Real-World Evidence use in medicines regulation

OHDSI symposium 3 Jul 2023
Disclaimer

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The presenter does not have any conflict of interests.
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-world evidence: convergence of general principles regarding planning and reporting with a focus on effectiveness of medicines’ → public consultation
Supply: Real-world evidence

**EMA**
- Performs studies using in-house databases
- Procures studies through EMA framework contracts
- Conducts studies via DARWIN EU

**NCAs**
- Direct access to national data sources e.g. DKMA (Danish registries), ANSM (SNDS database), AEMPS (BIFAP database)
- EHDS Regulation foresees that national Health Data Access Bodies will facilitate access to national datasets

**Medicine developers**
- Submit RWE/RWD to inform the safety of medicines and to support efficacy/effectiveness claims

**Independent academia / Patients’ associations**
- Perform independent studies (ideally registered in the EU PAS Register - study protocol and report)
- Participate in consortia involved in studies carried out via EMA framework contractors
## Overview of 3 studies on the use of RWE in marketing authorisation applications

<table>
<thead>
<tr>
<th>Study</th>
<th>Key message</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flynn et al. (2021)</td>
<td>Widespread use of RWE to support evaluation of marketing applications</td>
</tr>
<tr>
<td></td>
<td>RWE in pre-authorization (1/3) and post-authorization (2/3)</td>
</tr>
<tr>
<td></td>
<td>RWE included to support safety (87.3%) and efficacy (49.2%)</td>
</tr>
<tr>
<td></td>
<td>Most common data sources were registries (60.3%) followed by hospital data (31.7%)</td>
</tr>
<tr>
<td>Eskola et. al. (2021)</td>
<td>The study confirms that RWD/RWE contribute to medicines development learning and regulatory decisions</td>
</tr>
<tr>
<td></td>
<td>in virtually all phases</td>
</tr>
<tr>
<td></td>
<td>across different therapeutic areas</td>
</tr>
<tr>
<td></td>
<td>product characteristics</td>
</tr>
<tr>
<td>Purpura et al. (2021)</td>
<td>Successful use of RWE in regulatory approvals required:</td>
</tr>
<tr>
<td></td>
<td>• fit-for-purpose data</td>
</tr>
<tr>
<td></td>
<td>• good study design, appropriate data collection, and thoughtful data analysis</td>
</tr>
<tr>
<td></td>
<td>• proactive communication with FDA</td>
</tr>
</tbody>
</table>

### Number of products reviewed

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of products reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flynn et al. (2021)</td>
<td>158</td>
</tr>
<tr>
<td>Eskola et. al. (2021)</td>
<td>111</td>
</tr>
<tr>
<td>Purpura et al. (2021)</td>
<td>136</td>
</tr>
</tbody>
</table>

### Period

<table>
<thead>
<tr>
<th>Study</th>
<th>Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flynn et al. (2021)</td>
<td>Jan 2018 – Dec 2019 (submitted marketing applications, including non-published information)</td>
</tr>
<tr>
<td>Eskola et. al. (2021)</td>
<td>Jan 2018 – Dec 2019 (approved marketing applications, only published information)</td>
</tr>
<tr>
<td>Purpura et al. (2021)</td>
<td>Jan 2019 – June 2021 (approved marketing applications, only published information)</td>
</tr>
</tbody>
</table>

### Number of products with RWE included

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of products with RWE included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flynn et al. (2021)</td>
<td>63 (39.9%)</td>
</tr>
<tr>
<td>Eskola et. al. (2021)</td>
<td>111 (100%)</td>
</tr>
<tr>
<td>Purpura et al. (2021)</td>
<td>116 (85.2%)</td>
</tr>
</tbody>
</table>

### Therapeutic area with higher use of RWE

- Oncology and anti-infectives
- Oncology, hematology and anti-infectives
- Oncology and anti-infectives
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
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

**Pre-authorisation**
- Orphan designation
  - COMP
  - RWE
- Scientific advice
  - CHMP SAWP CAT
  - RWE
- Paediatric investigation plan
  - PDCO
  - RWE

**Evaluation**
- Marketing authorisation application
  - CHMP CAT PRAC
  - RWE

**Post-authorisation**
- Post-authorisation
  - CHMP PRAC CAT HMPC CMDh
  - RWE
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®

- 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 In-house
- 8 DARWIN EU
- 4 FWC

Feasible: 36
- Completed: 27
- Ongoing: 3
- Not accepted: 6
- In-house: 24
- DARWIN EU®: 3

Not Feasible: 19
- Ongoing feasibility/on hold: 6
Research topics by committees/requester

Numbers of researched topics

- **PRAC**: 22 feasible, 3 not feasible, 1 ongoing feasibility/On hold
- **PDCO**: 8 feasible, 1 not feasible, 1 ongoing feasibility/On hold
- **COMP**: 5 feasible, 1 not feasible
- **SAWP**: 2 feasible, 1 ongoing feasibility/On hold
- **CMDh/NCA**: 2 feasible, 1 ongoing feasibility/On hold
- **Other**: 1 feasible, 1 ongoing feasibility/On hold
- **CHMP**: 1 feasible, 1 ongoing feasibility/On hold
- **CAT**: 1 feasible
Use case categories

- **Effectiveness**
  - Number of research topics
  - Feasible: 17, Not feasible: 4, Ongoing feasibility/On hold: 1

- **Safety**
  - Number of research topics
  - Feasible: 17, Not feasible: 4, Ongoing feasibility/On hold: 1

- **Design and feasibility of future MAH/applicant studies**
  - Number of research topics
  - Feasible: 4, Not feasible: 6, Ongoing feasibility/On hold: 1

- **Drug utilisation**
  - Number of research topics
  - Feasible: 8, Not feasible: 2

- **Clinical management**
  - Number of research topics
  - Feasible: 1, Not feasible: 6, Ongoing feasibility/On hold: 3

- **Disease epidemiology**
  - Number of research topics
  - Feasible: 6, Not feasible: 1

- **Impact of regulatory actions**
  - Number of research topics
  - Feasible: 1

- **Representativeness and validity of completed study**
  - Number of research topics
  - Feasible: 1

- **Effectiveness**
  - Number of research topics
  - Feasible: 17, Not feasible: 4, Ongoing feasibility/On hold: 1
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

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EMA-funded (FWC) studies – the process

**Approx. 2-3 months**

- Identify research topic
- Draft Technical Specifications (TS)
- Consult Committee Rapporteurs
- Present to Scientific Committee
- Finalise TS
- Invitation to tender (reopening of competition among framework contractors)

**Receipt of proposals (tenders)**

**Evaluation**

**Award Decision**

**Contract signature**

**Approx. 12-18 months**

- Study start
- Research results
- Regulatory Decision-making

Approx. 2-3 months:
- Identify research topic
- Draft Technical Specifications (TS)
- Consult Committee Rapporteurs
- Present to Scientific Committee
- Finalise TS
- Invitation to tender (reopening of competition among framework contractors)

Approx. 12-18 months:
- Study start
- Research results
- Regulatory Decision-making
EMA FWC study based on registry data in collaboration with Aetion and TREAT NMD

A registry-based cohort study of Spinal Muscular Atrophy (SMA) disease to describe the natural history of SMA, the evolution of SMA care management and disease progression considering new disease modifying therapies (DMTs).
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
4. IDIAPJGol
5. Parc Salut Mar Barcelona, Hospital del Mar (IMIM)

Spain

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

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

~26 million active patients
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

<table>
<thead>
<tr>
<th>Studies</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Option I</th>
<th>Option II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off the shelf</td>
<td>2</td>
<td>6</td>
<td>30</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Routine repeated</td>
<td>1</td>
<td>6</td>
<td>30</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Complex study</td>
<td>1</td>
<td>4</td>
<td>12</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Very complex</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Data Partners (total)</td>
<td>10</td>
<td>20</td>
<td>30</td>
<td>40</td>
<td>40</td>
</tr>
</tbody>
</table>
Studies started in 2022 (year 1/ phase I)

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

<table>
<thead>
<tr>
<th>Type</th>
<th>Studies</th>
<th>Data Partners</th>
<th>Planned RWE use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Off the Shelf</td>
<td><strong>Population level epidemiology</strong> study on prevalence of <strong>rare blood cancers</strong> from 2010</td>
<td>NL, ES, UK, BE, DE</td>
<td>Support COMP in orphan designation decision making &amp; useful as background rates for other committees</td>
</tr>
<tr>
<td>Off the Shelf</td>
<td>Patient level <strong>drug utilization study of valproate-containing medicinal products</strong> in women of childbearing potential from 2010</td>
<td>NL, ES, UK, BE, DE, FI</td>
<td>Assess the use of valproate after safety referral</td>
</tr>
<tr>
<td>Off the Shelf</td>
<td>Patient level <strong>drug utilisation study of antibiotics</strong> on the Watch list of the WHO AWaRe classification, 2010-2021</td>
<td>NL, FR, ES, DE, UK</td>
<td>Inform PRAC/CHMP decision making, AMR strategy</td>
</tr>
<tr>
<td>Complex</td>
<td>Background all-cause <strong>mortality rates in patients with severe asthma aged ≥12 years</strong> old</td>
<td>NL, ES x2, UK, EE</td>
<td>Support CHMP post-authorisation inform future decision making</td>
</tr>
</tbody>
</table>
More detail in protocols + study reports in EU PAS Register + shiny apps
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

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

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

- **Naloxone use in treatment of opioid overdose.**
  - CHMP OTS

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

- **Drug utilisation study of prescription opioids.**
  - PRAC OTS

- **Erythromycin use as prokinetic**
  - NCA 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

Subscribe here to receive future issues of the Big Data Highlights
Any questions?

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Structure of the DARWIN EU® Coordination Centre

Executive Board

Director

Advisory Boards
- Scientific (SAB)
- Ethical (EAB)
- Data Source Prioritisation Committee (DSPC)
- General Assembly (GA)

Development
- QA/QC Procedures
- Vocabulary Extension
- CDM Development
- Methods Research
- Analytical Tools
- Dashboarding
- Training Material
- Protocol Templates

Operations
- Study execution
- Network management

Technology
- Infrastructure
- Security
- Collaboration Environment
- Analytics Platform
- Source Control Repository
- Website
- Service Desk
- Training Platform

Management
- Secretariat
- Legal / Contracting
- Finance
- COI management
- Risk management
- Reporting
- Recruitment
- Outreach
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
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

EstimateIncidence name and argument details

edward-burn opened this issue on Nov 17, 2022

@danielietaltumbras share your thoughts.
Do the argument names make sense?
Also, are you happy with the name?

edward-burn commented on Nov 21, 2022

mderider95 commented on Nov 21, 2022

How would 'database starting' be determined, is that earliest observation start date among the complete database population? Or among the persons in the denominator selection?
It would be related to the organization of the database if this is a reasonable definition. In theory it can be one person then determining this start, or a certain GP practice. I would be very careful on using this, but may be we should leave that to Concerning the name. I think it persons, fullPeriodsInDenominator.

edward-burn commented on Nov 21, 2022

mderider95 commented on Nov 22, 2022

I would prefer completeDatabaseIntervals

edward-burn added the enhancement label on Nov 21, 2022

edward-burn commented on Nov 22, 2022

albertpratu commented on Nov 21, 2022

It looks good to me.

edward-burn commented on Nov 21, 2022

mderider95 is this based on latest and observation period and study date periods instead

edward-burn commented on Nov 22, 2022

albertpratu fullPeriods database capture all if 1st July 2017, if we ra (but is set to FALSE) or was thinking this opt particularly seasonal c.
I agree the name is not

edward-burn added the enhancement label on Nov 21, 2022

edward-burn commented on Nov 22, 2022

albertpratu fullPeriods database capture all if 1st July 2017, if we ra (but is set to FALSE) or was thinking this opt particularly seasonal c.
I agree the name is not
User contributions

add information from drug_strength table #43

Select statements #86

Update estimatePrevalence function to check for "overall" time interv...
Package Reviewer (PaRe)

Summary of package functions

<table>
<thead>
<tr>
<th>Function</th>
<th>Number of arguments</th>
<th>Lines of code</th>
<th>Cyclomatic complexity</th>
<th>Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>runSearch</td>
<td>18</td>
<td>631</td>
<td>63</td>
<td>runSearch.R (from line: 34)</td>
</tr>
<tr>
<td>getCandidateCodes</td>
<td>18</td>
<td>148</td>
<td>8</td>
<td>getCandidateCodes.R (from line: 97)</td>
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<tr>
<td>mockVocabRef</td>
<td>1</td>
<td>218</td>
<td>7</td>
<td>mockVocabRef.R (from line: 28)</td>
</tr>
<tr>
<td>getMatches</td>
<td>2</td>
<td>32</td>
<td>7</td>
<td>runSearch.R (from line: 690)</td>
</tr>
<tr>
<td>getMappings</td>
<td>3</td>
<td>95</td>
<td>5</td>
<td>getMappings.R (from line: 46)</td>
</tr>
<tr>
<td>getFuzzyMatches</td>
<td>3</td>
<td>29</td>
<td>5</td>
<td>runSearch.R (from line: 736)</td>
</tr>
<tr>
<td>getConceptClassId</td>
<td>3</td>
<td>64</td>
<td>4</td>
<td>vocabUtilities.R (from line: 176)</td>
</tr>
<tr>
<td>getDomains</td>
<td>2</td>
<td>56</td>
<td>3</td>
<td>vocabUtilities.R (from line: 66)</td>
</tr>
<tr>
<td>checkDbType</td>
<td>3</td>
<td>7</td>
<td>2</td>
<td>utils.R (from line: 17)</td>
</tr>
<tr>
<td>checkTableExists</td>
<td>3</td>
<td>8</td>
<td>2</td>
<td>utils.R (from line: 26)</td>
</tr>
</tbody>
</table>
Software validation: Incidence Prevalence

- Anaphylaxis
- Appendicitis
- Bell's Palsy
- Deep vein thrombosis
- Immune thrombocytopenia
- Myocarditis
- Pericarditis
- Pulmonary embolism

Sex
- Female
- Male

Age groups (years)
- 0-5
- 6-17
- 18-34
- 35-54
- 55-64
- 65-74
- 75-84
- 85-114

Incidence rate per 100,000 persons
## Software performance: Incidence Prevalence

<table>
<thead>
<tr>
<th>Task</th>
<th>CPRD AURUM (n=39,999,011)</th>
<th>CPRD GOLD (n=15,662,217)</th>
<th>SIDIAP (n=8,265,343)</th>
<th>IPCI (n=2,612,850)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generating denominator (8 cohorts)</td>
<td>19 mins</td>
<td>8 mins</td>
<td>3 mins</td>
<td>1 min</td>
</tr>
<tr>
<td>Yearly period prevalence</td>
<td>11 mins</td>
<td>5 mins</td>
<td>5 mins</td>
<td>1 min</td>
</tr>
<tr>
<td>Monthly period prevalence</td>
<td>17 mins</td>
<td>6 mins</td>
<td>8 mins</td>
<td>2 mins</td>
</tr>
<tr>
<td>Yearly incidence</td>
<td>8 mins</td>
<td>3 mins</td>
<td>4 mins</td>
<td>1 min</td>
</tr>
<tr>
<td>Monthly incidence</td>
<td>13 mins</td>
<td>5 mins</td>
<td>7 mins</td>
<td>1 min</td>
</tr>
</tbody>
</table>
Overview of development activities

Example use of DARWIN EU® R packages
CDMConnector and PatientProfiles

Create a CDM reference object from a database connection

Usage

```r
# CDMConnector

cdm_from_con(
  con,
  cdm_schema = NULL,
  write_schema = NULL,
  cohort_tables = NULL,
  cdm_version = "5.3",
  cdm_name = NULL
)

cdm_from_rowCon(
  con,
  cdmSchema = NULL,
  writeSchema = NULL,
  cohortTables = NULL,
  cdmVersion = "5.3",
  cdmName = NULL
)
```

Compute demographic characteristics at a certain date

Usage

```r
addDemographics(
  cdm,
  IndexDate = "cohort_start_date",
  sex = TRUE,
  ageName = "age",
  ageDefaultMonth = 1,
  ageDefaultDay = 1,
  ageImproveDay = FALSE,
  ageImproveMonth = FALSE,
  ageGroup = NULL,
  sex = TRUE,
  sexName = "sex",
  priorObservation = TRUE,
  priorObservationName = "prior_observation",
  futureObservation = TRUE,
  futureObservationName = "future_observation",
  tablePrefix = NULL
)
```
### CodelistGenerator

**Vocabulary based code list**

Get descendant codes for drug ingredients

#### Usage

```java
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 descendant 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**

Generate candidate codelist for the OMOP CDM

#### Usage

```java
getCandidateCodes(
    cdm,
    keywords,
    exclude = NULL,
    domain = "Condition",
    conceptClassId = NULL,
    doseForm = NULL,
    vocabularyId = NULL,
    standardConcept = "Standard",
    exactMatch = FALSE,
    searchInSnomed = FALSE,
    searchInIsSynonyms = FALSE,
    searchInTsSynonyms = FALSE,
    searchInNonStandard = FALSE,
    includeSequences = FALSE,
    includeDescendants = TRUE,
    includeAncestor = FALSE,
    fuzzyMatch = FALSE,
    maxDistanceCost = 0.5,
    vorScore = FALSE
)
```
DrugExposureDiagnostics and DrugUtilisation

Execute all checks on Drug Exposure.

Usage

```r
executeChecks(
  cdm,
  ingredients = c(123515),
  subsetToFctoid = NULL,
  checks = c("missing", "exposureDuration", "type", "route", "sourceConcept",
             "daysSupply", "verbatimedate", "dose", "sig", "quantity", "histogram"),
  minCellCount = 5,
  sample = 1e+06,
  tablePrefix = NULL,
  earliestStartDate = "2010-01-01",
  verbose = FALSE
)
```

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

Usage

```r
summariseDrugUse(
  cohort,
  cdm,
  strata = list(),
  drugUseVariables = drugUseColumns(cohort),
  drugUseEstimates = c("median", "25", "75"),
  minCellCount = 5
)
```
IncidencePrevalence

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

Estimate period prevalence

Usage

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

Executive Board

Director

Advisory Boards
- Scientific (SAB)
- Ethical (EAB)
- Data Source Prioritisation Committee (DSPC)
- General Assembly (GA)

Development
- QA/QC Procedures
- Vocabulary Extension
- CDM Development
- Methods Research
- Analytical Tools
- Dashboarding
- Training Material
- Protocol Templates

Operations
- Study execution
- Network management

Technology
- Infrastructure
- Security
- Collaboration Environment
- Analytics Platform
- Source Control Repository
- Website
- Service Desk
- Training Platform

Management
- Secretarial
- Legal / Contracting
- Finance
- COI management
- Risk management
- Reporting
- Recruitment
- Outreach
What analyses and studies will DARWIN EU® deliver?

<table>
<thead>
<tr>
<th>Category of observational analyses and studies</th>
<th>Description</th>
</tr>
</thead>
</table>
| 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

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phases</td>
<td>Phase I</td>
<td>Phase II</td>
<td>Phase III</td>
<td>Option 1</td>
</tr>
<tr>
<td>Routine Repeated analysis</td>
<td>At least 1 study</td>
<td>6</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>Off the shelf studies</td>
<td>At least 2 studies</td>
<td>6</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>Complex Studies</td>
<td>1</td>
<td>4</td>
<td>12</td>
<td>24</td>
</tr>
<tr>
<td>Very Complex Studies</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
## Expected number of studies

<table>
<thead>
<tr>
<th>Phases</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
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</thead>
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<td>Phases</td>
<td>Phase I</td>
<td>Phase II</td>
<td>Phase III</td>
<td>Option 1</td>
<td>Option 2</td>
</tr>
<tr>
<td>Routine Repeated analysis</td>
<td>At least 1 study</td>
<td>-</td>
<td>30</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Off the shelf studies</td>
<td>At least 2 studies</td>
<td>6 + 8</td>
<td>30</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>Complex Studies</td>
<td>1</td>
<td>4</td>
<td>12</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Very Complex Studies</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
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
<table>
<thead>
<tr>
<th>Study Title</th>
<th>Committees</th>
<th>Study Type</th>
<th>Type of analysis</th>
<th>Data bases</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>DARWIN EU® - <strong>Prevalence of rare blood cancers in Europe</strong></td>
<td>COMP</td>
<td>OTS</td>
<td>Disease Epidemiology</td>
<td>IPCI (NI) SIDIAP (Spain) CPRD Gold (UK) IQVIA LPD (Be) IQVIA DA (Ge)</td>
<td>Completed</td>
</tr>
<tr>
<td>DARWIN EU® - <strong>Drug utilisation of valproate-containing medicinal products in women of childbearing potential</strong></td>
<td>Following safety referral</td>
<td>OTS</td>
<td>Drug Utilisation Study</td>
<td>IPCI (NI) SIDIAP (Spain) CPRD Gold (UK) IQVIA LPD (Be) IQVIA DA (Ge) HDSF (Fi)</td>
<td>Completed</td>
</tr>
<tr>
<td>DARWIN EU® - <strong>DUS of Antibiotics in the ‘Watch’ category of the WHO AWARe classification of antibiotics for evaluation and monitoring of use</strong></td>
<td>PRAC/CHMP</td>
<td>OTS</td>
<td>Drug Utilisation Study</td>
<td>IPCI (NI) SIDIAP (Spain) CPRD Gold (UK) IQVIA DA (Ge) CHUBX (France) SIDIAP (Spain) IMASIS (Spain) IQVIA DA (Ge) CPRD Gold (UK)</td>
<td>Completed</td>
</tr>
<tr>
<td>DARWIN EU® - <strong>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.</strong></td>
<td>CHMP</td>
<td>Complex (complex phenotype)</td>
<td>Disease Epidemiology</td>
<td>IPCI (NI) SIDIAP (Spain) IMASIS (Spain) CPRD Gold (UK) Estonian Biobank</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Study Title</td>
<td>Committees</td>
<td>Study Type</td>
<td>Type of analysis</td>
<td>Data bases</td>
<td>Status</td>
</tr>
<tr>
<td>-------------</td>
<td>------------</td>
<td>------------</td>
<td>------------------</td>
<td>------------</td>
<td>--------</td>
</tr>
<tr>
<td>DARWIN EU® - <strong>Multiple myeloma</strong>: patient characterisation, treatments and survival in the period 2012-2022</td>
<td>HTA/Payers</td>
<td>OTS</td>
<td>Disease Epidemiology and Treatment Pattern analysis</td>
<td>IQVIA DA (Ge) SIDIAP (Spain) IMASIS (Spain) Estonian Biobank ACI Varha (Fi) CHUBX (France) IKNL (NI)</td>
<td>Ongoing</td>
</tr>
<tr>
<td>DARWIN EU® <strong>Drug Utilisation Study of prescription opioids.</strong></td>
<td>PRAC</td>
<td>OTS</td>
<td>Drug Utilisation Study</td>
<td>Estonian Biobank IPCI (NI) SIDIAP (Spain) CHUBX (France) IQVIA LPD (Be) IQVIA DA (Ge) ACI Varha (Fi)</td>
<td>Ongoing</td>
</tr>
<tr>
<td>DARWIN EU® – <strong>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</strong></td>
<td>EC/EHDS</td>
<td>Complex</td>
<td>SIR</td>
<td>IPCI (NL) SIDIAP (Spain) IQVIA DA (Ge) Estonian Biobank CPRD GOLD (UK)</td>
<td>Ongoing</td>
</tr>
<tr>
<td>DARWIN EU® - Co-prescribing of endothelin receptor antagonists (ERAs) and phosphodiesterate-5 inhibitors (PDE-5is) in <strong>pulmonary arterial hypertension</strong> (PAH)</td>
<td>CHMP</td>
<td>OTS</td>
<td>Disease Epidemiology and Treatment Pattern analysis</td>
<td>CHUBX (France) CPRD GOLD (UK) Estonian Biobank IQVIA DA (Ge)</td>
<td>Ongoing</td>
</tr>
<tr>
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<tr>
<td>-------------</td>
<td>------------</td>
<td>------------</td>
<td>------------------</td>
<td>------------</td>
<td>--------</td>
</tr>
<tr>
<td>DARWIN EU® - Use of take-home naloxone for opioid overdose treatment</td>
<td>CHMP</td>
<td>OTS</td>
<td>Drug Utilisation Study</td>
<td>IQVIA DA (Ge) IQVIA DA (Be) CPRD Gold (UK) SIDIAP</td>
<td>Ongoing</td>
</tr>
<tr>
<td>DARWIN EU® DUS of medicines with prokinetic properties in children and adults diagnosed with gastroparesis</td>
<td>NCA</td>
<td>OTS</td>
<td>Drug Utilisation Study</td>
<td>IPCI (NI) CHUBX (France) SIDIAP (Spain) IMASIS (Spain) IQVIA DA (Ge) IQVIA LPD (Be) CPRD Gold (UK)</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
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<tr>
<td>Very Complex Studies</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>
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@idiapigol.org
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

Classified as public by the European Medicines Agency
● 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
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

www.sidiap.org

SIDIAP OMOP-CDM

● EMIF (2015) → EHDEN (2019 and 2020)

● Evidence generating in local and network studies
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 in **adolescent and adult patients with severe asthma**

SIDIAP has also participated in many **feasibility assessments**
Challenges as DPs

- **Time**
  - For approvals
  - Study execution
  - Review results

- **Technical issues**
- **Funding**
Opportunities and Benefits for DPs

- Collaborations
- Development of standardized analytical tools
- Accelerate research
- Broader public health impact
- Visibility
- Support regulatory decision-making
- Improve data quality
- Training
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
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
Acknowledgements
Thank you!

Talita Duarte-Salles
Real World Epidemiology Research Group
IDIAPJGol, Barcelona-Spain

Twitter: TDuarte_Salles
Email: tduarte@idiapjgol.org
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

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Introduction of the DARWIN EU® Coordination Centre

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**
Clinical Practice Research Datalink (CPRD GOLD)

**Belgium**
IQVIA Belgium Longitudinal Patient Data

**France**
Bordeaux University Hospital

**Spain**
IDIAPJGol
Parc Salut Mar Barcelona, Hospital del Mar (IMIM)

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

**Estonia**
University of Tartu (Biobank)

**Netherlands**
Integrated Primary Care Information

**Germany**
IQVIA Germany Disease Analyser

**Netherlands Comprehensive Cancer Organisation**
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**
<table>
<thead>
<tr>
<th>STUDY TYPE</th>
<th>STUDY CLASSIFICATION</th>
<th>TYPE OF ANALYSIS</th>
</tr>
</thead>
</table>
| 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 – 15\(^{th}\) July*

*Approval Feasibility – 26\(^{th}\) July*

*Protocol Submission – 1\(^{st}\) September*

*Protocol Approval - 24\(^{th}\) October*

*KO meeting - 17\(^{th}\) November*

*Study package execution – November - January*

*Final Results – 6\(^{th}\) January*

*Final Report – 17\(^{th}\) 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

<table>
<thead>
<tr>
<th>Database</th>
<th>CPRD GOLD</th>
<th>IPCI</th>
<th>SIDIAP</th>
<th>IQVIA Belgium</th>
<th>IQVIA Germany</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number subjects</td>
<td>6416</td>
<td>1241</td>
<td>10398</td>
<td>945</td>
<td>4002</td>
</tr>
<tr>
<td>Sex, N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6416</td>
<td>1241</td>
<td>10398</td>
<td>945</td>
<td>4002</td>
</tr>
<tr>
<td></td>
<td>(100%)</td>
<td>(100%)</td>
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<td>Age</td>
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<td>40</td>
<td>41</td>
<td>43</td>
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<td>[p25 - p75]</td>
<td>[29 - 47]</td>
<td>[32 - 49]</td>
<td>[30 - 48]</td>
<td>[31 - 49]</td>
<td>[31 - 50]</td>
</tr>
</tbody>
</table>
## Results Patient Level

<table>
<thead>
<tr>
<th>Database</th>
<th>Anxiety</th>
<th>Asthma</th>
<th>Chronic Kidney Disease</th>
<th>Chronic Liver Disease</th>
<th>COPD</th>
<th>Dementia</th>
<th>Depressive disorder</th>
<th>Diabetes</th>
<th>GERD</th>
<th>Heart failure</th>
<th>HIV</th>
<th>Hypertension</th>
<th>Hypothyroidism</th>
<th>Infertility</th>
<th>Inflammatory Bowel Disease</th>
<th>Malignant neoplastic disease</th>
<th>Myocardial Infarction</th>
<th>Osteoporosis</th>
<th>Pneumonia</th>
<th>Rheumatoid Arthritis</th>
<th>Stroke</th>
<th>Venous Thromboembolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDR GOLD</td>
<td>2260 (35.2%)</td>
<td>1017 (15.9%)</td>
<td>146 (2.3%)</td>
<td>20 (0.3%)</td>
<td>82 (1.3%)</td>
<td>23 (0.4%)</td>
<td>2460 (38.3%)</td>
<td>252 (3.9%)</td>
<td>174 (2.7%)</td>
<td>13 (0.2%)</td>
<td>6 (0.1%)</td>
<td>333 (5.2%)</td>
<td>366 (5.7%)</td>
<td>63 (1%)</td>
<td>40 (0.6%)</td>
<td>199 (3.1%)</td>
<td>10 (0.2%)</td>
<td>44 (0.7%)</td>
<td>89 (1.4%)</td>
<td>25 (0.4%)</td>
<td>81 (1.3%)</td>
<td>88 (1.4%)</td>
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<tr>
<td>IPCL</td>
<td>392 (31.6%)</td>
<td>102 (6.2%)</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td>21 (1.7%)</td>
<td>&lt;5</td>
<td>194 (15.6%)</td>
<td>57 (4.6%)</td>
<td>19 (1.5%)</td>
<td>6 (0.5%)</td>
<td>NA</td>
<td>96 (7.7%)</td>
<td>56 (4.5%)</td>
<td>NA</td>
<td>6 (0.5%)</td>
<td>59 (4.8%)</td>
<td>&lt;5</td>
<td>7 (0.5%)</td>
<td>6 (0.5%)</td>
<td>9 (0.7%)</td>
<td>37 (3%)</td>
<td>25 (2%)</td>
</tr>
<tr>
<td>SIDIAP</td>
<td>4099 (39.4%)</td>
<td>343 (9.2%)</td>
<td>128 (1.2%)</td>
<td>103 (1%)</td>
<td>96 (0.9%)</td>
<td>57 (0.4%)</td>
<td>2610 (25.1%)</td>
<td>366 (3.5%)</td>
<td>262 (2.5%)</td>
<td>18 (0.2%)</td>
<td>53 (0.5%)</td>
<td>601 (5.8%)</td>
<td>896 (8.6%)</td>
<td>144 (1.4%)</td>
<td>36 (0.3%)</td>
<td>332 (3.2%)</td>
<td>16 (0.2%)</td>
<td>84 (0.8%)</td>
<td>369 (3.5%)</td>
<td>24 (0.2%)</td>
<td>142 (1.4%)</td>
<td>59 (0.6%)</td>
</tr>
<tr>
<td>IQVIA Belgium LPD</td>
<td>307 (32.5%)</td>
<td>143 (15.1%)</td>
<td>&lt;5</td>
<td>NA</td>
<td>113 (12%)</td>
<td>&lt;5</td>
<td>414 (43.8%)</td>
<td>59 (6.2%)</td>
<td>172 (18.2%)</td>
<td>&lt;5</td>
<td>NA</td>
<td>166 (17.6%)</td>
<td>104 (11%)</td>
<td>&lt;5</td>
<td>7 (0.7%)</td>
<td>27 (2.9%)</td>
<td>&lt;5</td>
<td>22 (2.3%)</td>
<td>29 (3.1%)</td>
<td>5 (0.5%)</td>
<td>14 (1.5%)</td>
<td>28 (3%)</td>
</tr>
<tr>
<td>IQVIA Germany DA</td>
<td>806 (20.1%)</td>
<td>254 (5.6%)</td>
<td>63 (1.6%)</td>
<td>16 (0.4%)</td>
<td>135 (3.4%)</td>
<td>64 (1.6%)</td>
<td>1420 (35.5%)</td>
<td>208 (5.2%)</td>
<td>84 (2.1%)</td>
<td>43 (1.1%)</td>
<td>5 (0.1%)</td>
<td>431 (7.8%)</td>
<td>313 (7.8%)</td>
<td>&lt;5</td>
<td>30 (0.7%)</td>
<td>137 (3.4%)</td>
<td>13 (0.3%)</td>
<td>32 (0.8%)</td>
<td>115 (2.9%)</td>
<td>32 (0.8%)</td>
<td>81 (2%)</td>
<td>65 (1.6%)</td>
</tr>
<tr>
<td>Database</td>
<td>PRD GOLD</td>
<td>IPCI</td>
<td>SIDIAP</td>
<td>IQVIA Belgium LPD</td>
<td>IQVIA Germany DA</td>
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<tr>
<td>Agents acting on Renin Angiotensin System</td>
<td>366 (5.7%)</td>
<td>132 (10.6%)</td>
<td>618 (5.9%)</td>
<td>59 (6.2%)</td>
<td>228 (5.7%)</td>
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<tr>
<td>Antibacterials (systemic)</td>
<td>3043 (47.4%)</td>
<td>395 (31.8%)</td>
<td>3668 (35.3%)</td>
<td>308 (32.6%)</td>
<td>441 (11%)</td>
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<tr>
<td>Antidepressants</td>
<td>3774 (58.8%)</td>
<td>381 (30.7%)</td>
<td>6243 (60%)</td>
<td>365 (38.6%)</td>
<td>1102 (27.5%)</td>
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<tr>
<td>Antiinflammatory and Antirheumatic Agents</td>
<td>2233 (34.8%)</td>
<td>460 (37.1%)</td>
<td>5357 (51.5%)</td>
<td>368 (38.9%)</td>
<td>627 (15.7%)</td>
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<tr>
<td>Antineoplastic agents</td>
<td>&lt;5</td>
<td>18 (1.5%)</td>
<td>100 (1%)</td>
<td>11 (1.2%)</td>
<td>18 (0.4%)</td>
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<tr>
<td>Antithrombotics</td>
<td>448 (7%)</td>
<td>78 (6.3%)</td>
<td>263 (2.5%)</td>
<td>27 (2.9%)</td>
<td>101 (2.5%)</td>
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<tr>
<td>Beta Blocking Agents</td>
<td>1079 (16.8%)</td>
<td>242 (19.5%)</td>
<td>695 (6.7%)</td>
<td>167 (17.7%)</td>
<td>270 (6.7%)</td>
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<tr>
<td>Calcium Channel Blockers</td>
<td>220 (3.4%)</td>
<td>50 (4%)</td>
<td>219 (2.1%)</td>
<td>30 (3.2%)</td>
<td>86 (2.1%)</td>
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<tr>
<td>Drugs for Acid related disorder</td>
<td>1861 (29%)</td>
<td>382 (30.8%)</td>
<td>3519 (33.8%)</td>
<td>258 (27.3%)</td>
<td>507 (12.7%)</td>
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<tr>
<td>Drugs for obstructive airway diseases</td>
<td>1242 (19.4%)</td>
<td>315 (25.4%)</td>
<td>1858 (17.9%)</td>
<td>207 (21.9%)</td>
<td>197 (4.9%)</td>
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<tr>
<td>Drugs used in diabetes</td>
<td>262 (4.1%)</td>
<td>45 (3.6%)</td>
<td>283 (2.7%)</td>
<td>47 (5%)</td>
<td>102 (2.5%)</td>
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<tr>
<td>Hormonal contraceptives (systemic)</td>
<td>1291 (20.1%)</td>
<td>136 (11%)</td>
<td>415 (4%)</td>
<td>150 (15.9%)</td>
<td>59 (1.5%)</td>
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<tr>
<td>Immunosuppressants</td>
<td>48 (0.7%)</td>
<td>12 (1%)</td>
<td>76 (0.7%)</td>
<td>&lt;5</td>
<td>18 (0.4%)</td>
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<tr>
<td>Lipid modifying agents</td>
<td>414 (6.5%)</td>
<td>82 (6.6%)</td>
<td>736 (7.1%)</td>
<td>63 (6.7%)</td>
<td>97 (2.4%)</td>
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</tbody>
</table>
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/
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 Ramirez-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

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

- 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

<table>
<thead>
<tr>
<th>CPRD GOLD</th>
<th>IPCI</th>
<th>SIDIAP</th>
<th>IMASIS</th>
<th>CHUBX</th>
<th>IQVIA Germany</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>Antibiotic</td>
<td>Incidence</td>
<td>Antibiotic</td>
<td>Incidence</td>
<td>Antibiotic</td>
</tr>
<tr>
<td>3,577 (3,571; 3,583)</td>
<td>Clarithromycin</td>
<td>1,862 (1,853; 1,870)</td>
<td>Azithromycin</td>
<td>3,165 (3,160; 3,169)</td>
<td>Fosfomycin</td>
</tr>
<tr>
<td>2,073 (2,068; 2,078)</td>
<td>Erythromycin</td>
<td>1,462 (1,455; 1,470)</td>
<td>Ciprofloxacin</td>
<td>2,567 (2,563; 2,571)</td>
<td>Azithromycin</td>
</tr>
<tr>
<td>1,023 (1,020; 1,026)</td>
<td>Ciprofloxacin</td>
<td>1,190 (1,184; 1,197)</td>
<td>Fosfomycin</td>
<td>2,098 (2,094; 2,101)</td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>868 (865; 871)</td>
<td>Lymecycline</td>
<td>828 (822; 834)</td>
<td>Clarithromycin</td>
<td>1,485 (1,482; 1,488)</td>
<td>Levofloxacin</td>
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<tr>
<td>518 (515; 520)</td>
<td>Oxytetracycline</td>
<td>517 (512; 521)</td>
<td>Pheneticillin</td>
<td>959 (956; 961)</td>
<td>Cefuroxime</td>
</tr>
</tbody>
</table>

**Number of new users/100,000 PY**
Results (3) – Incidence of ciprofloxacin & ceftriaxone use
### Results (4) – Duration of antibiotic use

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>CPRD GOLD Duration (median, p25-p75)</th>
<th>IPCI Duration (median, p25-p75)</th>
<th>SIDIAP Duration (median, p25-p75)</th>
<th>IMASIS Duration (median, p25-p75)</th>
<th>CHUBX Duration (median, p25-p75)</th>
<th>IQVIA Germany Duration (median, p25-p75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>3 (1 - 3)</td>
<td>4 (4 - 4)</td>
<td>3 (3 - 3)</td>
<td>3 (3 - 3)</td>
<td>1 (1 - 1)</td>
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<tr>
<td>Cefaclor</td>
<td>7 (5 - 7)</td>
<td>9 (8 - 9)</td>
<td>7 (6 - 7)</td>
<td>5 (1 - 7)</td>
<td>1 (1 - 1)</td>
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<tr>
<td>Ceftriaxone</td>
<td>7 (4 - 7)</td>
<td>5 (2 - 5)</td>
<td>30 (1 - 30)</td>
<td>7 (2 - 10)</td>
<td>2 (1 - 2)</td>
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<tr>
<td>Cefuroxime</td>
<td>7 (7 - 7)</td>
<td>8 (6 - 8)</td>
<td>7 (7 - 7)</td>
<td>6 (6 - 7)</td>
<td>1 (1 - 1)</td>
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</tr>
<tr>
<td>Ciprofloxacin</td>
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<td>7 (7 - 7)</td>
<td>5 (5 - 10)</td>
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<tr>
<td>Clarithromycin</td>
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<td>8 (8 - 8)</td>
<td>7 (7 - 7)</td>
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<tr>
<td>Erythromycin</td>
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<td>9 (8 - 9)</td>
<td>7 (7 - 7)</td>
<td>30 (8 - 30)</td>
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</tr>
<tr>
<td>Fosfomycin</td>
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<td>3 (3 - 3)</td>
<td>1 (1 - 1)</td>
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<td>1 (1 - 1)</td>
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<tr>
<td>Levofoxacin</td>
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<td>8 (8 - 8)</td>
<td>14 (7 - 14)</td>
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<td>Lymecycline</td>
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<td>Ofloxacin</td>
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<td>14 (7 - 14)</td>
<td>30 (5 - 30)</td>
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<tr>
<td>Oxytetracycline</td>
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<td>8 (4 - 8)</td>
<td>17 (12 - 17)</td>
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<td>Pheneticillin</td>
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<tr>
<td>Piperacillin_tazobactam</td>
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<td>37 (18 - 37)</td>
<td>30 (30 - 30)</td>
<td>6 (3 - 6)</td>
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<td>Vancomycin</td>
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<td>11 (6 - 11)</td>
<td>10 (7 - 10)</td>
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<td>4 (2 - 4)</td>
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<td>Azithromycin</td>
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<td>4 (4 - 4)</td>
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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!

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.

<table>
<thead>
<tr>
<th>Workgroup</th>
<th>2023 OKRs</th>
<th>Current Participants</th>
<th>2023 OKRs</th>
<th>Lead:</th>
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<tbody>
<tr>
<td>Asia-Pacific (APAC)</td>
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<td>207</td>
<td></td>
<td>Mu Van Zandt</td>
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<tr>
<td>ATLAS/WebAPI</td>
<td></td>
<td>203</td>
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<td>Anthony Sera</td>
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<td>Clinical Trials</td>
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<td></td>
<td>Mike Hamidi, Lin Zhen</td>
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<td>Common Data Model</td>
<td></td>
<td>694</td>
<td></td>
<td>Clair Blacketer</td>
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<td>CDM Vocabulary Subgroup</td>
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<td>Michael Kurth</td>
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<td>Data Network Quality</td>
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<td>Clair Blacketer</td>
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<td>Dentistry</td>
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<td>Robert Kose</td>
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<td>Early-Stage Researchers</td>
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<td>Fazah Ahmed, Ross Williams</td>
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</table>

There are 32 Workgroups!

July Community Calls

<table>
<thead>
<tr>
<th>Date</th>
<th>Topic</th>
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</thead>
<tbody>
<tr>
<td>July 4</td>
<td>No Meeting</td>
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<tr>
<td>July 11</td>
<td>European Symposium Review</td>
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<tr>
<td>July 18</td>
<td>Vulcan: An HL7 FHIR Accelerator Transforming Clinical &amp; Translational Research</td>
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<tr>
<td>July 25</td>
<td>Around The Asia-Pacific Region</td>
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</table>

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..
Join the OHDSI Band!
When you're down and troubled
And you need some love and care
Getting to the OHDSI Symposium this year was quite a ride for Patrick and Peter.
Thank You Erasmus MC Team!
We look forward to seeing you at the next OHDSI Symposium.

European OHDSI Symposium
July 3rd 2023 Rotterdam
Tutorials: July 1st and 2nd

“Full Steam Ahead!!”

Organised by:
Erasmus MC University Medical Center Rotterdam
Health Data Science