ADEPT: The utilisation of antiseizure medications in pregnant women, other women of childbearing potential, and men: a multi-database study from 7 European countries

First published: 17/06/2024

Last updated: 02/09/2025

Study Ongoing

Administrative details

EU PAS number

EUPAS1000000212

Study ID

1000000212

DARWIN EU® study

No

Study countries

Finland

France

Italy
Netherlands
Norway
Spain
United Kingdom

Study description

This will be a drug utilisation study for antiseizure medications (ASMs) in pregnant women, other women of childbearing potential, and men using data from 9 electronic healthcare databases in 7 European countries. This main objective has the following sub-objectives:

1. To estimate the annual incidence and prevalence rate of ASM use in women (12-55 years old) and men (≥12 years old) of childbearing potential;
2. To describe treatment duration, discontinuation, and treatment switches of ASMs to other ASMs or alternative medications and polytherapy in women of childbearing potential and men;
3. To estimate pre-pregnancy ASM use, and initiation and continuous use of ASMs during pregnancy period;
4. To estimate pre-pregnancy, early and late discontinuation of ASMs, treatment switches to other ASMs or alternative medications and polytherapy among pregnant women;
5. To estimate dose changes of ASMs in women prior to and during pregnancy.

We will leverage data, human resources, expertise, methods, and infrastructures that are available in the EU PE&PV, ConcepTION, and VAC4EU networks. For this specific purpose, we included 9 pre-selected data sources from 7 countries whose data quality will be characterised using available INSIGHT tools (level 1-2 quality checks) that operate on the ConcePTION CDM structure.

The source population comprises over 63 million persons. This study will be

conducted under the ENCePP code of conduct.
The protocol, reports, code lists, clinical definition forms and phenotype algorithms, results and programs will be made publicly available with digital object identifiers in line with FAIR principles.

Study status

Ongoing

Research institutions and networks

Institutions

Division of Pharmacoepidemiology & Clinical Pharmacology (PECP), Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University

Netherlands

First published: 01/03/2010

Last updated: 23/05/2024

Institution | **Educational Institution** | **ENCePP partner**

University Medical Center Utrecht (UMCU)

Netherlands

First published: 24/11/2021

Last updated: 22/02/2024

Institution | Educational Institution | Hospital/Clinic/Other health care facility | ENCePP partner

Toulouse University Hospital

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Finnish Institute for Health and Welfare (THL)

Finland

First published: 01/02/2024

Last updated: 01/02/2024

Institution | Educational Institution | Laboratory/Research/Testing facility

Health Services Research and Pharmacoepidemiology Unit (HSRP Unit) FISABIO

Spain

First published: 30/11/2023

Last updated: 30/11/2023

Institution | Other | ENCePP partner

Pharmacoepidemiology and Drug Safety Research Group (PharmaSafe), University of Oslo

Norway

First published: 19/10/2016

Last updated: 06/11/2025

Institution | Educational Institution | ENCePP partner

Clinical Pharmacology, Vall d'Hebron Institut de Recerca (VHIR)

Spain

First published: 18/05/2021

Last updated: 20/05/2021

Institution | Outdated | Hospital/Clinic/Other health care facility | ENCePP partner

Innovative Solutions for Medical Prediction And Big Data Integration In Real World Setting Srl (INSPIRE Srl), University Of Messina

Italy

First published: 15/11/2021

Last updated: 15/11/2021

Institution | Educational Institution | ENCePP partner

The PHARMO Institute for Drug Outcomes Research (PHARMO Institute)

Netherlands

First published: 07/01/2022

Last updated: 19/12/2025

Institution | Non-Pharmaceutical company | ENCePP partner

Fundació Institut Universitari per a la Recerca a l'Atenció Primària de Salut Jordi Gol i Gurina, IDIAPJGol

Spain

First published: 05/10/2012

Last updated: 23/05/2025

Institution | Educational Institution | Laboratory/Research/Testing facility | Not-for-profit | ENCePP partner

Agenzia regionale di sanità della Toscana (ARS Toscana)

Italy

First published: 01/02/2024

Last updated: 23/03/2026

Institution | EU Institution/Body/Agency | ENCePP partner

University of Manchester

United Kingdom

First published: 01/02/2024

Last updated: 01/02/2024

Institution | Educational Institution

Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency for Medicines and Medical Devices, AEMPS)

Spain

First published: 01/02/2024

Last updated: 04/09/2024

Institution | EU Institution/Body/Agency | Not-for-profit | Regulatory Authority | ENCePP partner

Teamit Institute

Spain

First published: 12/03/2024

Last updated: 12/03/2024

Institution | Other | ENCePP partner

Networks

EU Pharmacoepidemiology and Pharmacovigilance (PE&PV) Research Network

Netherlands

First published: 01/02/2024

Last updated: 24/09/2025

Network

Contact details

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Primary lead investigator

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Study timelines

Date when funding contract was signed

Planned: 29/02/2024

Actual: 18/04/2024

Study start date

Planned: 16/09/2024

Actual: 16/09/2024

Data analysis start date

Planned: 02/01/2025

Actual: 19/02/2025

Date of final study report

Planned: 16/09/2025

Sources of funding

- EMA

Study protocol

Study protocol_ADEPT Obj 1_D2_v3.0_clean version.pdf (909.06 KB)

Regulatory

Was the study required by a regulatory body?

Yes

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study type list

Study topic:

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Drug utilisation

Data collection methods:

Secondary use of data

Study design:

This will be a retrospective population-based cohort study.

Main study objective:

The main objective of this study is to describe the utilisation of antiseizure medications and related drugs (i.e., antiepileptics (ATC codes N03A), gabapentinoids (N02BF), and all benzodiazepines with antiepileptic properties) in pregnant women, other women of childbearing potential (12-55 years of age), and men (12 years and older).

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name, other

Methylphenobarbital, phenobarbital, primidone, barbexaclone, metharbital, ethotoin, phenytoin, amino(diphenylhydantoin) valeric acid, mephenytoin, fosphenytoin, paramethadione, trimethadione, ethadione, phensuximide, mesuximide, ethosuximide, combinations, clonazepam, carbamazepine, oxcarbazepine, rufinamide, valproic acid, valpromide, aminobutyric acid, vigabatrin, progabide, sultiame, phenacemide, lamotrigine, felbamate,

topiramate, pheneturide, levetiracetam, zonisamide, stiripentol, lacosamide, carisbamate, retigabine, perampanel, brivaracetam, cenobamate, fenfluramine, ganaxolone, beclamide, gabapentin, pregabalin, mirogabalin, eslicarbazepine, diazepam, lorazepam, clobazam, midazolam.

Study drug International non-proprietary name (INN) or common name

BRIVARACETAM

CARBAMAZEPINE

CENOBAMATE

FENFLURAMINE HYDROCHLORIDE

GABAPENTIN

LACOSAMIDE

LAMOTRIGINE

LEVETIRACETAM

PERAMPANEL

PHENOBARBITAL

PREGABALIN

RETIGABINE

RUFINAMIDE

STIRIPENTOL

TOPIRAMATE

VALPROIC ACID

VALPROMIDE

VIGABATRIN

ZONISAMIDE

Anatomical Therapeutic Chemical (ATC) code

(A08AA02) fenfluramine

fenfluramine

(N02BF) Gabapentinoids

Gabapentinoids

(N02BF01) gabapentin

gabapentin

(N02BF02) pregabalin

pregabalin

(N02BF03) mirogabalin

mirogabalin

(N03A) ANTIEPILEPTICS

ANTIEPILEPTICS

(N03AA01) methylphenobarbital

methylphenobarbital

(N03AA02) phenobarbital

phenobarbital

(N03AA03) primidone

primidone

(N03AA04) barbexaclone

barbexaclone

(N03AA30) metharbital

metharbital

(N03AB01) ethotoin

ethotoin

(N03AB02) phenytoin

phenytoin

(N03AB03) amino(diphenylhydantoin) valeric acid

amino(diphenylhydantoin) valeric acid

(N03AB04) mephenytoin

mephenytoin

(N03AB05) fosphenytoin

fosphenytoin

(N03AC01) paramethadione

paramethadione

(N03AC02) trimethadione

trimethadione

(N03AC03) ethadione

ethadione

(N03AD01) ethosuximide

ethosuximide

(N03AD02) phensuximide

phensuximide

(N03AD03) mesuximide

mesuximide

(N03AD51) ethosuximide, combinations

ethosuximide, combinations

(N03AE01) clonazepam

clonazepam

(N03AF01) carbamazepine

carbamazepine

(N03AF02) oxcarbazepine

oxcarbazepine

(N03AF03) rufinamide

rufinamide

(N03AG01) valproic acid

valproic acid

(N03AG02) valpromide

valpromide

(N03AG03) aminobutyric acid

aminobutyric acid

(N03AG04) vigabatrin

vigabatrin

(N03AG05) progabide

progabide
(N03AX03) sultiame
sultiame
(N03AX07) phenacemide
phenacemide
(N03AX09) lamotrigine
lamotrigine
(N03AX10) felbamate
felbamate
(N03AX11) topiramate
topiramate
(N03AX13) pheneturide
pheneturide
(N03AX14) levetiracetam
levetiracetam
(N03AX15) zonisamide
zonisamide
(N03AX17) stiripentol
stiripentol
(N03AX18) lacosamide
lacosamide
(N03AX19) carisbamate
carisbamate
(N03AX21) retigabine
retigabine
(N03AX22) perampanel
perampanel
(N03AX23) brivaracetam
brivaracetam
(N03AX25) cenobamate

cenobamate

(N03AX26) fenfluramine

fenfluramine

(N03AX27) ganaxolone

ganaxolone

(N03AX30) beclamide

beclamide

(N03AF04) eslicarbazepine

eslicarbazepine

(N05BA01) diazepam

diazepam

(N05BA06) lorazepam

lorazepam

(N05BA09) clobazam

clobazam

(N05CD08) midazolam

midazolam

Population studied

Short description of the study population

The source population comprises all persons from the 9 included data sources, BIFAP (ES), SIDIAP (ES), VID (ES), CPRD (UK), Finish registries (FI), EFEMERIS (FR), Norwegian registries (NO), PHARMO (NL), and Val Padana LHU (IT) between 01/01/2000 and latest availability.

From the source population, we will select a study cohort for each of the different study sub-objectives, as below:

For the denominators of rates in sub-objective 1, we use a ‘base population cohort’ of all individuals of childbearing age from the included data sources.

Here individuals must be at least 12 years old and have one year of available data (run-in period) in the data source. They will be followed up until the earliest of 56 years (for women only), death, moving out of database, last data available or last data extraction from data source.
For for numerators of rates in sub-objective 1, and the rest of outcome measures in sub-objective 2, we build an ‘ASM (new) user cohort’, which will be a sub-cohort from the base population cohort and comprises individuals therefrom who receive a new ASM prescription/dispensing. Patients will be followed from the start of an ASM prescription/dispensing, until the end of follow-up.
To address sub-objectives 3, 4 & 5, we will construct two cohorts. First, a ‘pregnancy cohort regardless of ASM’ will be built from the base population cohort by calculating start and end dates of pregnancies using the ConcePTION pregnancy algorithm.
Follow-up ends at the end date of the pregnancy, or the end of follow-up (as specified above), whichever is earliest.
Second, a 'pregnancy with ASM cohort' will be constructed from the pregnancies cohort with additional inclusion criteria of an ASM prescription/dispensing in 12 months prior to (3 months for THL and 2.5 months for EFEMERIS), or during pregnancy.
Follow-up starts here with the ASM prescription date, and ends at the end date of pregnancy, or end of follow-up (as specified above), whichever is earliest.
For the sub-objective 5, we use the same ‘pregnancy with ASM cohort' with additional inclusion criterion of availability of information on prescribed daily dose in the data sources.

Age groups

- Adolescents (12 to < 18 years)
- **Adult and elderly population (≥18 years)**

- Adults (18 to < 65 years)
  - Adults (18 to < 46 years)
  - Adults (46 to < 65 years)
- Elderly (≥ 65 years)
  - Adults (65 to < 75 years)
  - Adults (75 to < 85 years)
  - Adults (85 years and over)

Special population of interest

Pregnant women

Estimated number of subjects

63000000

Study design details

Setting

This study will be conducted using electronic health record data from 9 data sources in 7 countries in Europe comprising a total active population of 63 million persons.

This includes BIFAP (ES), SIDIAP (ES), VID (ES), CPRD (UK), Finish registries (FI), EFEMERIS (FR), Norwegian registries (NO), PHARMO (NL), and Val Padana LHU (IT).

The source population comprises all women of childbearing potential (12-55 years old) and men (≥12 years old). Data sources vary in the type of data banks that can be accessed.

Participation per sub-objective differs based on data availability for the specific objectives and the finite resources/timelines. Some Data Access Partners (DAPs) will re-use the data instance they use for ConcePTION (UiO, CHUT), whereas

other DAPs re-extract and use the requested populations (THL, AEMPS, SIDIAP, FISABIO, UU, PHARMO, INSPIRE).
More than 5 countries (i.e., 7) can participate in each sub-objective and more than 2 DAPs (i.e., 6 as UU, THL, CHUT, UiO, PHARMO, INSPIRE) have data completeness for 15 years.

Comparators

NA

Outcomes

The drug utilisation outcome measures that are covered here are: incidence and prevalence of ASM use among in women of childbearing potential and in men; treatment duration, discontinuation, and treatment switches to other ASMs or alternative medications and polytherapy in women of childbearing potential and men; pre-pregnancy ASM use, and initiation and continuous use of ASMs during pregnancy period; pre-pregnancy, early and late discontinuation of ASMs, treatment switches to other ASMs or alternative medications and polytherapy among pregnant women; and dose changes of ASMs in women prior to and during pregnancy.

Data analysis plan

In sub-objective 1, the annual incidence and prevalence rates of ASM use will be calculated in the total population among both women and men of childbearing age overall (N03A), by subgroup, and by individual generic substance, for each DAP, and stratified by sex, age group, calendar year.
In sub-objective 2, the duration of ASM use in the ASM user’s cohort, annual discontinuation rates of ASMs, use of alternative medications in prevalent users of ASMs, and annual incidence of treatment switches from an ASMs to another ASM or to an alternative medication will be estimated, for each DAP, and stratified by sex, age group, indication, comorbidities, and calendar year.

In sub-objective 3, the annual rates of pre-pregnancy ASM use, initiation of ASMs during pregnancy, and continuous use of ASMs during pregnancy for individual drugs, subgroups, and overall group, will be assessed among pregnant women.
In sub-objective 4, the annual rates of pre-pregnancy discontinuation of ASMs, early and late discontinuation during pregnancy, polytherapy, and switching from an ASM to another ASM or to an alternative medication will be estimated among pregnant women in all data sources, and stratified by indication.
In sub-objective 5, to report dosage change patterns before and during pregnancy in those pregnant women who use ASMs around pregnancy (including continuous ASM users, and late discontinuers of ASMs), we will calculate the mean weighted daily doses of ASMs, stratified as low (<0.5 DDD), mid (0.5-1.49 DDD), and high (>1.5 DDD) for each individual, and then will investigate descriptively and visualise (in bar chart, or Sankey diagram) the proportion of each stratum of the mean weighted daily doses of ASMs around pregnancy (i.e., from 3-months before the pregnancy to first, second and third trimesters), per each data source.

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s)

Clinical Practice Research Datalink (CPRD) GOLD

PHARMO Data Network

Norwegian Health Registers

EFEMERIS

BIFAP - Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público (Pharmacoepidemiological Research Database for Public Health Systems)

The Valencia Health System Integrated Database

The Information System for Research in Primary Care (SIDIAP)

Data source(s), other

Val Padana LHU.

Use of a Common Data Model (CDM)

CDM mapping

Yes

CDM Mappings

CDM name

ConcepTION CDM

CDM website

https://www.imi-conception.eu/

CDM release frequency

6 months

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Yes

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Yes

Data characterisation moment

after extract-transform-load to a common data model

after creation of study variables