Use cases for development, optimisation and implementation of artificial intelligence methods for real world data analyses in regulatory decision-making and health technology assessment along the product lifecycle (Real4Reg)

First published: 29/06/2023
Last updated: 23/04/2024

Study | Ongoing

Administrative details

PURI
https://redirect.ema.europa.eu/resource/105545

EU PAS number
EUPAS105544

Study ID
105545

DARWIN EU® study
No

Study countries
Denmark
Finland
Germany
Portugal

Study description
The use of real world data (RWD) is established in regulatory processes such as safety monitoring, but evidentiary value for further use cases, especially in the pre-authorisation and evaluation phase of medicinal products, is rudimentary. Also, the use of RWD in post-authorisation steps is constrained by data variability and by challenges in analysing data from different settings and sources. Moreover, there are emerging opportunities in the use of artificial intelligence (AI), but there is a lack of knowledge on its appropriate application to heterogeneous RWD sources to increase evidentiary value in the regulatory decision-making and health technology assessment (HTA) context. Thus, the development of new and optimised AI-supported methodologies for RWD analyses is essential. In addition, the four use cases to be investigated in this study contain phenotype-specific open questions of high regulatory interest.

Study status
Ongoing

Research institution and networks

Institutions

Pharmacoepidemiology Research, Federal Institute for Drugs and Medical Devices (BfArM)

Germany
First published: 02/06/2023
Last updated 23/04/2024

Institution | Regulatory Authority | ENCePP partner

School of Pharmacy/Kuopio Research Center of Geriatric Care, University of Eastern Finland (Gerho)

Finland
First published: 20/12/2017
Last updated 13/12/2018

Institution | Educational Institution | ENCePP partner

Aarhus University & Aarhus University Hospital DEPARTMENT OF CLINICAL EPIDEMIOLOGY

Denmark
First published: 20/07/2021
Last updated
02/04/2024

Institution | Educational Institution | ENCePP partner

Data Analytic Center (DAC), Danish Medicine Agency

Denmark
First published: 17/04/2023
Last updated
17/04/2023

Institution | EU Institution/Body/Agency | ENCePP partner

National Authority of Medicines and Health Products, I.P. (Infarmed) Lisboa, Portugal; Fraunhofer Society, Fraunhofer Institute for Algorithms and Scientific Computing (SCAI), Research Group AI and Data Science Sankt Augustin, Germany; IT Centre for Science (CSC) Espoo, Finland; German Centre for Neurodegenerative Diseases (DZNE), Research Group Pharmacoepidemiology Bonn, Germany; European Organization for Professionals and Patients with ALS (EUpALS) Leuven, Belgium; European Institute of Women's Health (EIWH) Dublin, Ireland.

Networks

Real4Reg

Belgium
Denmark
Finland
Germany
Ireland
Portugal

First published: 01/02/2024
Last updated 08/05/2024

Network

Contact details

Study institution contact
Joana Fernandes
Study contact

real4reg@infarmed.pt

Primary lead investigator
Britta Haenisch
Primary lead investigator

ORCID number:
0000-0002-4828-6058

Study timelines

Date when funding contract was signed
Planned:
05/11/2022
Actual:
11/11/2022

Study start date
Planned:
01/09/2023
Actual:
11/09/2023

Date of final study report
Planned:

31/12/2026

Sources of funding

- Other

More details on funding

HORIZON Europe (European Union, European Comission)

Study protocol

Study_protocols_Real4Reg_2023_June_29.pdf(1.35 MB)

Study_protocols_Real4Reg_2024_April_11.pdf(1.48 MB)

Regulatory

Was the study required by a regulatory body?
No

Is the study required by a Risk Management Plan (RMP)?
Not applicable

Methodological aspects

Study type

Study type list

Study topic:
Disease /health condition
Human medicinal product

Study type:
Non-interventional study

Scope of the study:
Assessment of risk minimisation measure implementation or effectiveness
Disease epidemiology
Drug utilisation
Effectiveness study (incl. comparative)
Method development or testing
Safety study (incl. comparative)

Data collection methods:
Secondary data collection

Study design:
See study protocols.

Main study objective:
The study develops tools & technologies for the effective analyses of real-world data (RWD) in regulatory decision-making & HTA based on four highly relevant uses cases along the pre-& post-authorisation steps of the product life cycle. Portugal, Finland, Denmark, & Germany provide routine care RWD.

Study Design

Non-interventional study design
Cohort
Other

Non-interventional study design, other
External control arm study

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code
(A10BH) Dipeptidyl peptidase 4 (DPP-4) inhibitors
(A10BK) Sodium-glucose co-transporter 2 (SGLT2) inhibitors
(J01) ANTIBACTERIALS FOR SYSTEMIC USE
(J01MA) Fluoroquinolones

Medical condition to be studied
Type 2 diabetes mellitus
Amyotrophic lateral sclerosis
Breast neoplasm

Additional medical condition(s)
Cardiac arrythmias, Peripheral neuropathies, Drug-induced liver injury, Cardiac failure, Sudden cardiac death

Population studied

Short description of the study population
The source population come from health registers for the entire adult population (?18 years) in Denmark, Finland, and Portugal and from claims records of public health insurance providers in Germany (~90% of population). Populations studied vary by use case, see settings below.

Age groups
Adults (18 to < 46 years)
Adults (46 to < 65 years)
Adults (65 to < 75 years)
Adults (75 to < 85 years)
Adults (85 years and over)

Estimated number of subjects
88000000

Study design details

Setting
Adult population (?18 years unless otherwise specified).
Inpatient and outpatient data is used.

Setting varies by use case, in short:
1&2: a) persons diagnosed with incident primary breast cancer and external controls,
b) persons diagnosed with incident ALS and external controls,
3. persons with prescriptions of oral antibiotics,
4. persons with prescriptions of noninsulinic antidiabetes drugs (?40 years).

Study period:
for use cases 1&2: 2000/2005/2008*-2021;
for use case 3: 2010-2021*;
for use case 4: 2012-2021*.

*depending on data availability

Comparators
Use case 3: fluoroquinolones compared to active comparators
Use case 4: SGLT-2 inhibitors compared to active comparators

Outcomes
For details, see protocols.

Use case 1&2: incidence, prevalence, survival time, mortality; further outcomes see protocol;

Use case 3: number of prescriptions, trends in user characteristics, sudden cardiac death or cardiac arrhythmia, sudden cardiac death, aortic aneurysm and dissection, acute toxic liver disease, polyneuropathy;

Use case 4: proportion of SGLT-2 inhibitor prescription/non-insulin antidiabetic prescriptions, change in user characteristics, hospital admission, heart failure diagnosis, mortality.

Data analysis plan
* Define a simplified common data model based on OMOP to harmonise metadata

Use Case (UC) 1

* Determine the population as well as rates of occurrence and outcome using the STROBE standards (Strengthening the Reporting of Observational studies in Epidemiology).

* Examine heterogeneity within the dataset, including coding practices in the four partners, representativeness etc.

UC 2

* Develop a workflow to subset and display RWD by user definable inclusion/exclusion criteria; workflow allows to display summary statistics and disease trajectories of selected patients.
* Construct synthetic and external control arms for RWD ALS patients (based on data from the ProACT database: https://ncri1.partners.org/ProACT) by implementing different propensity score matching algorithms from the literature
* Explore, whether one of the RCTs contained in ProACT can be emulated using RWD, depending on availability of treatments in data

UCs 3 and 4

* Drug utilisation study: description of outcomes:
UC 3: proportion of fluorquinolone (FQ) and comparison antibiotics prescriptions out of all oral antibiotic prescriptions, change in user characteristics;
UC 4: proportion of SGLT-2 inhibitors users and DPP-4 inhibitors users out of all non-insulin antidiabetic drug users, change in user characteristics

* Adverse drug reaction study concerning FQ use (UC 3) and effectiveness analysis concerning SGLT-2 inhibitor use (UC4):

· Use active comparator new user (ACNU) design,

· Derive propensity scores for ACNU design derived from pre-specified covariates using logistic regression,

· Fit IPT-weighted Cox regression (if assumptions are met) for the entire follow-up

· Outcomes:

- UC3: Sudden cardiac death and cardiac arrhythmia, aortic aneurysm and dissection, acute toxic liver diseases (drug-induced liver injury), polyneuropathy (drug-induced peripheral polyneuropathy)

- UC4: heart failure diagnosis, all-cause and cause-specific hospital admissions and mortality.

Data management

ENCePP Seal

This study has been awarded the ENCePP seal

Conflicts of interest of investigators
Declarations_of_Interest_Real4Reg.pdf(3 MB)

Composition of steering group and observers
WP leaders R4R.pdf(99.94 KB)

Signed code of conduct
ENCePPCoCAnnex3_DeclarationofcompliancewiththeENCePPCodeofConduct_Real4Reg.pdf (411.29 KB)

Signed code of conduct checklist
Checklist_Code_of_Conduct_Real4Reg.pdf(2.64 MB)

Signed checklist for study protocols
Checklist_study_protocols_Real4Reg_spring_2024.pdf(1.52 MB)

Data sources

Data source(s)
Danish registries (access/analysis)

Data source(s), other
- Registo Oncológico Nacional (RON) - Portugal;
- Individual-level data collected from the Finnish national healthcare, mortality and population registers and censuses - Finland;
- Health Data Lab - Germany.

Data sources (types)
Administrative data (e.g. claims)
Disease registry
Drug dispensing/prescription data
Electronic healthcare records (EHR)
Population registry

Use of a Common Data Model (CDM)

CDM mapping
Yes

CDM Mappings

CDM name
OMOP

CDM website
https://www.ohdsi.org/Data-standardization/

Data quality specifications

Check conformance
Unknown

Check completeness
Unknown

Check stability
Unknown

Check logical consistency
Unknown

Data characterisation

Data characterisation conducted
Unknown