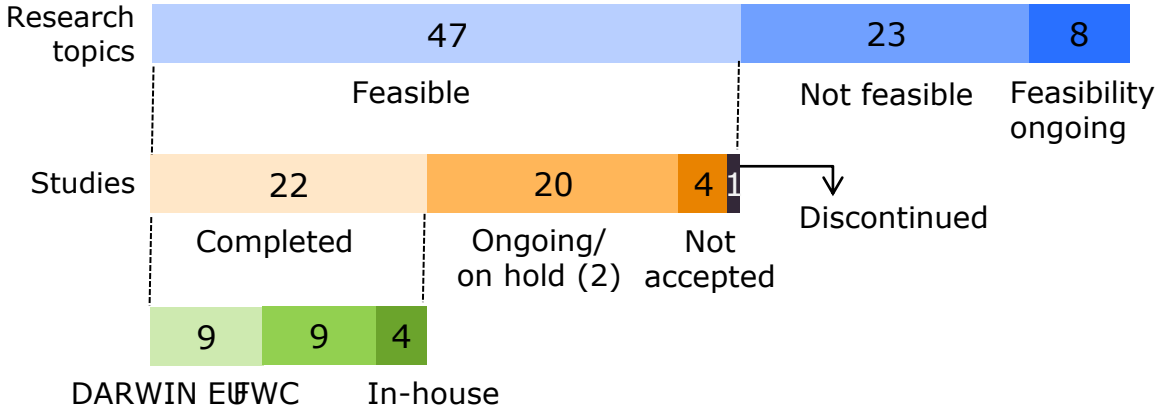
60
NEW research topics
(Feb '23 – Feb '24)

+18
Prior research topics

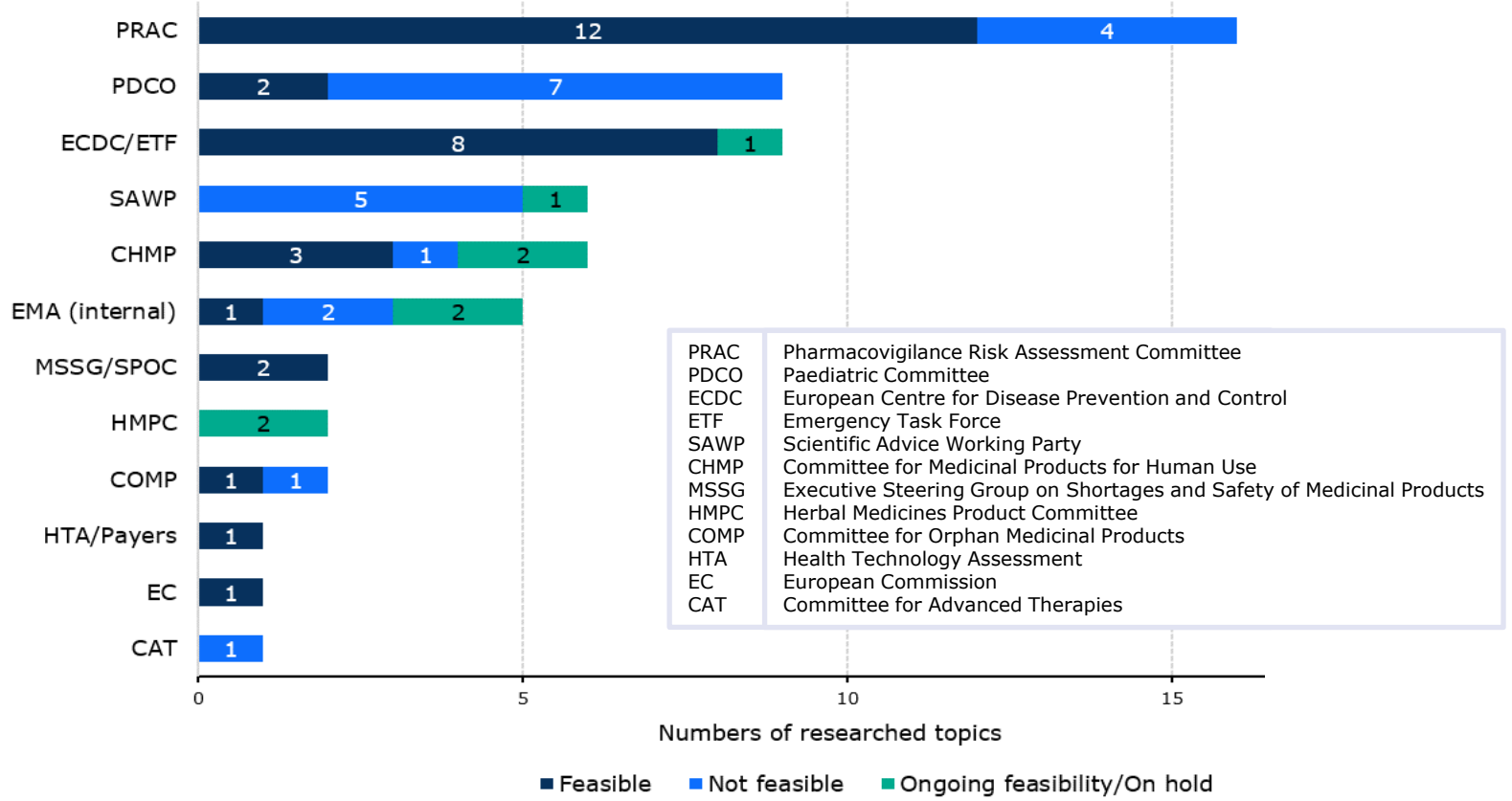
38
DARWIN EU

16
In-house

6
FWC

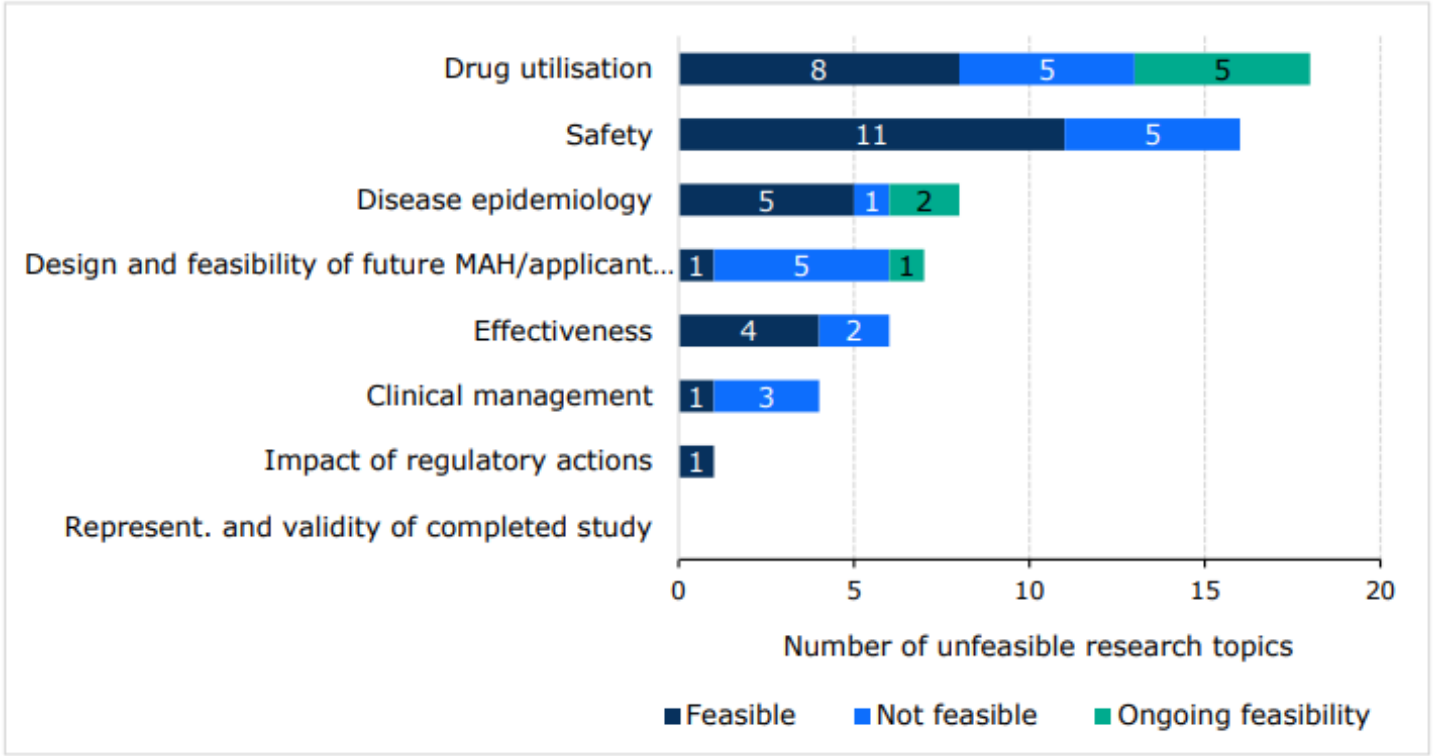


Study topics by ‘requester’ from Feb ‘23 to Feb ‘24

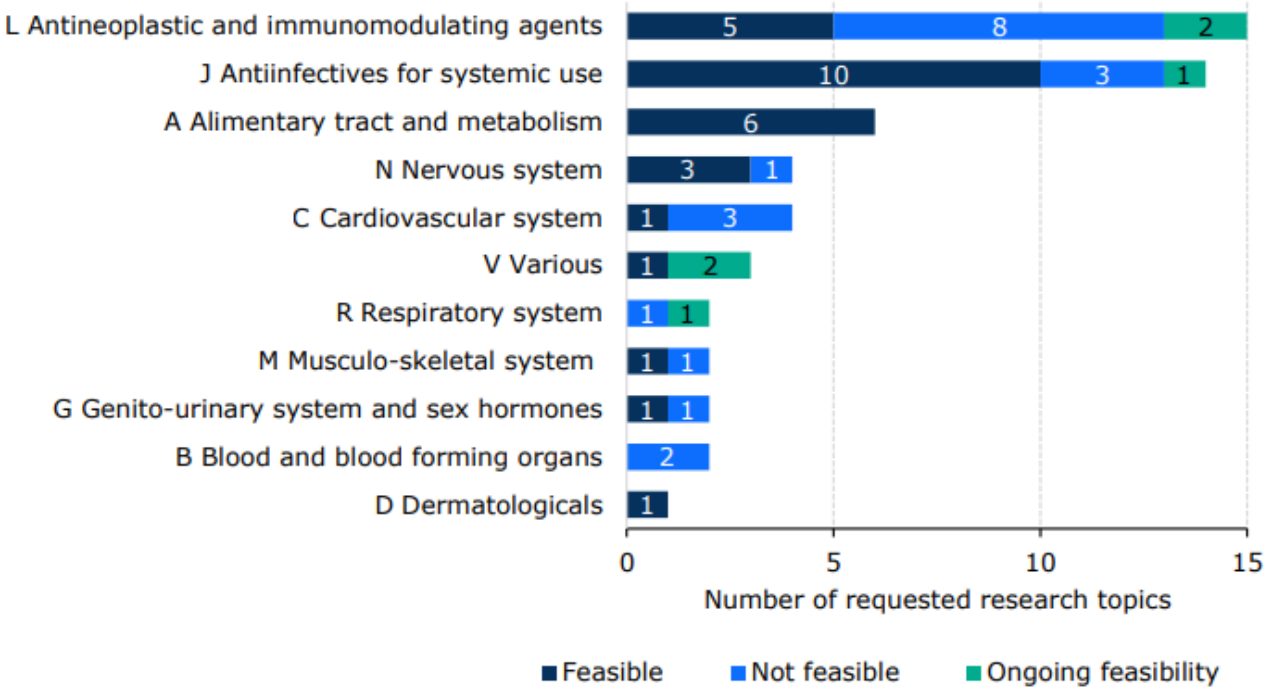


PRAC	Pharmacovigilance Risk Assessment Committee
PDCO	Paediatric Committee
ECDC	European Centre for Disease Prevention and Control
ETF	Emergency Task Force
SAWP	Scientific Advice Working Party
CHMP	Committee for Medicinal Products for Human Use
MSSG	Executive Steering Group on Shortages and Safety of Medicinal Products
HMPC	Herbal Medicines Product Committee
COMP	Committee for Orphan Medicinal Products
HTA	Health Technology Assessment
EC	European Commission
CAT	Committee for Advanced Therapies

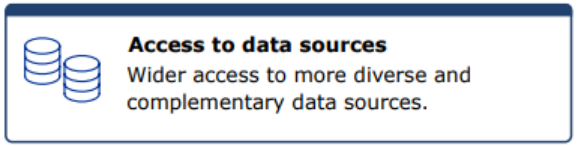
Type of research topic by use case and feasibility status



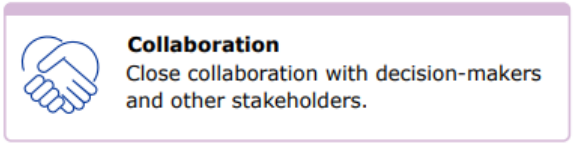
Research topics by Anatomical Therapeutic Chemical (ATC) classification



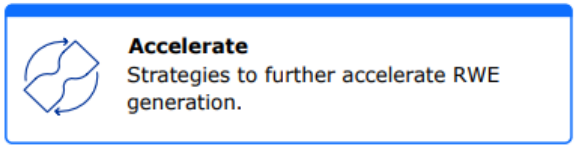
Recommendations for enabling the use of RWE



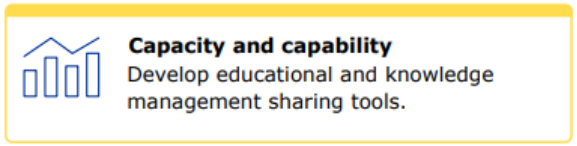
Access to data sources
Wider access to more diverse and complementary data sources.



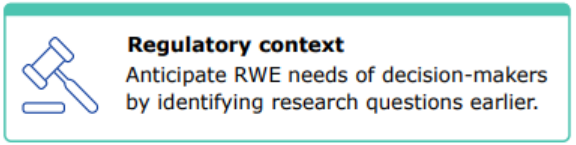
Collaboration
Close collaboration with decision-makers and other stakeholders.



Accelerate
Strategies to further accelerate RWE generation.

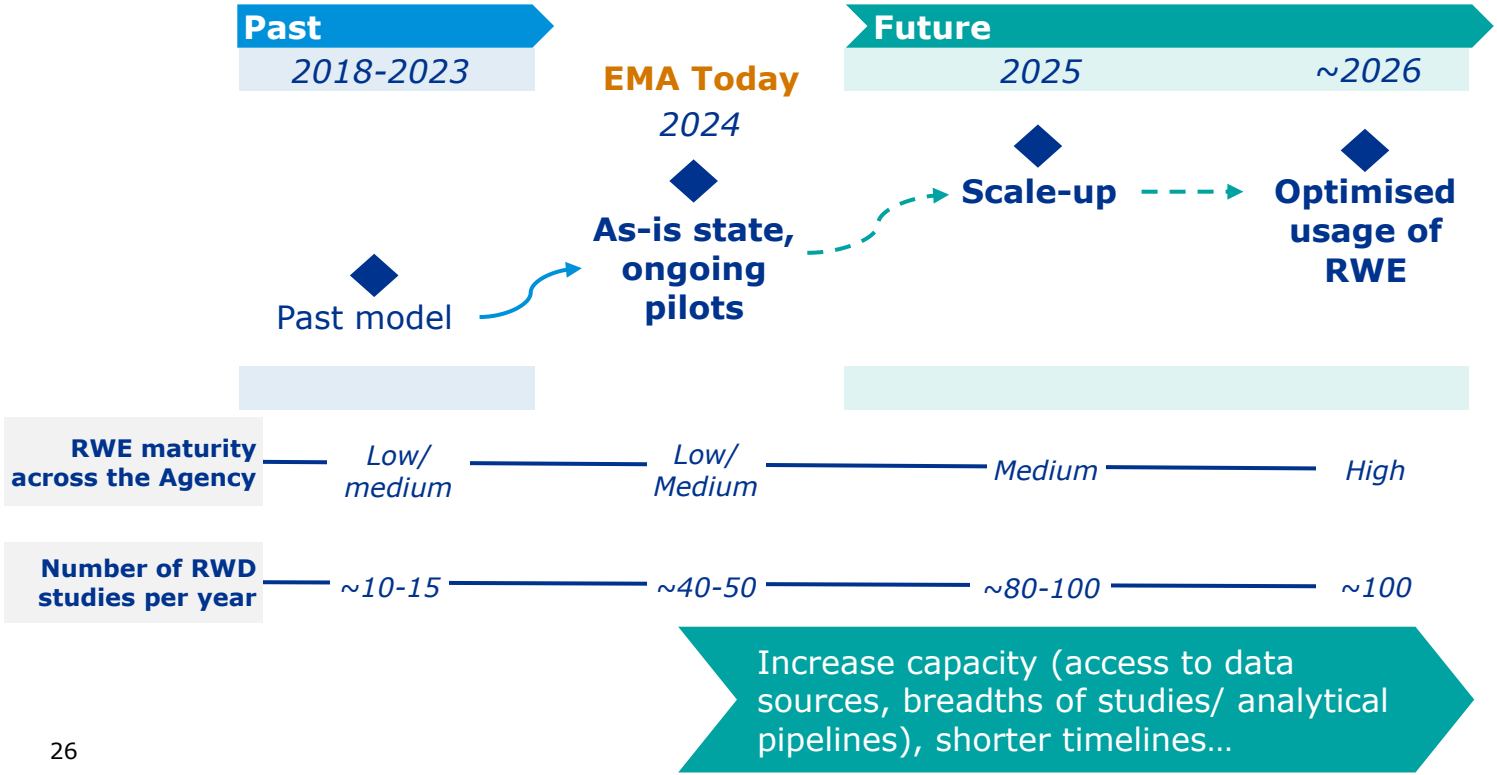


Capacity and capability
Develop educational and knowledge management sharing tools.



Regulatory context
Anticipate RWE needs of decision-makers by identifying research questions earlier.

In summary…



Our vision

By 2025 enable use & establish value of RWE


PERSPECTIVE

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

Thank you!

Further information

Contact me at patrice.verpillat@ema.europa.eu

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Introduction to DARWIN-EU the Co-ordination Center

EUROPEAN MEDICINES AGENCY

DARWIN EU

Introduction to DARWIN EU: the Co-Ordination Centre

Dani Prieto-Alhambra
Deputy Director, DARWIN EU

AGENDA

- The Co-ordination Centre
- Development: Standardised analytics
- Study Operations

AGENDA

- **The Co-ordination Centre**
- Development: Standardised analytics
- Study Operations

DARWIN EU® Coordination Centre

Executive Director
Prof. Peter Rijnbeek
Head of the Department of Medical Informatics
Erasmus MC

Deputy Director
Prof. Daniel Prieto Alhambra
Erasmus MC, Oxford University

Deputy Director
Associate Prof. Katia Verhamme
Erasmus MC

Contractor

Erasmus MC
Universitair Medisch Centrum Rotterdam

Sub-contractors

University of Oxford

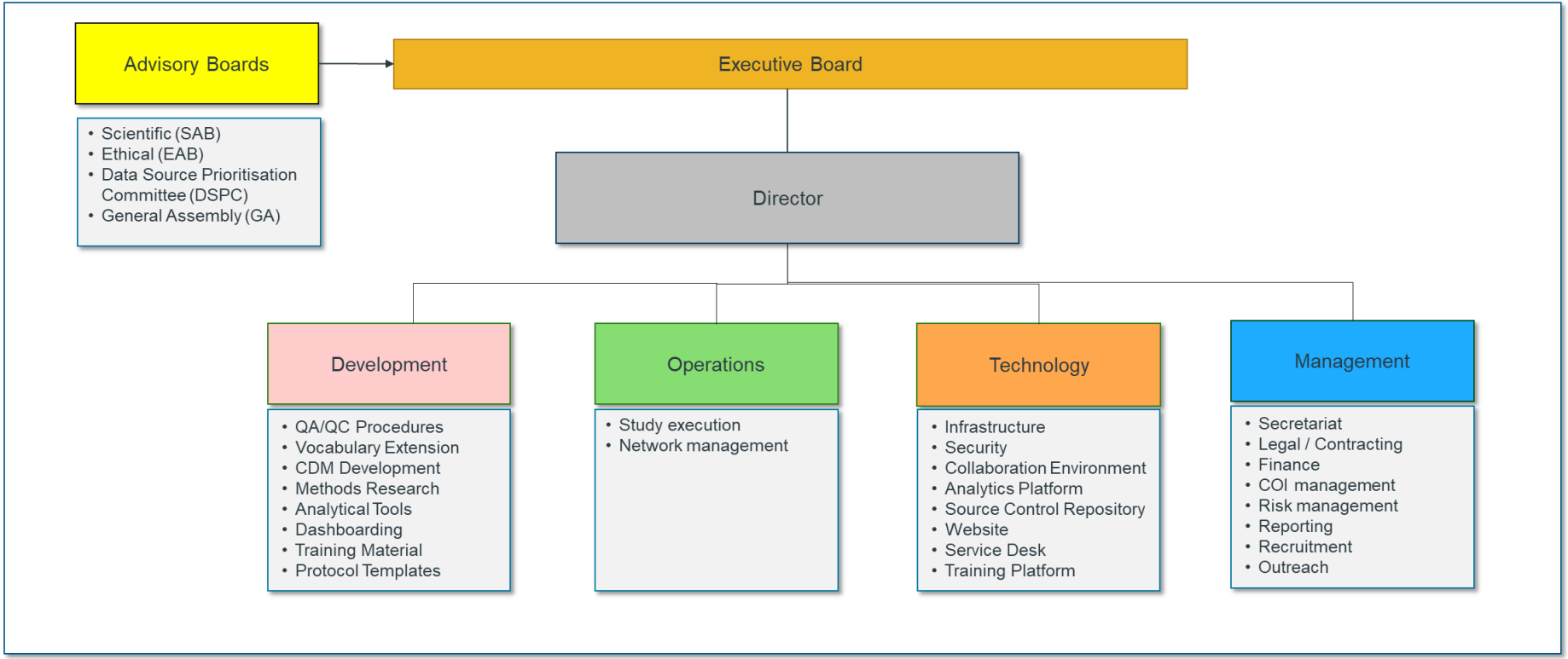
SYNAPSE
RESEARCH MANAGEMENT PARTNERS

IQVIA

The Hyve

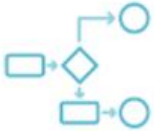
ODYSSEUS
DATA SERVICES INC

Establishment and Evolution of the Coordination Centre

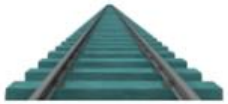


What is needed to facilitate observational studies at scale?

Data interoperability



Standardised analytics

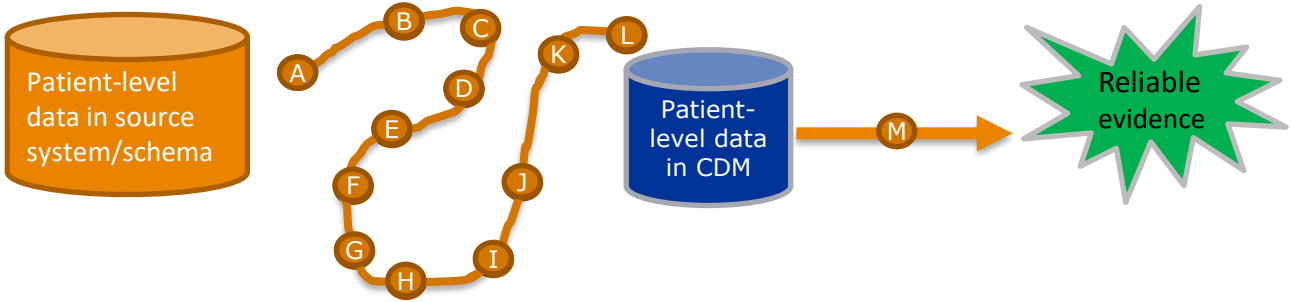


Technical Infrastructure

Data network

Generating Reliable Evidence using the OMOP Common Data Model

We need to make studies repeatable, reproducible, replicable, generalisable, and robust



A Common Data Model enables standardised analytics to generate reliable evidence.

AGENDA

- The Co-ordination Centre
- **Development: Standardised analytics**
- Study Operations

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.

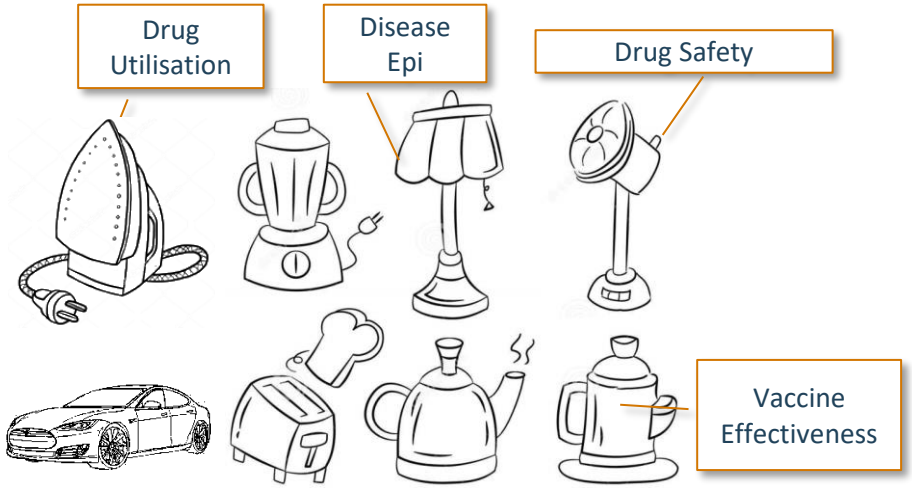
- Patient-level characterisation
- Patient-level DUS analyses
- Population-level DUS analyses
- Population-level descriptive epidemiology

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

From Data Standardization To Standardised Analytics

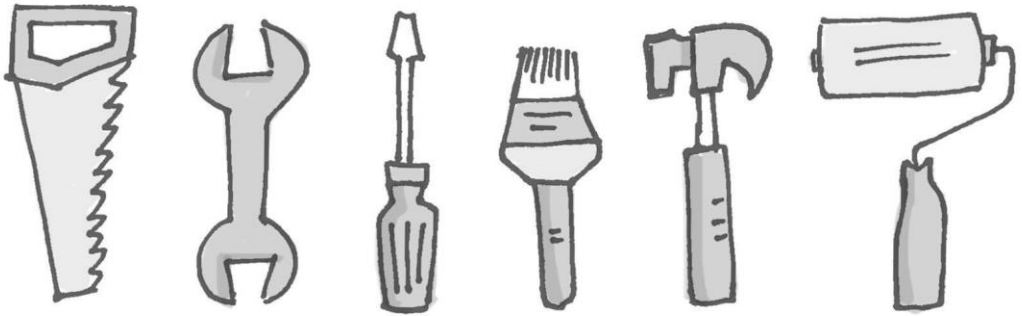


Standardized analytics → Standardized data

38

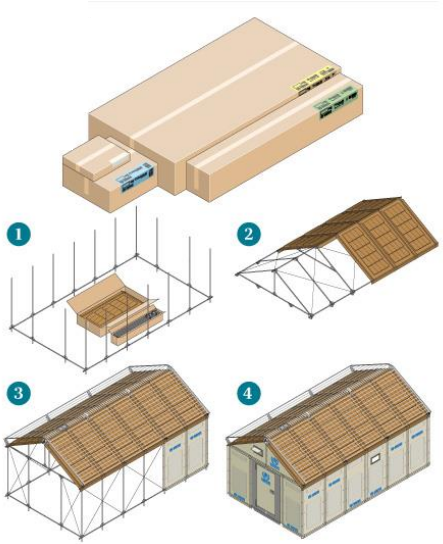
Building tools

Primary focus of the development pillar is providing tools (mostly R packages) to help users to perform standard data analyses, and training to facilitate the use of the resulting tools



Hacking a hard problem: Scaling up

Off the shelf
Fully STD



Complex
Pre-specified
(some bespoke)

Very complex
Bespoke code

Draft Catalogue of Standard Analyses:

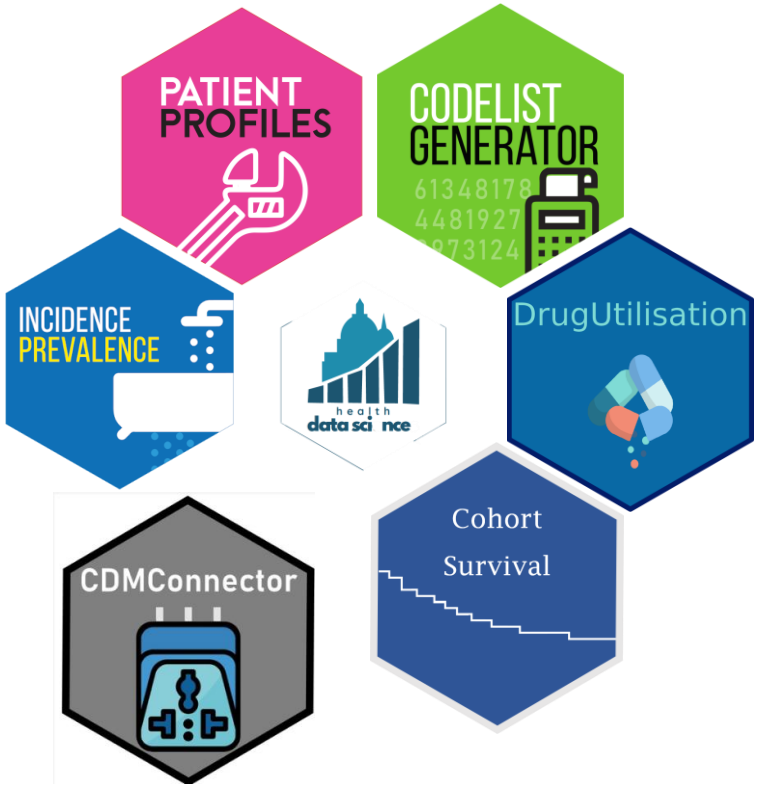
Off-the-shelf studies and examples

Standard Analysis	Regulatory example
Population-level disease epidemiology	• Prevalence of rare disease/s • Background rates of AESI or DMEs
Patient-level disease epidemiology	• Natural history/prognosis • Current practice/treatment patterns
Population-level DUS	• Incidence and prevalence of use of medicine/s over time
Patient-level DUS	• Describing indication/s for drug/s • Treatment duration, cumulative use

Building the tools:

Developing OMOP-Std

Analytical Pipelines



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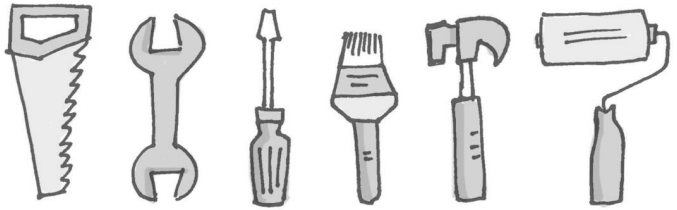
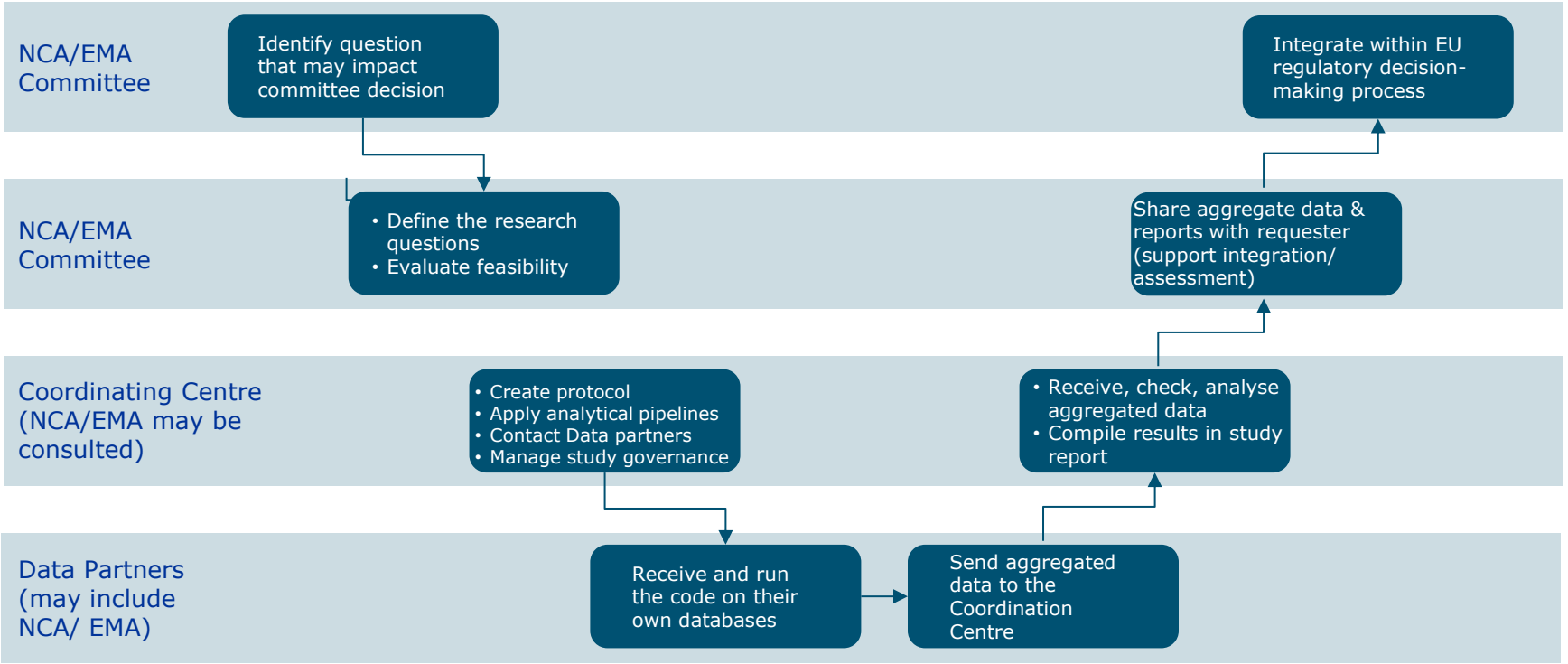


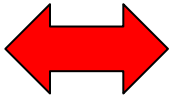
AGENDA

- The Co-ordination Centre
- Development: Standardised analytics
- **Study Operations**

What is the DARWIN EU® process for conducting studies?



1. Study Exploration	Study Feasibility- Study request by EMA: - Do we have the data? – Darwin Portal - Do we have the analytical pipelines? (OTS)
2. Study Initiation	- Work Order Form Data Partners - Creation of Study Team: PI/data analyst - Declaration of Interest
3. Study Implementation	- Study outline/Protocol – Upload to EUPAS register - IRB approval - Kick-off meeting - Phenotyping – Cohort Diagnostics - Study Package – Test Run
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



EMA

Database Partners

Darwin CC:
- Network Pillar
- Development Pillar
- Technology Pillar
- Management Pillar

Some impactful DARWIN EU studies …

Example: Prevalence of Valproate use

Prevalence estimates

Prevalence estimates are shown below....

Database and study outcome

Database 6 items selected

Outcome Valproate valpror

Population settings

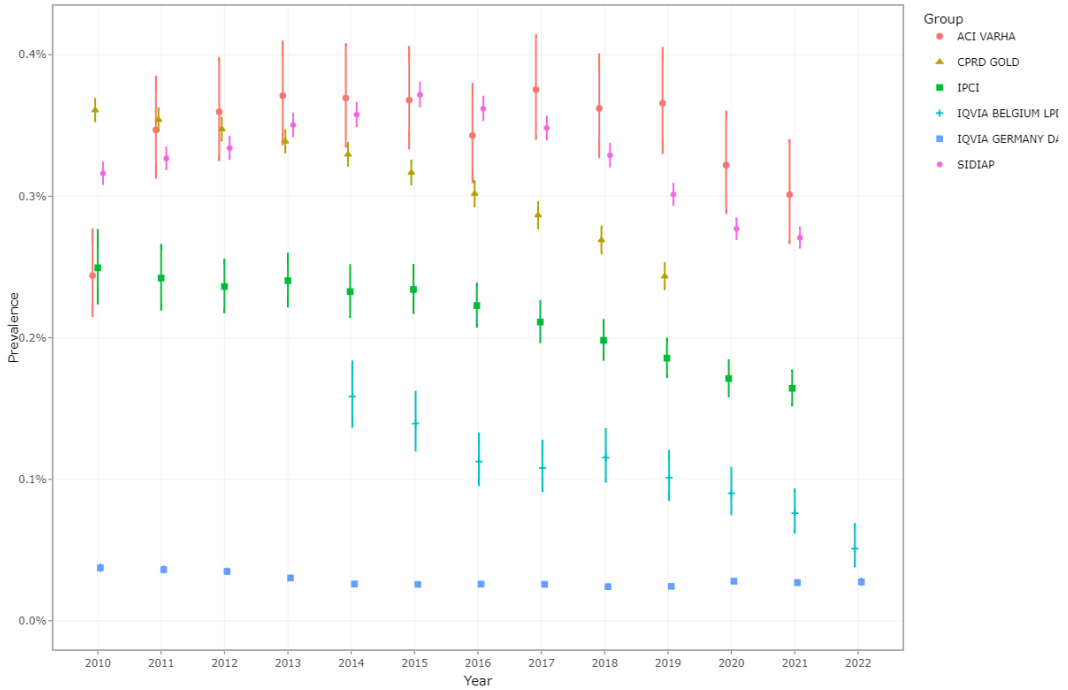
Age group 12 to 55

Sex Female

Days prior history 365

Analysis settings

Prevalence start date 13 items selected



Example: Incidence of Valproate use

Incidence estimates

Incidence estimates are shown below....

Database and study outcome

Database 6 items selected

Outcome Valproate valpror

Population settings

Age group 12 to 55

Sex Female

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Analysis settings

incidence start date

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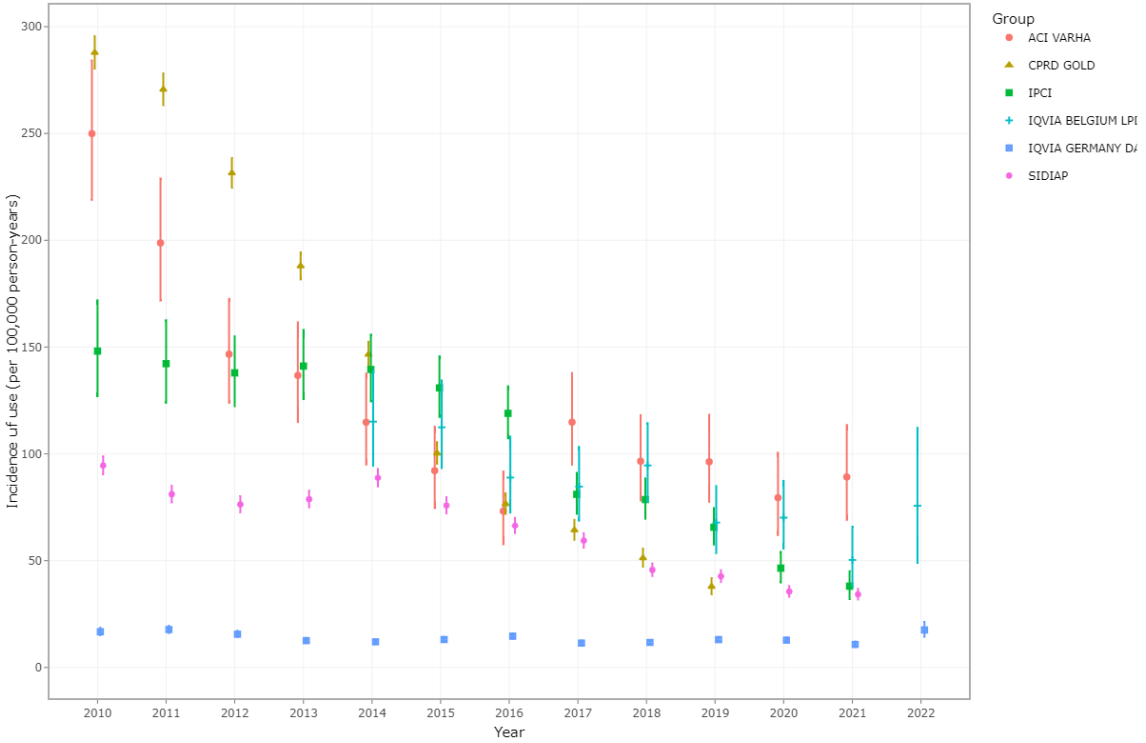
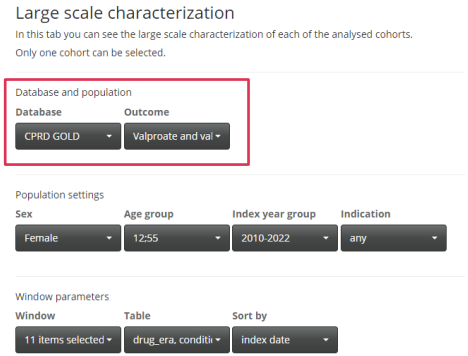


Large-Scale characterisation of Valproate users



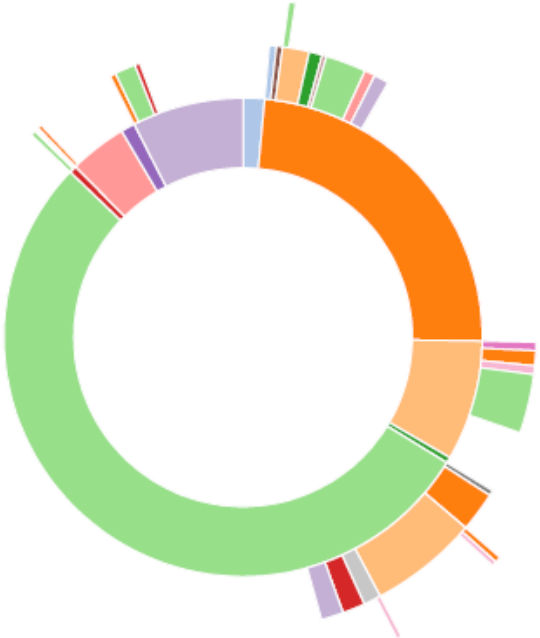
Show 100 entries Search:

covariate	Any time to -366 days	-365 to -91 days	-365 to -31 days	-90 to -1 day	-30 to -1 day	index date	+1 to +30 days	+1 to +90 days	+31 to +365 days	+91 to 365 days	+366 days to any time
drug_era: 745466 (valproate)	1137/6412 (17.7%)					6416/6416 (100%)	6413/6413 (100%)	6413/6413 (100%)	5050/6315 (80%)	4247/6132 (69.3%)	2886/5346 (54%)
drug_era: 1125315 (acetaminophen)	4000/6412 (62.4%)	1927/6416 (30%)	2096/6416 (32.7%)	1293/6416 (20.2%)	922/6416 (14.4%)	872/6416 (13.6%)	1078/6413 (16.8%)	1420/6413 (22.1%)	2047/6315 (32.4%)	1854/6132 (30.2%)	2653/5346 (49.6%)
drug_era: 923645 (omeprazole)	1773/6412 (27.7%)	1010/6416 (15.7%)	1103/6416 (17.2%)	766/6416 (11.9%)	608/6416 (9.5%)	644/6416 (10%)	752/6413 (11.7%)	891/6413 (13.9%)	1192/6315 (18.9%)	1078/6132 (17.6%)	1845/5346 (34.5%)
drug_era: 723013 (diazepam)	2151/6412 (33.5%)	1061/6416 (16.5%)	1214/6416 (18.9%)	833/6416 (13%)	632/6416 (9.9%)	641/6416 (10%)	730/6413 (11.4%)	883/6413 (13.8%)	1135/6315 (18%)	1022/6132 (16.7%)	1653/5346 (30.9%)
drug_era: 766814 (quetiapine)	764/6412 (11.9%)	635/6416 (9.9%)	695/6416 (10.8%)	551/6416 (8.6%)	438/6416 (6.8%)	553/6416 (8.6%)	592/6413 (9.2%)	652/6413 (10.2%)	780/6315 (12.4%)	716/6132 (11.7%)	878/5346 (16.4%)
drug_era: 1201620 (codeine)	3056/6412 (47.7%)	1331/6416 (20.7%)	1474/6416 (23%)	816/6416 (12.7%)	571/6416 (8.9%)	536/6416 (8.4%)	651/6413 (10.2%)	889/6413 (13.9%)	1405/6315 (22.2%)	1273/6132 (20.8%)	2142/5346 (40.1%)
drug_era: 1154343 (albuterol)	1891/6412 (29.5%)	988/6416 (15.4%)	1060/6416 (16.5%)	717/6416 (11.2%)	526/6416 (8.2%)	526/6416 (8.2%)	647/6413 (10.1%)	863/6413 (13.5%)	1155/6315 (18.3%)	1062/6132 (17.3%)	1515/5346 (28.3%)
drug_era: 797617 (citalopram)	1989/6412 (31%)	779/6416 (12.1%)	831/6416 (13%)	579/6416 (9%)	461/6416 (7.2%)	470/6416 (7.3%)	516/6413 (8%)	576/6413 (9%)	686/6315 (10.9%)	629/6132 (10.3%)	832/5346 (15.6%)
drug_era: 1501700 (levothyroxine)	464/6412 (7.2%)	444/6416 (6.9%)	451/6416 (7%)	430/6416 (6.7%)	391/6416 (6.1%)	447/6416 (7%)	477/6413 (7.4%)	507/6413 (7.9%)	546/6315 (8.6%)	523/6132 (8.5%)	601/5346 (11.2%)
drug_era: 19044883 (zopiclone)	1595/6412 (24.9%)	766/6416 (11.9%)	868/6416 (13.5%)	559/6416 (8.7%)	401/6416 (6.2%)	430/6416 (6.7%)	519/6413 (8.1%)	632/6413 (9.9%)	870/6315 (13.8%)	768/6132 (12.5%)	1254/5346 (23.5%)
drug_era: 710062 (amitriptyline)	1602/6412 (25%)	818/6416 (12.7%)	923/6416 (14.4%)	585/6416 (9.1%)	454/6416 (7.1%)	382/6416 (6%)	422/6413 (6.6%)	500/6413 (7.8%)	661/6315 (10.5%)	595/6132 (9.7%)	1011/5346 (18.9%)
drug_era: 739138 (sertraline)	1056/6412 (16.5%)	549/6416 (8.6%)	600/6416 (9.4%)	437/6416 (6.8%)	358/6416 (5.6%)	379/6416 (5.9%)	406/6413 (6.3%)	462/6413 (7.2%)	596/6315 (9.4%)	535/6132 (8.7%)	1042/5346 (19.5%)

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

The management of juvenile SLE

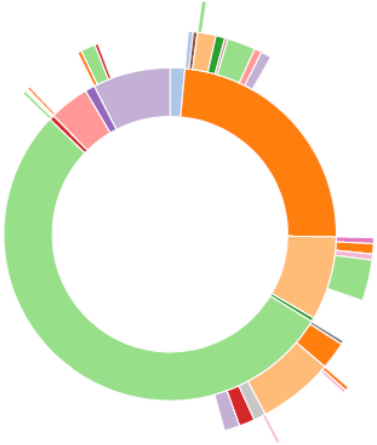
Adult SLE

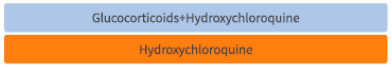


- Azathioprine
- Glucocorticoids
- Glucocorticoids+Hydroxychloroquine
- Glucocorticoids+Methotrexate
- Hydroxychloroquine
- Hydroxychloroquine+Tacrolimus
- Methotrexate
- Mycophenolate mofetil
- Tacrolimus
- Azathioprine+Glucocorticoids
- Glucocorticoids+Mycophenolate mofetil
- Azathioprine+Glucocorticoids+Hydroxychloroquine
- Glucocorticoids+Hydroxychloroquine+Methotrexate
- Azathioprine+Hydroxychloroquine

Results dashboard

The management of juvenile SLE (2)



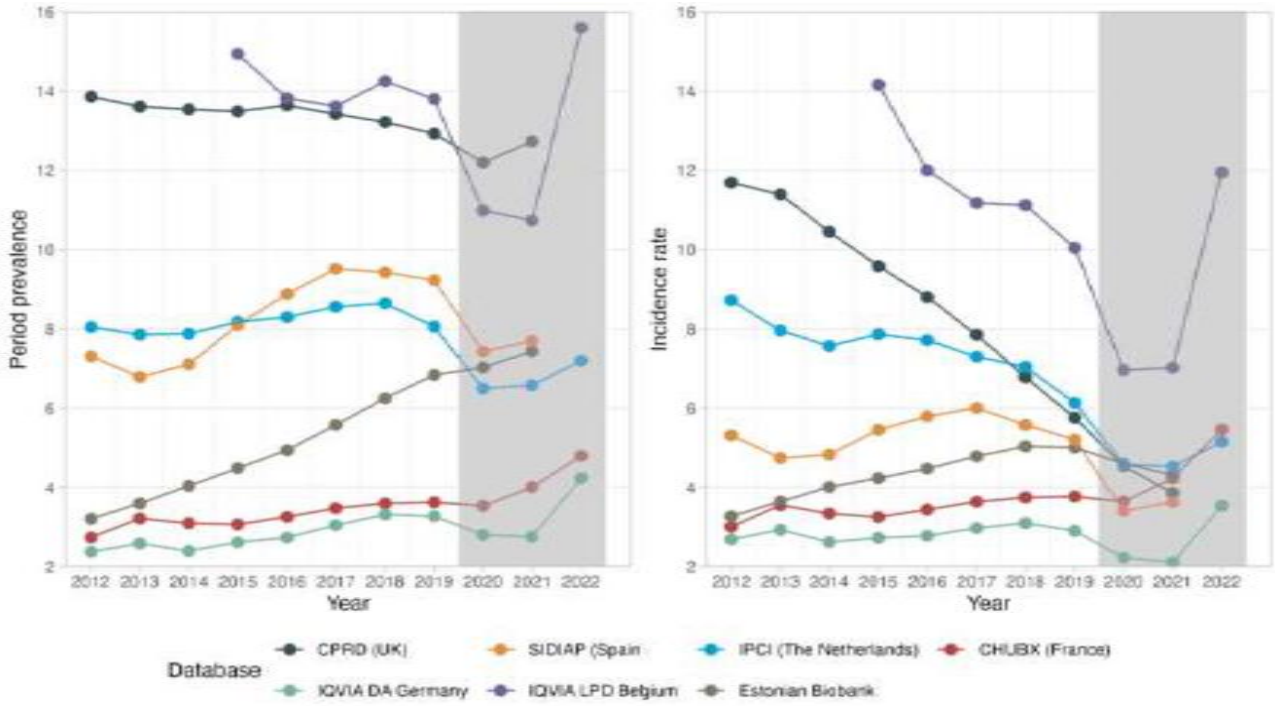


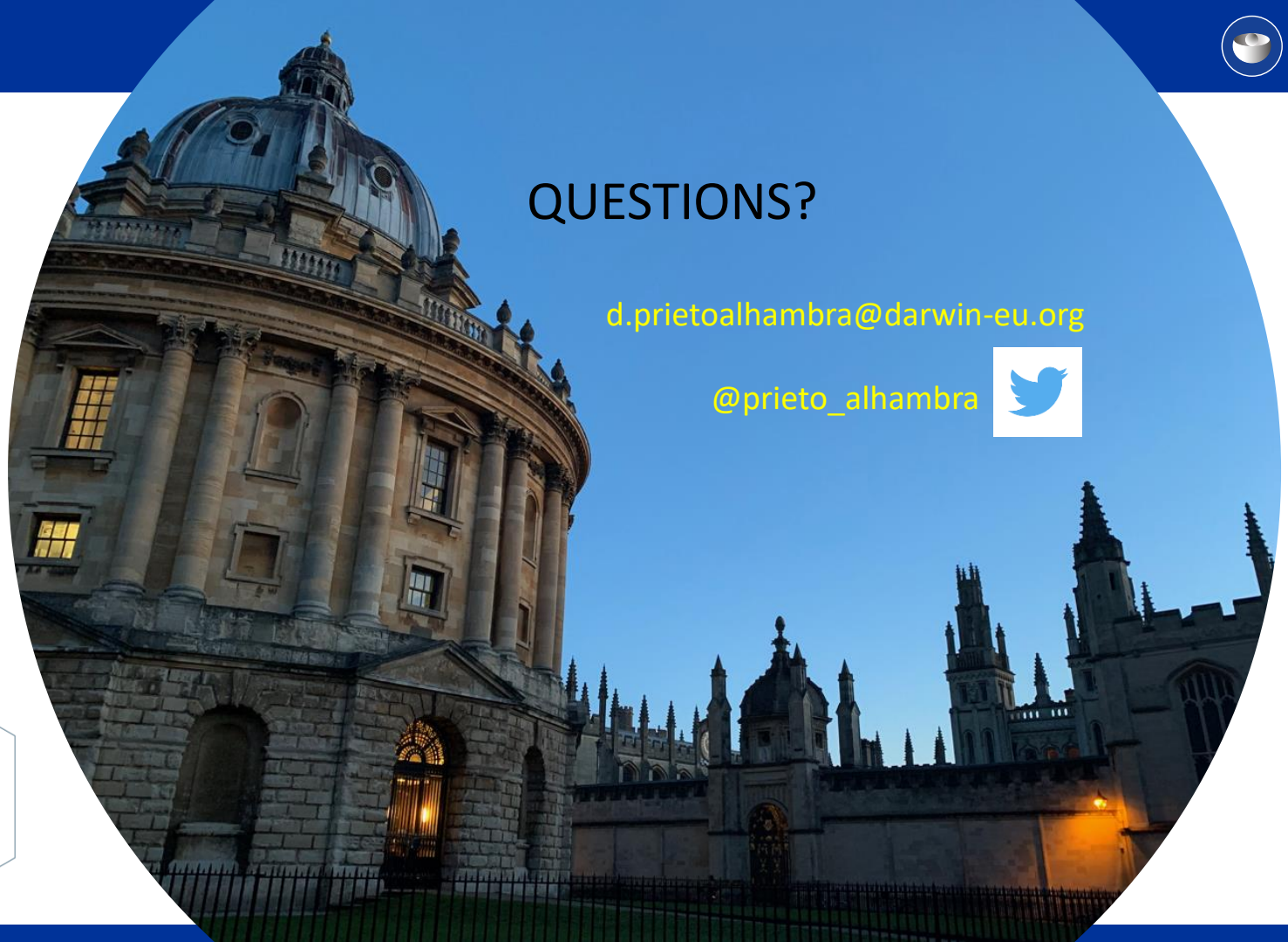
Adult SLE

Juvenile SLE

[Results dashboard]

The use of (prescribed) opioids in Europe





QUESTIONS?

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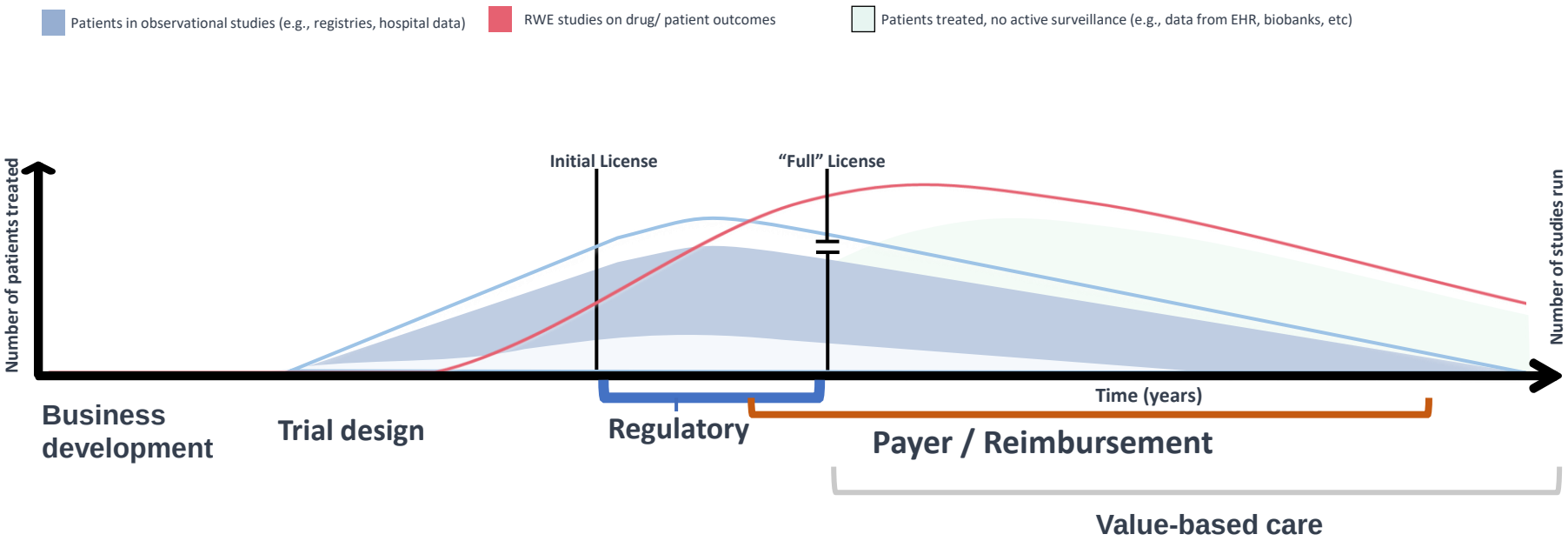
3

Opportunities for Multi-stakeholder Collaboration (Industry perspective)

DARWIN EU : Opportunities for multi-stakeholder collaboration
An Industry perspective

RWE informs decision-making across the product life-cycle, for multiple stakeholders



DARWIN EU: an opportunity for stakeholders to become collaborators

Stakeholder	Historical role	DARWIN EU Collaborator role
Patients	Information Receivers	Research (data) contributors
Providers	Guideline/policy implementation	Data-driven /value–based outcomes
Regulators	Market approval authorizers	‘Real time’ risk-benefit evaluators
Payers	Manage populations	Manage patients, prevent diseases, fund value-driven care
Pharma	Medicine manufacturer and creator of information specific to their innovation	Patient-centric Innovators & quality and value of care improver

Adapted from: http://pharmamarketresearchconference.com/usa/member-presentations-canada/member-presentations-canada-2014/the-value-of-real-world/the-value-of-real-world-evidence-improving-patient-outcomes_page_06/

DARWIN-EU: Collaboration Opportunities

- Greater collaboration will further strengthen the RWE eco-system
  - Rationale for Research topic and product selection
  - Fit-for-purpose assessment methods and agreement on data quality requirements
  - Rationale for choice of study design and analytic methods for complex studies
  - Interpretation / contextualization of findings and impact on downstream (e.g. HTA) decision-making
  - Efficient sharing / re-use of data quality assessment tools, methods and infrastructure across stakeholders.

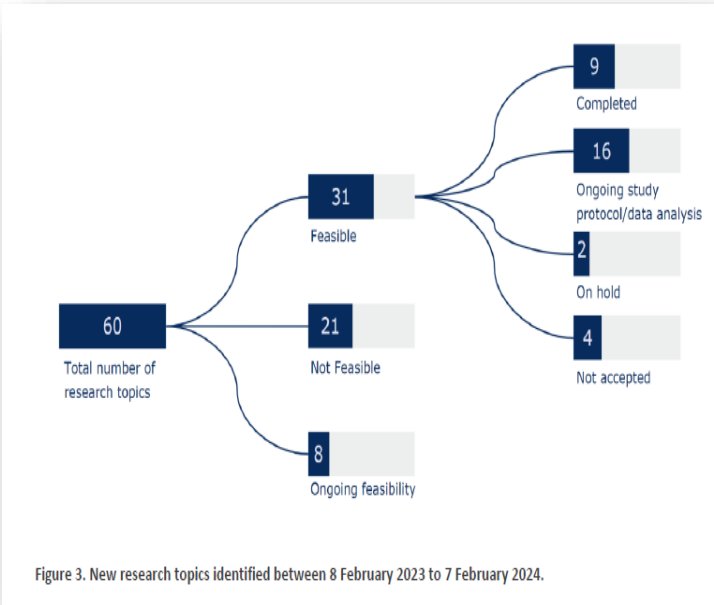


Figure 3. New research topics identified between 8 February 2023 to 7 February 2024.

EMA DARWIN-EU, 2nd report, 2024

DARWIN-EU: Collaboration opportunities

- How can we make the execution process more inclusive & findings more representative ?
  - Very short MAH[1] review timelines for new protocols.
  - Opportunity to include other stakeholders to clarify HTA relevance for specific findings.
  - Opportunity to co-develop well-defined strategy to establish representativeness of selected data sources
  - Opportunity to include research topics that focus on evaluating the representativeness and validity of completed studies.

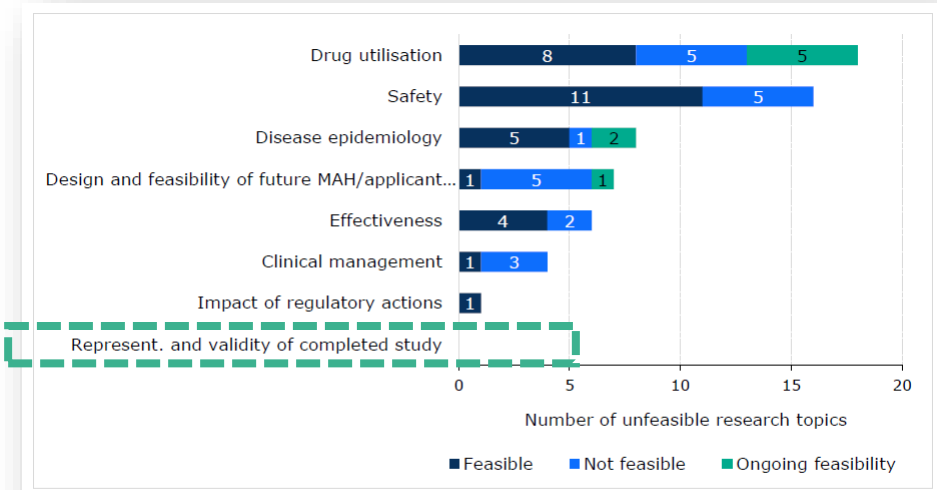
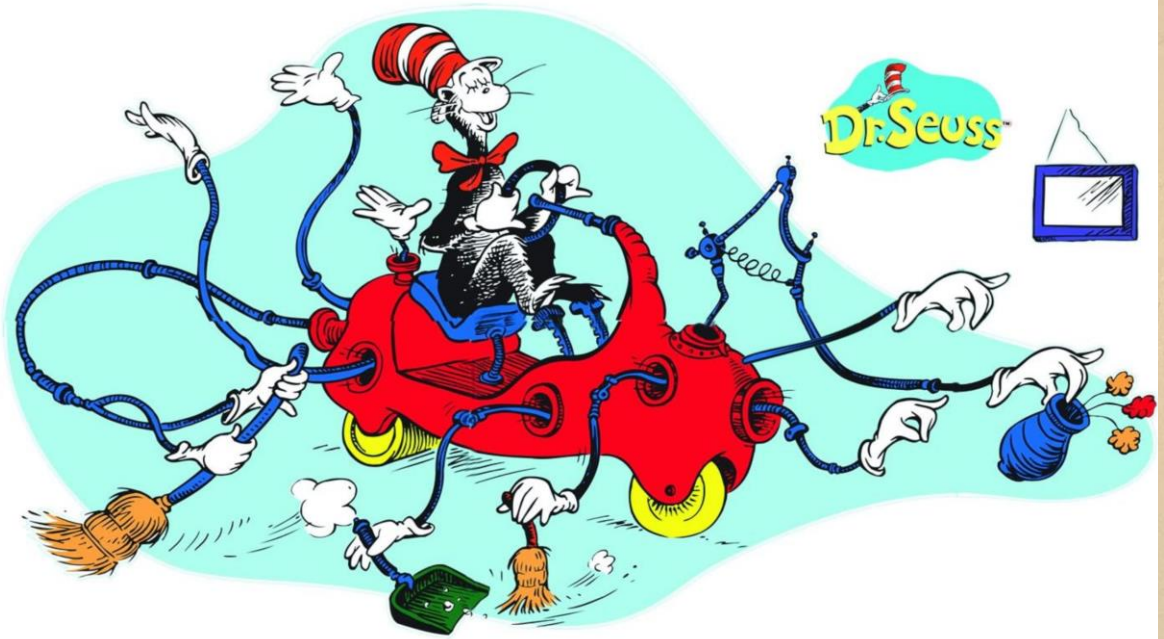


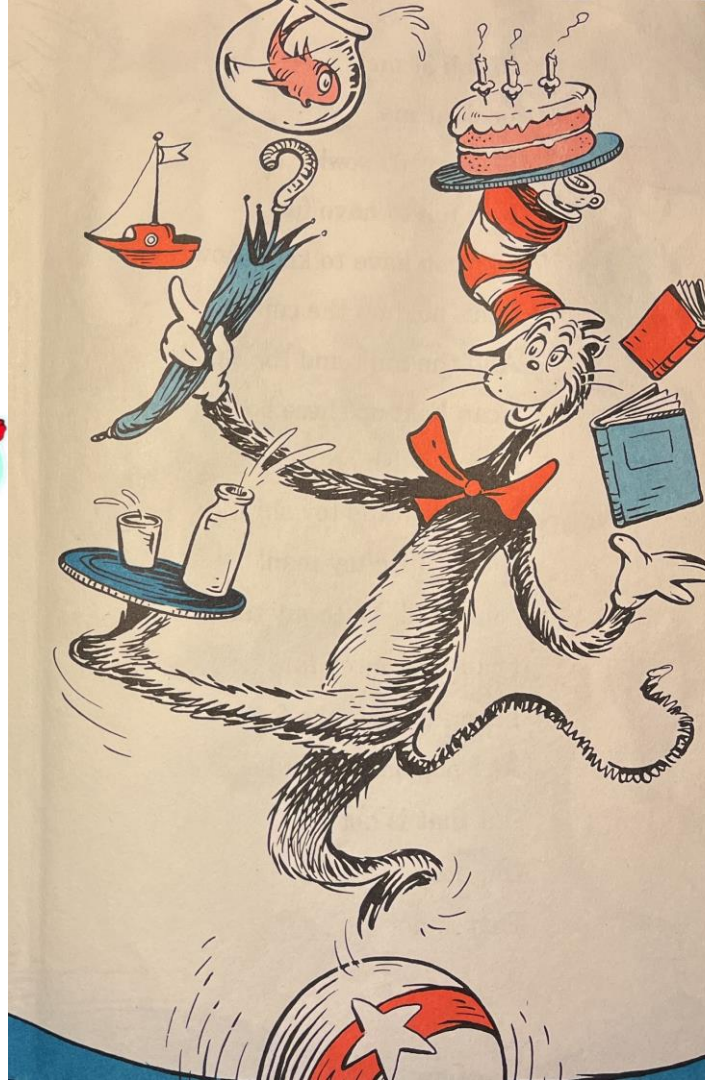
Figure 7. Type of research topic (new research questions identified during the reporting period) by use case and feasibility status (n=60).

1 – Manufacturing Authorization holder

Con



Let’s collaborate and harness the power of DARWIN EU, the Cat in the Hat



5

Q & A

ISPOR, the professional society for health economics and outcomes research (HEOR), is an international, multistakeholder, nonprofit dedicated to advancing HEOR excellence to improve decision making for health globally. The Society is the leading source for scientific conferences,
peer-reviewed and MEDLINE-indexed publications, good practices guidance, education, collaboration, and tools/resources in the field.

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