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

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.

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: 24/07/2024

Institution | Laboratory/Research/Testing facility | 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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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: 18/11/2024

Actual: 18/11/2024

Data analysis start date

Planned: 02/05/2025

Date of final study report

Planned: 16/03/2026

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

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:

Feasibility analysis

Data collection methods:

Secondary use of data

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, 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.

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.

Age groups

- Neonate
- Infants and toddlers (28 days – 23 months)
- Children (2 to < 12 years)
- 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

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.

Comparators

NA

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.

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 EUROPERISTAT), 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)

Data source(s), other

Val Padana LHU

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

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