

# ADEPT: feasibility of estimating the risk of adverse pregnancy, neonatal and child outcomes following either in utero ASM exposure through the mother, or peri-conceptional ASM exposure through the father

**First published:** 23/10/2024

**Last updated:** 01/10/2025

Study

Ongoing

## Administrative details

### EU PAS number

EUPAS1000000246

### Study ID

1000000246

### DARWIN EU® study

No

### Study countries

- Finland
- France
- Italy
- Netherlands
- Norway
- Spain
- United Kingdom

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## **Study description**

This study seeks to assess the feasibility of estimating the risk of adverse pregnancy, neonatal and child outcomes after periconceptional maternal or paternal exposure to antiseizure medications (ASM), or in-utero ASM exposure, using data from 9 electronic healthcare databases in Europe.

This main objective has the following sub-objectives:

- a. To estimate the availability of relevant information/characteristics for pregnant women, using the 15 different parameters that will inform the assessment of fitness for purpose.
- b. To estimate availability of relevant information/characteristics for men and linkage with pregnancies, using 9 different parameters that will inform the assessment of fitness for purpose.
- c. To estimate availability of relevant information/characteristics for neonates/children, using the following 17 parameters and comparing them between those that can and cannot be linked to mother and/or father where possible.
- d. To assess fitness for purpose to different types of studies of pre conceptional/prenatal exposure to antiepileptics and the development of adverse pregnancy and child outcomes.

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 48 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.

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### **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**

## Utrecht University

### 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**

**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)

Italy

**First published:** 01/02/2024

**Last updated:** 12/03/2024

**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

**Study institution contact**

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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

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**Study start date**

Planned: 18/11/2024

Actual: 18/11/2024

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**Data analysis start date**

Planned: 02/05/2025

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**Date of final study report**

Planned: 16/03/2026

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## Sources of funding

- EMA

## Study protocol

[D3\\_ROC20\\_ADEPT\\_Protocol Obj. 2\\_v4.0.pdf](#) (1.26 MB)

## Regulatory

**Was the study required by a regulatory body?**

Yes

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

Not applicable

## Methodological aspects

### Study type

#### Study type list

**Study topic:**

Human medicinal product

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**Study type:**

Non-interventional study

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**Scope of the study:**

Feasibility analysis

**Data collection methods:**

Secondary use of data

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**Study design:**

Study using four different retrospective cohorts.

**Main study objective:**

To assess the feasibility of estimating the risk of adverse pregnancy, neonatal and child outcomes after periconceptional maternal or paternal exposure to antiseizure medications (ASM), or in-utero ASM exposure, using data from 9 electronic healthcare databases in Europe.

## 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, phenosuximide, mesuximide, ethosuximide, combinations, clonazepam, carbamazepine, oxcarbazepine, rufinamide, valproic acid, valpromide, aminobutyric acid, vigabatrin, progabide, sultiame, phenacetamide, lamotrigine, felbamate, topiramate, pheneturide, levetiracetam, zonisamide, stiripentol, lacosamide,

carisbamate, retigabine, perampanel, brivaracetam, cenobamate, fenfluramine, ganaxolone, beclamide, gabapentin, pregabalin, mirogabalin.

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### **Anatomical Therapeutic Chemical (ATC) code**

(N02BF) Gabapentinoids

Gabapentinoids

(N03A) ANTIEPILEPTICS

ANTIEPILEPTICS

## Population studied

### **Short description of the study population**

The source population comprises 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. We will assess many different parameters in different groups with the aim to generate indicators for the final fit-for- purpose assessment of different study questions using the Gatto framework (Gatto et al. 2022). For objectives a-c multiple cohorts (all population, mother, father, neonate/child) will be created which depend on the parameter that is being assessed.

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### **Age groups**

- Neonate
- Infants and toddlers (28 days – 23 months)
- Children (2 to < 12 years)
- Adolescents (12 to < 18 years)
- **Adult and elderly population ( $\geq 18$  years)**
  - Adults (18 to < 65 years)

- Adults (18 to < 46 years)
- Adults (46 to < 65 years)
- Elderly ( $\geq$  65 years)
  - Adults (65 to < 75 years)
  - Adults (75 to < 85 years)
  - Adults (85 years and over)

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## **Special population of interest**

Pregnant women

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## **Estimated number of subjects**

40000000

# 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 49 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 individuals, men and women, of childbearing age and their offspring. 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 All countries (i.e., 7) and DAPS will 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.

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## **Comparators**

NA

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## **Outcomes**

Outcome parameters for Objective 2 are evaluated for each sub-objective using several pre-established parameters. Here are some examples:

### Objective 2a: Feasibility Parameters for Women

-Percentage of pregnant individuals with complete ATC codes for each antiepileptic drug by data source, in the year before and during pregnancy. This inspects potential exposure misclassification and compares data sources.

-Proportion of adverse pregnancy outcomes, such as spontaneous pregnancy loss, induced abortion, stillbirth (>20-28 weeks), and preterm birth (<37 weeks' gestation). This inspects potential outcomes misclassification, benchmarks against national statistics, and compares data sources.

### Objective 2b: Feasibility Parameters for Men and Paternal Linkage

-Percentage of men with complete ATC codes for each antiepileptic drug (ATC N03A) by data source, calendar year, and age group. This inspects potential exposure misclassification and compares data sources.

-Percentage of pregnancies identified using the ConcePTION algorithm with a linked father, by linkage method (deterministic, probabilistic), data source, and calendar year. This inspects father-pregnancy linkage and compares data sources.

### Objective 2c: Feasibility Parameters for Neonates/Children

-Duration of follow-up after birth among those registered from birth, including the percentage in follow-up at 1, 2, 3, 5, 11, and 15 years. This inspects the length of follow-up.

-Percentage of neonates with recorded major congenital malformations within

90 days, used for descriptive purposes and benchmarking across data sources and against EUROCAT.

-Risk of ADHD at 5, 11, and 15 years using different algorithms in those registered within 1 month after birth, used for descriptive purposes and benchmarking across data sources.

-Percentage of neonates with information on paternal exposure to antiepileptic drugs preconception, used to assess the prevalence of exposure.

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## **Data analysis plan**

Feasibility parameters:

For objective 2a-2c we will estimate the 41 feasibility parameters.

Descriptive analyses will be used to report as well as graphics to show time trends and comparisons between data sources.

Benchmark data will be obtained from the literature (e.g. WHO or EUOPERISTAT), to have an external validation on pregnancies and outcomes.

Feasibility to determine associations of pre conceptional/prenatal parental exposure to antiepileptics and the development of adverse pregnancy and child outcomes:

We will use the parameters from objectives 1-2 plus metadata on the data sources and assess the fitness-for-purpose of the data instance by using, implementing, and adapting the framework from Gatto N, and colleagues. (Gatto et al., 2022).

This is an assessment tool aimed at conducting feasibility assessment to determine whether a data source is fit-for-purpose for specific real-world effectiveness and safety study. Gatto's feasibility assessment framework is composed of three operative steps:

- i) operationalization and ranking of minimal criteria required to answer the research question;
- ii) identification and narrowing down data sources options, and

iii) conducting detailed feasibility assessment.

This third step will allow us to tabulate different evaluation items and therefore to score an overall assessment.

## Documents

### **Study, other information**

[Abstract\\_ADEPT\\_Protocol Obj.2\\_v1.pdf](#) (15.01 KB)

## 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)**

The Information System for Research in Primary Care (SIDIAP)

The Valencia Health System Integrated Database

Clinical Practice Research Datalink (CPRD) GOLD

EFEMERIS

Norwegian Health Registers

PHARMO Data Network

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

Terveydenhuollon hoitoilmoitusrekisteri (Finland Care Register for Health Care)

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### **Data source(s), other**

Val Padana LHU

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### **Data sources (types)**

[Administrative healthcare records \(e.g., claims\)](#)

[Disease registry](#)

[Drug registry](#)

[Electronic healthcare records \(EHR\)](#)

[Population registry](#)

[Pregnancy registry](#)

## Use of a Common Data Model (CDM)

### **CDM mapping**

Yes

### **CDM Mappings**

#### **CDM name**

ConcepTION CDM

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#### **CDM website**

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

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**CDM release frequency**

6 months

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## Data quality specifications

**Check conformance**

Yes

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**Check completeness**

Yes

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**Check stability**

Yes

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**Check logical consistency**

Yes

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## Data characterisation

**Data characterisation conducted**

Yes

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**Data characterisation moment**

after extract-transform-load to a common data model

after creation of study variables