Antiseizure meDication Exposure and Pregnancy and neonaTal outcomes research: ADEPT

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

Protocol v3.0, 18 Dec 2024

Title	The utilisation of antiseizure medications in pregnant women, other women of childbearing potential, and men (ADEPT): a multi-database study from 7 European countries
Protocol version identifier	3.0
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Active substance	Methylphenobarbital, phenobarbital, primidone, barbexaclone, metharbital, ethotoin, phenytoin, amino(diphenylhydantoin) valeric acid, mephenytoin, fosphenytoin, paramethadione, trimethadione, ethadione, phensuximide, mesuximide, ethosuximide, 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.
Medicinal product	(See above)
Product reference	n/a
Procedure number	n/a
Marketing authorisation holder(s)	n/a
Research question and objectives	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: Objective 1.1 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; Objective 1.2 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; Objective 1.3 To estimate pre-pregnancy ASM use, and initiation and continuous use of ASMs during pregnancy period; Objective 1.4 To estimate pre-pregnancy, early and late discontinuation of ASMs, treatment switches to other ASMs or alternative medications and polytherapy among pregnant women; Objective 1.5 To estimate dose changes of ASMs in women prior to and during pregnancy.
Countries of study	Finland, France, Italy, the Netherlands, Norway, Spain, the United Kingdom
Authors	Shahab Abtahi Carlos Durán Salinas Elizabeth Comberg Miriam Sturkenboom
Reviewers	All consortium (or at least one person from each centre) has reviewed the draft protocol. Please see the table in section 5.1 Investigators.

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1 Title

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

2 Abbreviations

List of abbreviations

Abbreviation	Explanation
AEMPS	Spanish Agency of Medicines and Medical Devices
ARS	Agenzia regionale di sanità della Toscana
ASM	Antiseizure medications
BIFAP	Base de datos para la Investigación Farmacoepidemiológica en el Ámbito Público
BPE	Bordeaux PharmacoEpi platform
CHUT	Centre Hospitalier Universitaire de Toulouse
CDM	Common data model
CI	confidence interval
CPRD	Clinical Practice Research Datalink
CONSIGN	Covid-19 infectiON and medicineS In pregnancy
DAP	Data Access Provider (Partner)
DDD	Defined daily dose
EFEMERIS	Evaluation chez la Femme Enceinte des MEdicaments et de leurs RISques
EHR	electronic health records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ETL	Extract transform load
EU PAS Register	European Union Electronic Register of Post-Authorisation Studies
EU PE&PV	European Pharmacoepidemiology & Pharmacovigilance research network
FISABIO	Foundation for the Promotion of Health and Biomedical Research in the Valencian Community
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HES	Hospital episode statistics
HCU	health care utilisation
ICPC-2	*International Classification of Primary Care, 2nd Edition*
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-10	*International Classification of Diseases, 10th Revision*
MCM	Major congenital malformations
NDD	neurodevelopmental disorders
PASS	Post-authorisation safety study
PPRN	PHARMO perinatal research network
THL	Finnish Institute for Health and Welfare, Finland
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
UiO	University of Oslo
VAC4EU	Vaccine Monitoring Collaboration for Europe
VID	The Valencia Health System Integrated Database
VHIR	Vall d'Hebron - Institut de Recerca

3 Marketing Authorisation Holder

Not applicable.

4 Responsible Parties

4.1 Investigators

Note: the numbers under roles correspond to the numbers under key persons to clarify the role each person has in this study.

Organisation	Key person	Role(s)
Utrecht University, Division of Pharmacoepidemiology & Clinical Pharmacology, David de Wiedgebouw, Universiteitsweg 99, 3584 CG Utrecht, the Netherlands	1. Prof. Dr. Olaf Klungel 2. Dr. Shahab Abtahi 3. Ms. Elizabeth Comberg 4. Dr. Patrick Souverein 5. Prof. Dr. Helga Gardarsdottir 6. Drs. Magdalena Gamba 7. Drs. Svetlana Belitser 8. Drs. Katharina Jovic 9. Mr. Pieter Thijssen	1. Consortium management 2. Study co-lead 3. Support study co-leads 1-7. Data access provider CPRD 6. Programming 7. Statistical support 8, 9. Finances and legal affairs
UMC Utrecht (UMCU) Heidelberglaan 100, 3584 CX Utrecht, the Netherlands	1. Prof. Dr. Miriam Sturkenboom 2. Dr. Carlos E. Durán 3. Drs. Judit Riera-Arnau 4. Drs. Vjola Hoxhaj 5. Drs. Odette de Bruin 6. Drs. Nicoletta Luxi	1. Scientific coordination, and principal investigator 2. Study co-lead 3, 4. Data quality assessment 3, 5. Medical expertise 6. Scientific support (core team of ADEPT)
Agenzia regionale di sanità (ARS) della Toscana Via Pietro Dazzi, 1 - 50141 Florence, Italy	1. Dr. Rosa Gini 2. Dr. Giuseppe Roberto 3. Drs. Davide Messina	1-2. Programming support, expertise in and support with pregnancy algorithm expertise 3. Component analysis
IDIAPJGol, Spain	1. Dr. Maria Giner-Soriano 2. Dr. Rosa Morros 3. Dr. Dan Ouchi	1-3. Data access provider (SIDIAP database). Pharmacoepidemiology expertise
Fundacio Hospital Universitari Vall d'Hebron - Institut de Recerca (VHIR), Barcelona, Spain	1. Dr. Monica Sabaté 2. Drs. Judit Riera-Arnau 3. Ms. Elena Ballarín 4. Dr. Antònia Agustí	1-4. Medical expertise
University of Toulouse III, CHU Toulouse, CERPOP, France	1. Dr. Christine Damase-Michel 2. Dr Justine Benevent 3. Dr Anna-Belle Beau	1-3. Data access provider, expertise in conduct of pregnancy studies, pharmacoepidemiologic expertise

Finnish Institute for Health and Welfare (THL), Finland	1. Dr. Maarit Leinonen 2. Mr. Visa Martikainen	1-2. Data access provider, expertise in conduct of pregnancy studies
University of Oslo, Norway	1. Prof. Dr. Hedvig Nordeng 2. Mr. Saeed Hayati 3. Mr. Mahmoud Zidan	1-3. Data access provider, expertise in conduct of pregnancy studies
FISABIO, Health Services Research and Pharmacoepidemiology (HSRP) Unit, Valencia, Spain	1. Dr. Gabriel Sanfelix 2. Dr. Clara Rodriguez 3. Dr. Francisco Sanchez 4. Dr. Isabel Hurtado 5. Dr.. Celia Robles 6. Dr. Aníbal García	1-6. Data access provider, expertise in conduct of pregnancy studies, pharmacoepidemiologic expertise. 2. Scientific support (core team of ADEPT)
INSPIRE, Italy	1. Prof. dr. Gianluca Trifirò 2. Dr. Ylenia Ingrasciotta 3. Mr. Marco Villa 4. Dr. Katia Santacà 5. Drs.. Nicoletta Luxi	1-3. Data access provider, pharmacoepidemiologic expertise
PHARMO Institute, the Netherlands	1. Dr. Eleonora Iob 2. Dr. Eline Houben 3. Dr. Josine Kuiper 4. Prof. Dr. Ron Herings	1-4. Data access provider, expertise in conduct of pregnancy studies
University of Manchester, the UK	1. Dr. Rebecca Bromley	1. Expertise in neurodevelopmental outcomes
Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), Calle Campezo 1, Edif. 8, 28022, Madrid, Spain	1. Dr. Mar Martín Pérez 2. Dr. Elisa Martín Merino 3. Dr. Ana Llorente García 4. Dr. Patricia García Poza	1-4. Data Access Provider, pharmacoepidemiologic expertise

5 Abstract

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

Background: Currently there is substantial evidence on teratogenicity of several antiseizure medications (ASMs) and a potential increased risk of neurodevelopmental disorders in young children exposed *in utero* to ASMs. Recently, few evidence has emerged expanding this risk also when there was a paternal exposure before conception. On that line, EMA asked for an updated evaluation on trends in use of various ASMs and related drugs in pregnant women, in other women of childbearing potential, and in men.

Objectives: The main objective of this study is to describe the utilisation of ASMs 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). It has the following sub-objectives: 1.1) To estimate the annual incidence and prevalence rate of ASM use in women of childbearing potential and in men; 1.2) To describe treatment duration, discontinuation, and treatment switches to other ASMs or alternative medications and polytherapy in women of childbearing potential and men; 1.3) To estimate pre-pregnancy ASM use, and initiation and continuous use of ASMs during pregnancy period; 1.4) To estimate pre-pregnancy, early and late discontinuation of ASMs, treatment switches to other ASMs or alternative medications and polytherapy among pregnant women; 1.5) To estimate dose changes of ASMs in women prior to and during pregnancy.

Study Design: Retrospective population-based cohort study.

Study Population: The source population comprises over 63 million individuals in the included data sources (BIFAP, SIDIAP, VID, CPRD GOLD/Aurum, Finnish registries, EFEMERIS, Norwegian registries, PHARMO, and Val Padana LHU). Persons without information on age and sex, and those without at least one day of observation in the study period (1/1/2000- latest availability) will be excluded.

Exposure and outcomes: The main exposures of interest are ASMs (N03A), including gabapentinoids (N02BF) and benzodiazepines with antiepileptic properties. The drug utilisation outcome measures will be the incidence and prevalence of ASM use among women of childbearing potential and men, treatment duration of ASM, discontinuation of ASMs, initiation of ASM and continuous use during pregnancy, switching to another ASM or an alternative medication, dose changes of ASMs before and during pregnancy, and polytherapy of ASMs.

Data Management: The study will be conducted in a distributed manner using the EU PE&PV, ConcepTION, and VAC4EU tools, procedures, and programming pipeline. All partners will extract, transform, and load (ETL) their data instances into the ConcePTION CDM tables. To verify the correctness of the ETL process and validity of findings, the INSIGHT level 1 to 3 quality checks will be deployed.

Data Analysis: According to the sub-objectives stated above, statistical estimates will be produced, such as descriptives (counts, percentages), distributions (mean, percentiles), rates (incidence, prevalence), or other relevant measures. Various visualisations (e.g., flow diagrams, line and bar charts, and Sankey diagrams) will depict the findings. This will be conducted using a common R script.

6 Amendments and Updates

None

7 Milestones

Table 1. Milestones for the various stages of conduct of the study.

Contract signature	18/04/2024
Start of the project	16/05/2024
Start of data collection	15/11/2024*
End of data collection	28/02/2025
Study protocol	16/09/2024
Study report	16/09/2025
*This is 2022 for EFEMERIS, as they reuse a previously ETL-ed and quality checked data cut for this study.	

8 Rationale and Background

Valproates and older antiepileptic drugs

Antiseizure medications (ASMs) are frequently used for a range of indications from epilepsy to bipolar disorders and prophylaxis of migraine attacks. The use of several older ASMs by women during pregnancy has been associated with major congenital anomalies (MCA) and neurodevelopmental disorders (NDD) in the newborn.[1-4] These medications cause harm to the developing brain leading to poorer neurodevelopmental outcomes in childhood. Because of the increased risk of poorer neurodevelopmental outcomes in children with older ASMs (valproate, phenobarbital), the use of newer ASMs throughout pregnancy has increased. Due to this risk, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has already issued several risk minimisation measures (RMMs) to contain the use of valproate and topiramate in women of childbearing potential and pregnant women.[5,6] Awareness about these risks has increased and led to better evidence-based prescribing and preconceptual counselling regarding older ASMs for women of childbearing potential with epilepsy.[7]

Several studies investigated on the impact of 2014 and 2018 RMMs on valproate utilisation in Europe, where most reported a decline in valproate use and concurrent pregnancies with valproate exposure especially after the 2018 RMMs.[8-13] Two recent studies conducted for EMA showed a general decline in use of valproate in Europe in women of childbearing potential between 2010 and 2020,[8] and 2021.[9] There was between 3.3% (in the Netherlands) and 11.3% (in Spain) reduction in prevalent use of valproates in the studied countries/regions after the 2018 RMMs compared to the period before. However, a substantial number of concurrent pregnancies were still happening in the studied databases (ranging between 0.34-1.13 concurrent pregnancies per 1000 valproate user before the 2018 RMMs to 0.00-5.07 in the period after).[8]

Also, a study from PHARMO in the Netherlands reported a reduction in use of valproate in women of childbearing potential between 1998 and 2019 (-15%), but an increased use of other teratogenic ASMs, topiramate (+13%) and lamotrigine (+8%).[14] A multi-centre study showed that overall ASM use in 3-months before pregnancy continued to rise in Nordic countries, Australia and USA between 2006 and 2012 (or 2016 depending on data availability).[15] While valproate use showed a declining trend in almost all centres, use of lamotrigine and topiramate rose substantially. In the UK, despite reductions in sodium valproate prescriptions, the prevalence of ASM prescribing during pregnancy in the general population rose from around 6 to 12 per 1000 pregnancies between 2007 and 2016, largely due to increases in prescriptions of pregabalin, gabapentin and lamotrigine.[16] Discontinuation of ASMs before or during pregnancy is common (19%–38% of women prescribed any ASM before pregnancy are not prescribed

during pregnancy and the prevalence of prescription declines between the first and later trimesters of pregnancy),[15] but the discontinuation was clearly less common when ASM was prescribed for epilepsy.[17]

Newer (other) antiepileptic drugs

Valproate is the most teratogenic ASM, but also other ASMs have been associated with an increased risk of MCA. Comparatively, conclusions regarding exposure to newer ASMs and the potential negative impact on later child development remain limited. In a Cochrane review of 28 studies a paucity of research into lamotrigine, levetiracetam, and topiramate was highlighted, with no data available for oxcarbazepine, perampanel, eslicarbazepine, or zonisamide.[2,18] Although the study of newer ASMs has since increased, findings are mixed, and methodologies used to investigate child neurodevelopment following in utero exposure vary widely.[18] A recent multicentre study from Nordic countries, USA and Australia showed that lamotrigine-levetiracetam duo-therapy in first trimester was associated with a 59% lower risk of MCA than valproate monotherapy, while lamotrigine-topiramate was not associated with a reduced risk.[19] Recent concerns about the possible impact of levetiracetam monotherapy and duo-therapy exposures have been raised.[20,21] However, only few studies have the remit to assess short- and long-term outcomes, both of which are crucial to understanding the impact of ASMs on the trajectory of brain development from infancy to early adulthood.[22]

Paternal exposure to ASMs

In addition to the teratogenicity risk with maternal use of ASMs, a recent observational study from Denmark, Norway and Sweden suggests a 50% higher risk (pooled estimate) of NDD in children of men who were using valproate in 3-months before conception compared with men who used other ASMs such as lamotrigine/levetiracetam.[23] Based on this study, PRAC recommended precautionary measures, such as considering effective contraception for male patients who use valproates and close supervision by a specialist.[24] Also very recently, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) recommended a set of RMMs for male patients using valproate.[25] However, these positions from EMA and MHRA were criticised later and deemed without enough substantiation from underlying scientific evidence.[26] Additionally, there was another recent study from Denmark that failed to show such an association between paternal valproate exposure and offspring risk of MCA or NDD.[27] Hence, this possible link deserves further investigation.

Need for further information

Considering the current evidence on teratogenicity of several ASMs and a potential increased risk of NDD in young children not only exposed in utero to ASMs but also when there was a paternal exposure before conception, EMA requires an updated evaluation on trends in use of various ASMs and related drugs (ATC codes N03A and N02BF) in both women of childbearing potential and men in Europe. It is also deemed necessary to assess whether causal inference studies on ASMs and MCA or NDD will be feasible, particularly given that father-child linkage is a more challenging and less explored area than mother-child linkage when using real-world data.

9 Research Question and Objectives

The main objective of this study is to describe the utilisation of ASMs and related drugs (ATC codes N03A and N02BF) in pregnant women, other women of childbearing potential, and men using data from 9 European electronic healthcare databases from two Nordic (Finland, Norway), two western (the Netherlands and the UK), and three southern European countries (France, Italy, Spain).

The main objective will be met with the following sub-objectives:

Objective 1.1 To estimate the annual incidence and prevalence rate of ASM use in women of childbearing age (12-55 years of age) and men (12 years and older) overall and by age group, data source and calendar year (population base cohort).

Objective 1.2 To describe treatment duration, discontinuation, and treatment switches to other ASMs or alternative medications and polytherapy in women of childbearing age (12-55 years of age) and men (12 years and older) who receive a new ASM prescription/dispensing in a specific calendar year, by data source, age, indication, key comorbidities, calendar year and ASM (ASM user cohort).

Objective 1.3 To estimate pre-pregnancy ASM use, and initiation and continuous use of ASMs during the pregnancy period, by data source, and age in all pregnant women.

Objective 1.4 To estimate pre-pregnancy, early and late discontinuation of ASMs, treatment switches to other ASMs or alternative medications and polytherapy among pregnant women, by data source, and indication of the ASM.

Objective 1.5 To estimate dose changes of ASMs in women prior to and during pregnancy, by data source, and indication.

10 Research Methods

10.1 Study design

This is a retrospective population-based cohort study to describe the utilisation patterns of ASMs in different population cohorts.

10.2 Study setting

This study will be conducted using electronic health record data from 9 data sources in 7 countries in Europe comprising a total population of over 63 million persons. Main characteristics of the participating data partners and access providers are presented in Table 2. 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. Some DAPs will re-use the data instance they use for ConcePTION (UiO, CHUT), whereas other DAPs will re-extract and use the requested ad-hoc populations (THL, AEMPS, IDIAPJGol, FISABIO, UU, PHARMO, INSPIRE).

Table 2: Overview of data sources.

DAP	Data source and country	Active Population size (mil)	Data provenances available for this study (Record linkage)	Vocabularies	Data update frequency	Years with complete data
AEMPS	BIFAP (ES)	17.0	Primary care records and hospital discharge diagnosis.	ICPC2/SNOMED ICD9CM, ICD10CM, ATC	6 months	2005- 2023
VHIR/IDIAPJGol	SIDIAP (ES, Catalonia)	6.0	Primary care records, specialist referrals, ICU admission, hospital discharge diagnosis, pregnancy register, child health records, pharmacy dispensing.	ICD10CM, ATC, ICD10-PCS	6 months	2010-June 2024
FISABIO	VID (ES, Valencia region)	5.0	Primary care records, outpatient specialist records, lab tests, emergency room visits, hospital admissions and procedures, ICU admission, pregnancy register, child health records, outpatient pharmacy prescribing and dispensing. Several	ICD10CM & ICD9CM, ATC	Yearly	2009-June 2023

			associated registries or information systems such as perinatal mortality register, congenital anomalies register, vaccines information system, etc.			
UU	CPRD-GOLD /Aurum (UK)	3.0 / 15.6	Primary care diagnoses, prescriptions, lab tests, hospital admissions and procedures (HES APC, A&E, OP), pregnancy data, living situation, child health records.	Read/Snomed BNF, ICD10CM OPCS	Few months for HES and pregnancy	1987-2024
THL	Finnish registries (FI)	5.5 (1.7 pregnancies)	Available instance restricted to pregnant women who gave birth or terminated pregnancy and their children. Primary care record, ICU, emergency room, hospital discharge diagnosis, pregnancy registry, congenital anomaly register, outpatient pharmacy dispensing.	ICD10CM, ATC, ICPC-2, NOMESCO	Depending on data source, from 1 month to 1 year.	1996-2022
CHUT*	EFEMERIS (FR)	1.4 (0.18 pregnancies)	Available instance restricted to pregnant women who gave birth or terminated pregnancy and their children. Hospital discharge diagnosis, outpatient pharmacy dispensing, and child health records, no ICU, no primary care.	ICD10CM, ATC	Yearly	2005-2021
UiO	Norwegian registries (NO)	5.3 (2.1 mother or father/children)	Primary care records (KUHR), outpatient specialist diagnosis (KUHR/NPR), emergency room visits (KUHR), hospital discharge diagnosis (NPR), outpatient pharmacy dispensing (NorPD).	ICD10, ICPC, ATC	Yearly†	2008-2021
PHARMO	PHARMO (NL)	4 (0.7 pregnancies)	Primary care records, hospital discharge diagnosis, ambulatory visit diagnosis, hospital procedures, out-patient pharmacy dispensings, ICU admissions, birth registry (perined).	ICPC, ICD9CM, ICD10, ATC	Yearly	2000-2022
INSPIRE	Val Padana LHU (IT)	0.78	Hospital discharge diagnosis, pharmacy records, ICU admission, emergency room, outpatient specialists, congenital anomalies, birth registry.	iCD9CM, ATC, Italian code system for exemptions	yearly	2008-2024

* Pregnancies only

† The 2008-2021 data set will be used, no updates in this project.

10.3 Source and study population

The source population comprises all persons in the data sources that will participate in this study. From the source population, we will select various cohorts that feed data for the different sub-objectives in this study (Figure 1). Persons will be included in the study population when they have:

- Information on age and sex available.
- Have at least one day of observation in the study period (1/1/2000- latest availability).

Follow-up will start and end based on in-and exclusion criteria which differ per sub-objective.

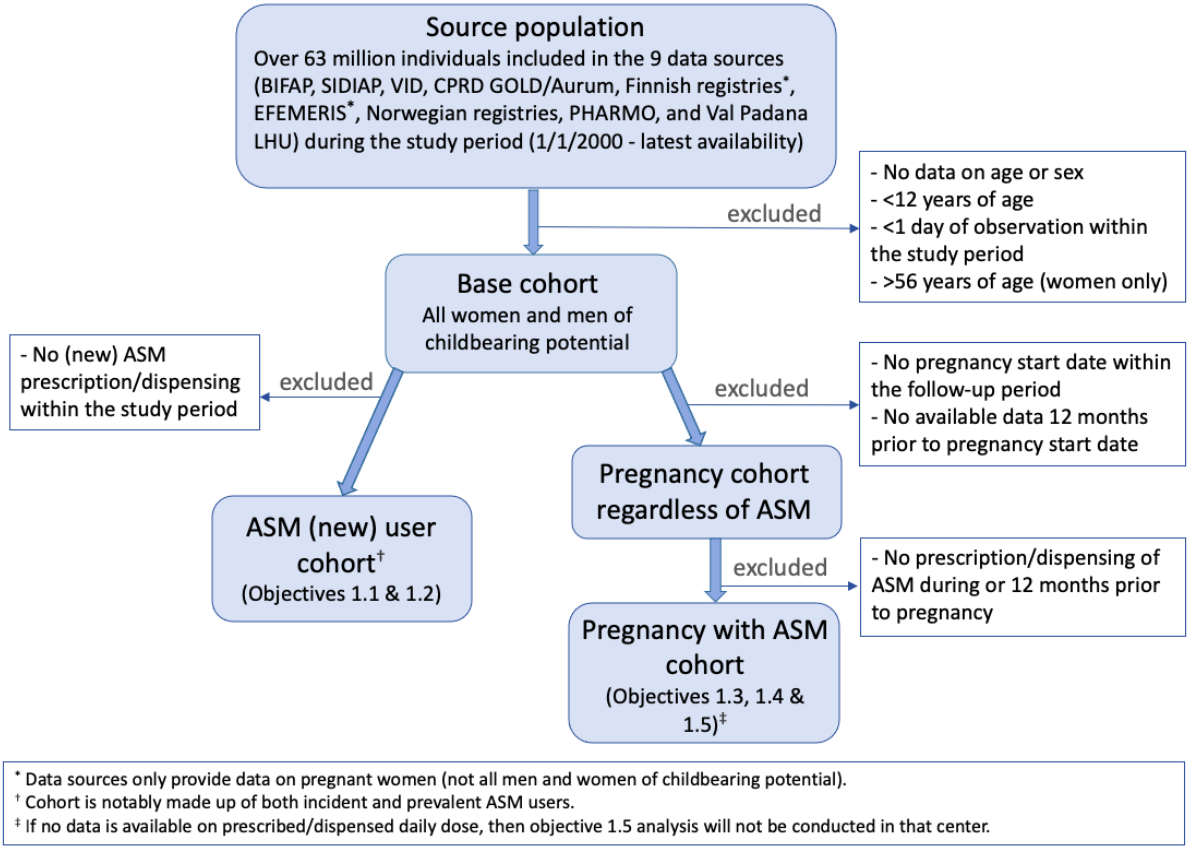


Figure 1. Establishment of various study cohorts used to feed objectives of ADEPT.
ASM: Antiseizure medication.

10.3.1 Base cohort

This base cohort provides data used in denominators of rates in objective 1.1. The eligibility criteria for the base cohort are shown in Figure 1.

Follow-up will start at the latest date of the following criteria:

- Reaching 12 years of age.
- One year of available data (run-in period) in the data source.

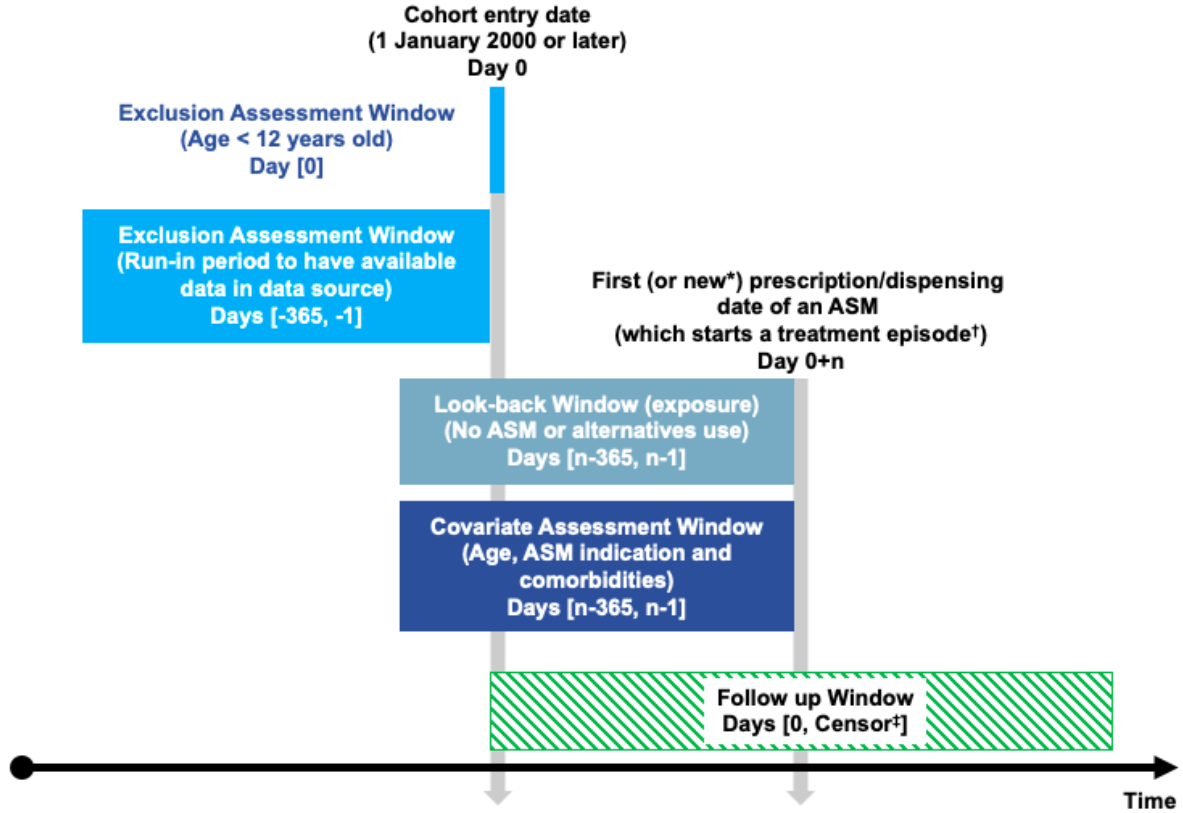
Follow-up will end at the earliest of any of the following criteria:

- Reaching age 56 years for women only (there is no upper age limit for men)
- Death

- Moving out of the data source (disenrollment)
- Last data available from the data source (or parts of it)
- Last data extraction for relevant data sources.

10.3.2 ASM (new) user cohort

This cohort provides data for numerators of rates in objective 1.1, and the rest of outcome measures in objective 1.2. The (new) ASM user cohort will be a sub-cohort from the base cohort and comprises individuals therefrom who receive at least one ASM prescription/dispensing (Figure 2). These individuals may be either new or prevalent ASM users. New (incident) ASM users will be defined as no ASM use in the 1-year look-back period (i.e., 365 days prior to the prescription/dispensing date of an ASM). While prevalent ASM users will be those individuals with ASM use in the 1-year look-back period. All ASM users will be followed from the start of the 1st ASM prescription/dispensing, until the end of follow-up as defined under the base cohort 10.3.1, or if earlier until 8 months after the last prescription/dispensing date of an ASM.



Abbreviation: ASM: Antiseizure medication.
* A new prescription/dispensing record is contingent on no such use in the 1-year look-back period.
† Treatment episodes are defined in section 10.4.1.3.
‡ Earliest of age 56 (only for women), death, disenrollment, last data extraction data for each data source.

Figure 2. Study designs for the base cohort, and ASM (new) user cohort.

10.3.3 Pregnancy cohort regardless of ASM

From the base cohort defined in objective 1.1, we will create a sub-cohort of pregnancies. One individual may have multiple pregnancy episodes. The start of pregnancy will be defined as the estimated first day of the last menstrual period (LMP); end of pregnancy will be the date of delivery

or abortion (elective/spontaneous). Pregnancy start and end dates will be assessed based on the data banks used to detect the pregnancy periods using the ConcePTION pregnancy algorithm https://github.com/ARS-toscana/ConcePTIONAlgorithmPregnancies. The algorithm allows the identification of pregnancies from 4 streams of information:

- Stream PROMPTS: uses data source specific information (e.g. LMP, end of pregnancy) from birth registries, terminations registries, and spontaneous abortion registries: the existence of one of such record implies readily that a pregnancy has ended.
- Stream EUROCAT: records of the EUROCAT table in the CDM. Some data sources include a data bank that is compliant with the standard of EUROCAT, the European network of population-based registries for the epidemiological surveillance of congenital anomalies (https://eu-rd-platform.jrc.ec.europa.eu/eurocat_en). Such records are copied with minimal conversion to a special table of the ConcePTION CDM, named EUROCAT. "Stream EUROCAT": are the records retrieved from the EUROCAT table when the pregnancy algorithm of ConcePTION is applied.
- Stream CONCEPTSETS: this stream uses a large list of diagnostic codes from the events or procedure codes referring to a start, end or an ongoing pregnancy.
- Stream ITEMSETS: variables from ordinary healthcare that are only populated when a woman is pregnant. Some data sources include data banks that contain surveillance data, for example birth registries, or results from diagnostic tests. In such data, information is labelled as a 'data item'.[28] For example an item is the question 'what is the gestational age at the visit date?' and the answer may be a number (in weeks, or in days, or in months), or a categorical variable ('at term', 'preterm', …). An 'itemset' is a set of records retrieved from the data source that have such complex structure. The Stream ITEMSET is the set of itemset records that are retrieved from the data source with the purpose of identifying a pregnancy and its characteristics

The resulting sets of pregnancies of the same person are then compared with each other, to identify which pregnancies are in fact the same recorded on multiple occasions. The algorithm first identifies pregnancies from any possible records and subsequently establishes the start and end date of pregnancy by processing all the available information in a hierarchical manner. Hierarchy is based on how the identification of the start and end dates of the pregnancy was performed.

The output of the ConcePTION Pregnancy algorithm is the start and end date of pregnancy, or ongoing pregnancies. Pregnancies will be included in the cohort of pregnancies when the following criteria apply:

- Start date of pregnancy is during follow-up period as defined under objective 1.1.
- One year of available data (run-in period) in the data source at the start date of the pregnancy (LMP). For EFEMERIS this is 2.5 months and for THL 3 months.

Follow-up will end at the end date of the pregnancy, or the end of follow-up (as specified in objective 1.1), whichever is earliest. This includes ongoing pregnancies.

10.3.4 Pregnancy with ASM cohort

This cohort will be used to address objectives 1.3, 1.4 and 1.5. Here, we will use the pregnancy cohort regardless of ASM (see above) with additional inclusion criteria of:

- A prescription/dispensing for ASM in the 12 months (3 months for THL and 2.5 months for EFEMERIS) prior to pregnancy start date, or
- A prescription/dispensing for ASM during pregnancy.
- Availability of information on prescribed daily dose in the data sources (only for objective 1.5).

Start of follow-up (t=0) in this cohort will be the ASM prescription/dispensing date. Pregnancies without ASM in the year prior or during pregnancy will be excluded.

Follow-up will end at the end date of the pregnancy, or the end of follow-up (as specified in objective 1.1), using the same principles as depicted in Figure 2.

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10.4 Variables

10.4.1 Exposure

10.4.1.1 Antiseizure medications (ASMs)

The main exposures of interest are ASMs (N03A and N02BF) and benzodiazepines with antiepileptic properties. Table 3 shows the ATC codes and the DDDs for all products listed in these classes. Some may not be used anymore or are not yet approved, but this will be observed in the study. We included gabapentinoids (ATC code N02BF) because they were widely used for similar indications as other ASMs and were classified as 'Other antiepileptics' under N03AX by the WHO Collaborating Centre for Drug Statistics Methodology until March 2022.

All ASM records will be extracted, transformed, and loaded (ETL) from the local data source drug nomenclature to ATC codes or available ATC or BNF codes into the MEDICINES and PRODUCTS table of the ConcePTION CDM v2.2. The PRODUCTS table will comprise information on the strength of the drugs.

Table 3. Exposure of interest, with ATC codes and defined daily dose values as per WHO/ATC system.

ATC code	Name of ASM	DDD value	DD unit	Route of administration	Indication
N03AA01	methylphenobarbital	0.5	g	O	Relief of anxiety, tension, and apprehension, anticonvulsant*
N03AA02	phenobarbital	0.1	g	O, P	All types of seizures (except absence seizures), sedation*
N03AA03	primidone	1.25	g	O	Management of grand mal, psychomotor, and focal epileptic seizures, essential tremor*
N03AA04	barbexaclone				Epilepsy*
N03AA30	metharbital	0.2	g	O	Epilepsy†
N03AB01	ethotoin	2.5	g	O	Control of generalised tonic-clonic (grand mal) and complex-partial (psychomotor) seizures*
N03AB02 N03AB52	phenytoin	0.3	g	O, P	Focal and generalised onset seizures, status epilepticus*
N03AB03	amino(diphenylhydantoin) valeric acid	0.3	g	O	n/a
N03AB04 N03AB54	mephenytoin	0.4	g	O	Refractory partial epilepsy†
N03AB05	fosphenytoin	0.45	g	P	Various seizures (generalised tonic-clonic status epilepticus and prophylaxis during craniotomy)*
N03AC01	paramethadione	0.9	g	O	Refractory absence (petit mal) seizures†
N03AC02	trimethadione	1.5	g	O	Refractory absence (petit mal) seizures†
N03AC03	ethadione				n/a
N03AD02	phensuximide	2	g	O	Absence (petit mal) seizures†
N03AD03	mesuximide	0.9	g	O	Refractory absence (petit mal) seizures*
N03AD01 N03AD51	ethosuximide	1.25	g	O	Absence (petit mal) seizures*

N03AE01	clonazepam	8	mg	P, O	Panic disorder, refractory seizures, seizure disorders (Lennox-Gastaut syndrome, akinetic, myoclonic seizures, and absence seizures), REM sleep behavioral disorders*,‡
N03AF01	carbamazepine	1	g	O, R	Bipolar disorder, focal (partial) and generalised onset seizures (except absence seizures), neuropathic pain*
N03AF02	oxcarbazepine	1	g	O	Focal (partial) onset seizure*
N03AF03	rufinamide	1.4	g	O	Lennox-Gastaut syndrome*
N03AG01	valproic acid	1.5	g	O, P, R	Bipolar disorder, focal (partial) and generalised onset seizures, prevention of migraine attacks*
N03AG02	valpromide	1.5	g	O	Bipolar disorder, depression, epilepsy, psychomotor agitation†
N03AG03	aminobutyric acid	1	g	O, P	Epilepsy§
N03AG04	vigabatrin	2	g	O	Infantile spasms, refractory complex partial seizures*
N03AG05	progabide				Epilepsy†
N03AX03	sultiame	0.4	g	O	Focal epilepsy†
N03AX07	phenacemide	1.5	g	O	Epilepsy†
N03AX09	lamotrigine	0.3	g	O	Bipolar disorder, focal (partial) and generalised onset seizures*
N03AX10	felbamate	2.4	g	O	Focal (partial) onset seizures, Lennox-Gastaut syndrome*
N03AX11	topiramate	0.3	g	O	Prevention of migraine attacks, various seizures*
N03AX13	pheneturide				Seizures*
N03AX14	levetiracetam	1.5	g	O, P	Focal (partial) and generalised onset seizures*
N03AX15	zonisamide	0.2	g	O	Focal (partial) onset seizures*
N03AX17	stiripentol	1	g	O	Dravet syndrome-associated seizures*
N03AX18	lacosamide	0.3	g	O, P	Focal (partial) onset seizures, primary generalised tonic-clonic seizures*
N03AX19	carisbamate				Adjunctive treatment of partial onset seizures with or without secondary generalisation¶ *Withdrawn application to EMA*
N03AX21	retigabine	0.9	g	O	Partial-onset seizures*
N03AX22	perampanel	8	mg	O	Partial-onset seizures, primary generalised tonic-clonic seizures*
N03AX23	brivaracetam	0.1	g	O, P	Partial-onset seizures*
N03AX25	cenobamate	0.2	g	O	Adjunctive treatment of focal-onset seizures with or without secondary generalisation¶
N03AX26	fenfluramine	8	mg	O	Seizures associated with Dravet syndrome and Lennox-Gastaut syndrome¶
N03AX27	ganaxolone	n/a	n/a	n/a	Epileptic seizures associated with cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD)¶
N03AX30	beclamide	n/a	n/a	n/a	Epilepsy and epilepsy related behavioural disorders†
N02BF01	gabapentin	1.8	g	O	Epilepsy, neuropathic pain#
N02BF02	pregabalin	0.3	g	O	Epilepsy, neuropathic pain, generalised anxiety disorder¶
N02BF03	mirogabalin	25	mg	O	Peripheral neuropathic pain‖
N03AF04	eslicarbazepine	0.8	g	O	Focal onset seizures, Seizures, partial onset*
N05BA01	diazepam	10	mg	O, P, R	first-line treatment of status epilepticus‡
N05BA06	lorazepam	2.5	mg	O, P, SL	first-line treatment of status epilepticus‡
N05BA09	clobazam	20	mg	O	adjunctive treatment for Lennox-Gastaut syndrome; difficult-to-treat seizures, drop seizures‡

N05CD08	midazolam	5, 15, 10	mg	N, O, P, SL	first-line treatment for status epilepticus (off-label)[‡]

[*] Uptodate.com/Lexicomp
[†] DrugBank (www.go.drugbank.com)
[‡] Brigo F, Lattanzi S. Anti-convulsant Agents: Benzodiazepines (Clobazam, Clonazepam, Diazepam, Lorazepam, Midazolam). *NeuroPsychopharmacotherap.* 2022. Springer.[29]
[§] Bryson A, Reid C, Petrou S. Fundamental neurochemistry review: GABAA receptor neurotransmission and epilepsy: principles, disease mechanisms and pharmacotherapy. Journal of neurochemistry. 2023 Apr;165(1):6-28.[30]
[¶] European Public Assessment Report (www.ema.europa.eu/en/glossary/european-public-assessment-report)
[#] CIMA, AEMPS (https://cima.aemps.es/cima/publico/home.html)
[ǀ] Deeks ED. Mirogabalin: first global approval. Drugs. 2019 Mar 1;79(4):463-8.[31]
Abbreviation: n/a: not available.

10.4.1.2 Alternative medications of ASMs

In sub-objectives 1.2 and 1.4, we will explore switching trends from ASM to alternative medications based on the different indications listed in Table 4. The list of alternative medications that will be retrieved are presented in Table 4**.** Noteworthy, not all products are available in all data sources.

Table 4. List of alternative medications for ASMs per indication area of the ASM.

Indication	*Alternative medications of ASMs*
Epilepsy (drug resistant)	Cannabidiol
Bipolar diseases	Lithium, quetiapine, olanzapine, aripiprazole, risperidone, asenapine, lurasidone, or paliperidone.
Prevention of migraine attacks	Beta-blockers (Metoprolol, propranolol, timolol, atenolol and nadolol), calcium channel blockers (nifedipine, verapamil, nimodipine, and flunarizine), ACE inhibitors/ARBs (lisinopril and candesartan), antidepressants (amitriptyline and venlafaxine), CGRP antagonists (erenumab, fremanezumab, galcanezumab, eptinezumab, rimegepant, atogepant), NSAIDs (naproxen), pizotifen.
Generalised anxiety disorder	SSRIs (paroxetine, sertraline, citalopram, escitalopram, fluoxetine and fluvoxamine), SNRIs (venlafaxine, and duloxetine); benzodiazepine (e.g., lorazepam), hydroxyzine, buspirone, mirtazapine
Neuropathic pain (or nociplastic, centralized pain, or fibromyalgia)	TCAs (amitriptyline, doxepin, imipramine, nortriptyline, desipramine, maprotiline), SNRIs (venlafaxine, duloxetine, milnacipran), topical therapy (e.g., topical NSAIDs, topical lidocaine, or capsaicin patch), opioids and botulinic acid,
Restless legs syndrome	Iron supplementation, carbidopa-levodopa, benzodiazepines (clonazepam, and zolpidem)
Essential tremor	Beta-blockers (propranolol, sotalol, nadolol, atenolol, metoprolol); benzodiazepines (alprazolam and clonazepam)
Major Depression	SSRIs (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline), SNRIs (desvenlafaxine, duloxetine, levomilnacipran, milnacipran, venlafaxine), TCAs (amitriptyline, clomipramine, doxepin, imipramine, trimipramine, desipramine, nortriptyline, protriptyline, maprotiline), atypical antidepressants (bupropion and mirtazapine), serotonin modulators (nefazodone, trazodone, vilazodone, vortioxetine), MAOIs (isocarboxazid, moclobemide, phenelzine, selegiline, and tranylcypromine).
Schizophrenia (psychosis)	first- and second-generation long-acting injectable antipsychotics (fluphenazine, haloperidol, paliperidone, aripiprazole, olanzapine, risperidone)

* Uptodate.com/Lexicomp
Abbreviation: CGRP: Calcitonin gene-related peptide, ACE: angiotensin-converting enzyme, ARBs: angiotensin receptor blockers, TCAs: tricyclic antidepressants, SSRIs: Selective serotonin reuptake inhibitors, SNRIs: serotonin-norepinephrine reuptake inhibitors, MAOI: Monoamine oxidase inhibitors, NSAIDs: non-steroidal anti-inflammatory drugs.

10.4.1.3 Operational definitions of exposure

Calculation of ASM exposure episodes

To be able to estimate the treatment duration and the proportion of discontinuers and switchers, we will construct treatment episodes. Treatment episodes are defined as the treatment periods from index prescription/dispensing to the expected end date of a continued last prescription/dispensing, including a grace period of 30 days between prescription/dispensing of the same ATC code (and dose) (see Figure 3-A).

First, we will calculate the duration of prescriptions/dispensings. This will be estimated from a prescribed/dispensed regimen if available. Implausible values for number of tablets taken per day and total quantity of tablets prescribed/dispensed will be changed to missing. Then imputation methods will be used to replace missing values for quantity and number of tablets taken per day, using similar prescriptions first within the individual and then within similar individuals. Prescription/dispensing length will then be calculated by dividing the quantity of tablets by the number taken per day. If prescribed/dispensed duration is not available in the data source, we will use a defined daily dose approach or fixed period approach.

We will use the CreateDot function that was developed for ConcePTION to harmonise the calculation of days of exposure associated to a single record of utilisation of a medicinal product (i.e. prescription, dispensing or administration), or set of medicinal products, across different observational healthcare data sources (https://github.com/IMI-ConcePTION/CreateDoT/wiki). This information will feed the previously validated AdhereR function that will generate the treatment episodes.[32]

Calculating daily dose of ASM exposure

The prescribed daily dose for a prescription/dispensing will be calculated for each prescription/dispensing by multiplying the number of tablets taken per day by the dose per tablet. We will classify each exposure as low, mid, and high dose based on DDD equivalents: <0.5 DDD as low, 0.5-1.49 DDD as mid and >1.5 DDD as high. Previous research has shown that daily dose of ASMs in DDDs from prescription fills has a high correlation with blood levels of the used drugs during pregnancy.[33] This cannot be done for data sources without information on dispensed/prescribed dosing regimen.

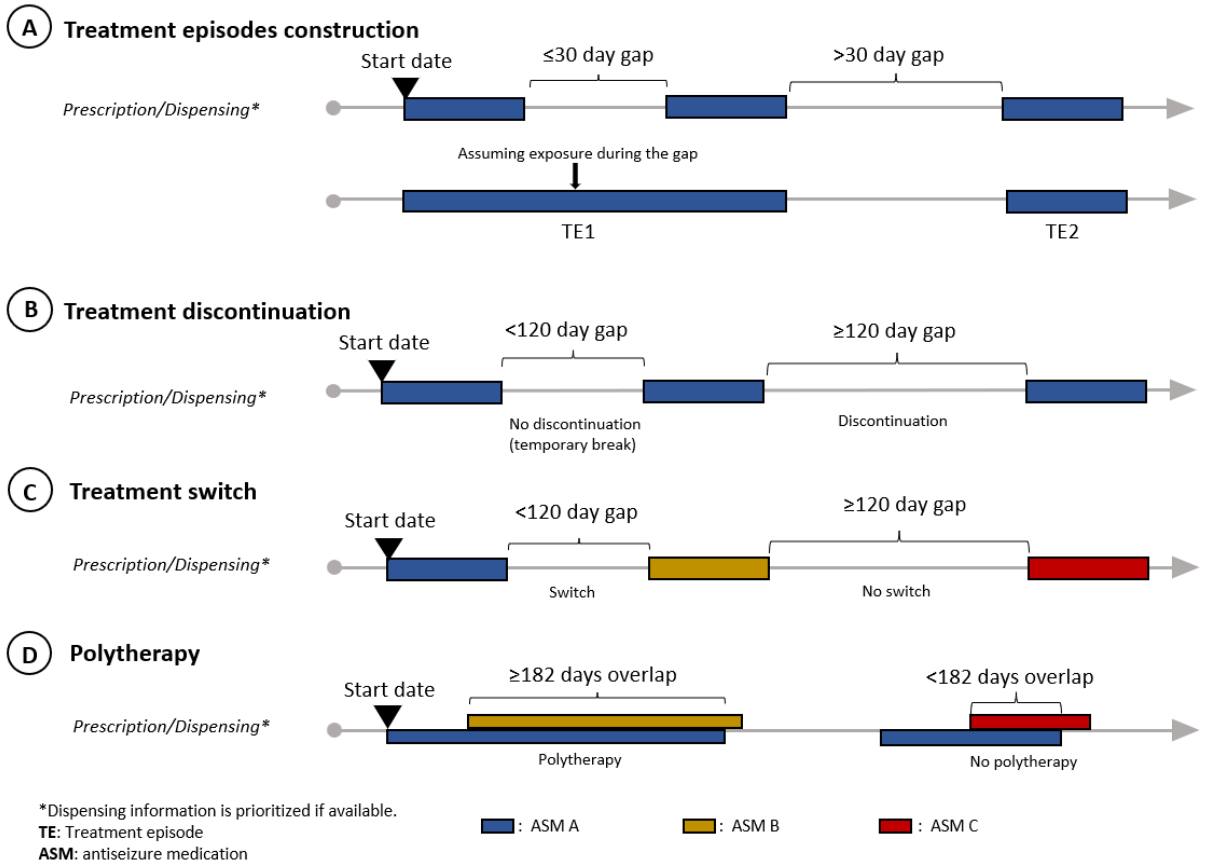

Figure 3. Handling of treatment gaps, treatment discontinuation, treatment switch, and polytherapy (adapted from Durán CE et al.).[34] The various colour boxes represent different antiseizure medications that are prescribed for a hypothetical patient.

10.4.2 Drug utilisation outcomes

The drug utilisation outcome measures that will be covered in this study protocol are the incidence and the prevalence of use among pregnant women, other women of childbearing potential, and men, treatment duration of ASM, discontinuation of ASMs, initiation of ASM use during pregnancy, switching to another ASM or an alternative medication, dose changes of ASMs before and during pregnancy, and polytherapy of ASMs.

10.4.2.1 Operational definitions of outcomes

Incidence & prevalence of ASM use

Incident use of ASM is defined as a prescription of an ASM without any ASM use in the look-back period (365-days before). Prevalence of ASM is defined as the users (either existing or starting) in a defined period (period prevalence), which will be on a yearly basis for the base population. Due to shorter look-back periods, THL only contributes to prevalence estimations.

Treatment duration of ASMs

Treatment duration is defined as the number of days of the treatment episode of an ASM from the start until discontinuation or end of follow-up, including the collapsed grace periods (permissible gaps of ≤ 30 days) in between treatment episodes.

Discontinuation of ASMs

In general, we will assume an individual has discontinued the specific drug of interest if no new prescription/dispensing for that drug is identified within 120 days of the last treatment episode (see Figure 3-B). A gap of >30 and <120 days between two treatment episodes will be considered as a 'temporary break' in treatment and no discontinuation. If the distance between end of follow-up and end of treatment episode is less than 120 days, we will not consider the person to have discontinued.

Switching to another ASM

Switching from an ASM to another ASM will be defined when there is an occurrence of a prescription/dispensing of another ASM (different ATC code) during the last treatment episode of the ASM or within the discontinuation period of the ASM (0 to 120 days after the episode end date) (see Figure 3-C). If a record for ASM occurs in the same treatment episode as the new ASM, and the conditions for discontinuation and switch are not met, this will be assessed for classification as polytherapy (see below, Figure 3-D).

Switching to alternative medication is defined as an occurrence of a prescription/dispensing of another medication (see 10.4.1.2 & Table 3) during the last treatment episode of the ASM or within the discontinuation period of the ASM.

Polytherapy

For non-pregnant people, polytherapy is defined as having prescriptions/dispensings filled of two or more different ASMs in a single treatment episode for at least 6 months (i.e., 182 days), where the conditions of a switch (see above) are not met (Figure 3-D).[35] The prerequisite of concomitant use of two medications for at least 6 months (i.e., 182 days) is set to exclude practical situations of a switch, where the first medication needed to be tapered and the new one titrated up slowly, which might take a few months. This can be either among women or men of childbearing potential. Noteworthy, the construction of treatment episodes by the CreateDot and AdhereR functions will consider the specific dosing regimens (for example, prescribed quantity) of various ASMs to accurately estimate polytherapy.

Definitions during pregnancy

Within pregnancy, we will classify continuation/discontinuation patterns of ASMs before and during pregnancy inspired from Madley-Dowd et al,[36] but based on treatment episodes that will be constructed using the CreateDot and AdhereR functions (see above), with the following categories:

- **Pre-pregnancy ASM use** is defined as a treatment episode of an ASM in the year before pregnancy, which falls within both 12 to 6 months before pregnancy and 6 to 0 months before pregnancy to exclude inconsistent or temporary users.
- **Initiators of ASMs during pregnancy** are those with an ASM treatment episode starting during any trimester, but no such ASM use (treatment episode) in the 12 months prior to pregnancy start. Due to shorter look-back periods, EFEMERIS and THL will not contribute to estimating this.
- **Continuous ASM use during pregnancy** is defined as pre-pregnancy ASM use (see above) that runs into the first, second and third trimester.
- **Pre-pregnancy discontinuation** is defined as pre-pregnancy ASM use (see above) that does not run into the pregnancy period.
- **Early discontinuation** is defined as pre-pregnancy ASM use (see above) that runs into the first-trimester but not into the second trimester.
- **Late discontinuation** is defined as pre-pregnancy ASM use (see above) that continues in the first and second trimesters, but ends before the third trimester.

- **Polytherapy** in pregnancy is defined as treatment episodes of ≥2 distinct ASMs in the first trimester that both take ≥3 months.
- **Switching** during pregnancy is defined as a particular ASM treatment episode in the year prior to pregnancy that ends before the pregnancy period, and initiation of a different ASM in one of the three trimesters.

Within pregnancy we will also assess dose changes of ASM, as below:

- Among the pregnant women who continue on ASMs (including continuous ASM use and late discontinuation), **dose changes of ASMs** will be estimated based on comparison of prescribed daily dose for mono- or polytherapy (in DDD equivalents), between the time periods with reference to start of pregnancy.

10.4.3 Covariates

10.4.3.1 Age groups

The different age groups considered in this study for stratifications purposes in various objectives are:

- 12.0 – 18.9 years old (for both women and men)
- 19.0 – 34.9 years old (for both women and men)
- 35.0 – 54.9 years old (for both women and men)
- 55.0 – 74.9 (for men)
- 75.0 and older (for men)

10.4.3.2 Indications for ASM exposure

We will include the following indications of the exposure drugs, which will be used for stratifying the analyses in sub-objectives 1.2, 1.4, & 1.5: Epilepsy, bipolar disorder, prevention of migraine attacks, generalised anxiety disorder, neuropathic pain (or nociplastic, centralised pain, or fibromyalgia), essential tremor, restless legs syndrome, major depression, schizophrenia (psychosis), and other (off-label) psychiatric use. To detect indications from electronic medical records in diverse data sources, we will search for indicators of primary indications in the 1-year look-back period (Table 5), based on a priority list and algorithm previously developed by ConcePTION. Multiple indications may be found for each person.

Table 5. possible algorithms for indication of drugs, modified from Madley-Dowd et al.[36]

Indication	**Derivation**
Epilepsy	One of the following during look-back period: Diagnosis of epilepsy, OR; Epilepsy-specific ASMs: Epilim, Brivaracetam, Brivaracetam, Eslicarbazepine, Ethosuximide, Felbamate, Fenfluramine, Lacosamide, Levetiracetam, Mesuximide, Oxcarbazepine, Perampanel, Phenobarbital, Phenytoin, Retigabine, Rufinamide, Stiripentol, Sultiame, Tiagabine, Vigabatrin, Zonisamide, OR; Epilepsy-specific co-prescribing: 1) Clobazam and an ASM or 2) rectal administration of diazepam and an ASM or 3) intranasal administration of Midazolam and ASM
Bipolar disorder	One of the following during look-back period: Diagnosis code for bipolar disorder OR;

	Mood-disorder specific co-prescribing (1-Quetiapine and [valproate or lamotrigine or carbamazepine] or 2-lithium and [valproate or lamotrigine or carbamazepine]) OR; The mood disorder-specific ASM divalproex sodium.
Prevention of migraine attacks	Diagnosis code for migraines during look-back period
Generalised anxiety disorder	Diagnosis code for generalised anxiety disorder during look-back period
Neuropathic pain (or nociplastic, centralized pain, or fibromyalgia)	Diagnosis code for a neuropathic pain disorder during look-back period
Essential tremor	Diagnosis code for essential tremor during look-back period
Restless legs syndrome	Diagnosis code for restless-legs syndrome during look-back period
Major Depression	Diagnosis code for major depression, during look-back period
Schizophrenia (psychosis)	Diagnosis code for schizophrenia, during look-back period
Other (off-label) psychiatric use	Where none of the above indications were identified, yet there was prescription of antipsychotics, lithium, or antidepressants

10.4.3.3 Key comorbidities

The following list of key comorbidities will be used for stratifying the analyses of sub- objective 1.2. These include the most common comorbidities that patients with epilepsy or those who use ASM might have:[37]

- Cognitive impairment and dementia.
- Sleep disorders (including obstructive sleep apnoea and insomnia).
- Hypertension (or use of anti-hypertensives).
- Cardiovascular diseases (including myocardial infarction and stroke).
- Respiratory disease (asthma and chronic obstructive pulmonary disease, or use of bronchodilating agents).
- Bone disease and fractures.
- Brain injury.
- Hypoxia.

Each of these co-morbidities will be identified by diagnostic codes and medications as proxies in the look-back period.

10.5 Data sources

The main characteristics of participating DAPs are presented in Table 2.

10.5.1 Spain (ES): VID (Valencia)

The Valencia health system integrated database (VID) is a set of multiple, public, population-wide electronic databases for the Valencia Region, the fourth most populated Spanish region, with ≈5 million inhabitants and an annual birth cohort of 48000 new-borns, representing 10.7% of the Spanish population and around 1% of the European population.[38] The VID provides exhaustive longitudinal information including sociodemographic and administrative data (sex, age, nationality, etc.), clinical (diagnoses, procedures, diagnostic tests, imaging, etc.), pharmaceutical (prescription, dispensation) and healthcare utilisation data from hospital care, emergency care departments, specialized care (including mental and obstetrics care), primary care and other public health services.[39] It also includes a set of associated population databases and registries of significant care areas such as cancer, rare diseases, vaccines, congenital anomalies, microbiology and others, and public health databases from the population screening programmes. All electronic health systems in the VID use the ICD-9-CM and the ICD-10-CM. All the information in the VID databases can be linked at the individual level through a single personal identification code. The databases were initiated at different moments in time, but all in all the VID provides comprehensive individual-level data fed by all the databases from 2008 to date. Information on PCR test results as well as serological/antibody tests results for the whole population of the Valencia region is available and linkable from the Microbiological Surveillance Network (RedMIVA). The Foundation for the Promotion of Health and Biomedical Research of Valencia Region (FISABIO) is Data Access Provider for VID. The ConcePTION pregnancy identification algorithm has already been used in VID. The results were compared with official statistics and within the knowledge gained from the source tables, with good agreement and confidence in the calculated pregnancy periods for the green, yellow and blue pregnancies.

10.5.2 Spain (ES): SIDIAP (Catalonia)

The Information System for the Development of Research in Primary Care (Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, SIDIAP) in Catalonia, Spain, is a primary care database set up by the Institute of Research in Primary Care (Institut Universitari D'Investigació en Atenció Primària Jordi Gol [IDIAPJGol]) and Catalan Institute of Health (Institut Català de la Salut) (https://www.sidiap.org/). The database collects information from 228 primary health care centres and includes more than 5.8 million patients covered by the Catalan Institute of Health (approximately 78% of the Catalan population) and is highly representative of the Catalan population.[40] SIDIAP data comprise the clinical and referral events registered by primary care health professionals (i.e., GPs, paediatricians, gynaecologists, midwives and nurses) and administrative staff in electronic medical records, comprehensive demographic information, community pharmacy invoicing data, specialist referrals, and primary care laboratory test results.[40] SIDIAP can also be linked to other data sources, such as the hospital discharge database, on a project-by-project basis. Health professionals gather this information using ICD-10-CM codes, ATC codes, and structured forms designed for the collection of variables relevant to primary care clinical management, such as country of origin, sex, age, height, weight, body mass index, tobacco and alcohol use, blood pressure measurements, and blood urine test results. SIDIAP is listed under the HMA-EMA catalogue of real world-data sources and studies.[41] The ConcePTION pregnancy algorithm to identify pregnancies has been previously used within SIDIAP. Approximately 50% to 60% of pregnant women in Catalonia are attended in the sexual and reproductive healthcare centres that contribute data to SIDIAP. Approximately 70% of infant records can be linked to maternal records and used for research.

10.5.3 Norway (NO): Norwegian data registries

The core data that UIO has access to are the health care administrative data banks of the entire Norwegian population, which amounts to approximately 5.3 million inhabitants.[42] Norway has a universal public health care system, consisting of primary health care services and specialist healthcare services. Many population-based health registries were established in the 1960s, with use of unique personal identifiers facilitating linkage between registries. The mandatory national health registries were established to maintain national functions. They are used for health analysis, health statistics, improving the quality of healthcare, research, administration and emergency preparedness. Information

about all Norwegian National Registries can be found here: www.fhi.no/en/more/access-to-data/about-the-national-health-registries2/. The Norwegian data sources in this project are the national mandatory Medical Birth Registry linked to the prescription registry and patient registries covering the secondary care (the National Patient Register) and the primary care (Norway Control and Payment of Health Reimbursement). The data set that will be used in this project has already been mapped onto the ConcePTION CDM, passed Data characterisation (quality checks). Moreover, the ConcePTION pregnancy algorithm has been quality assured on this data set (coverage 2008–2021).

10.5.4 United Kingdom (UK): CPRD

The CPRD is collated with the computerised medical records of GPs in the UK, who act as gatekeepers of the healthcare system and maintain patients' life-long electronic health records.[43] Here, GPs are not only responsible for primary health care and specialist referrals, but they also store information about those referrals and hospitalisations. Secondary care teams also provide information to GPs about their patients, including key diagnoses. CPRD is one of the largest primary care databases in the world, where it currently includes data on approximately 60 million individuals (acceptable for research purposes), of which 18 million are currently active (i.e., still alive and registered with the GP practice) with at least 20 years of follow-up for 25% of the patients, in over 2000 primary care practices across the country (https://cprd.com/Data). Both CPRD GOLD and Aurum databases will be used. The data recorded in the CPRD include demographic information, clinical events (signs, symptoms, diagnoses), prescription details, preventive care, immunisation, consultations (e.g., phone calls, letters, e-mails, in surgery, at home), laboratory tests, specialist referrals, hospital admissions, and major outcomes, including death.[44] CPRD data is coded using Read or SNOMED codes. Furthermore, validation studies are conducted regularly by comparing recorded data to written notes of general practitioners.[45] The population in the data source is generalisable to the UK population based on age, sex, socioeconomic class, and national geographic coverage. For the majority of the CPRD practices (>80%), the CPRD primary care data can be linked at the patient level to Hospital Episode Statistics (HES). HES includes all admission data to National Health Service (NHS) hospitals in England and private providers funded by NHS since 1997.[46] This dataset contains information on admission, discharge dates, diagnoses, specialist visits, and medical procedures. The diagnoses are classified based on the International Classification of Disease (ICD)-10 clinical coding system. Office for National Statistics (ONS) mortality data recording causes of death from death certificates are collated by ONS and routinely linked to CPRD and HES. Of relevance for this proposal, collaborative work between LSHTM and CPRD researchers has recently established a pregnancy register within the CPRD, identifying instances of pregnancy and pregnancy outcomes since 1987. The CPRD is listed under the ENCePP resources database, and access will be provided by Utrecht University, who has a licence to use CPRD data with HES linkage.

10.5.5 Finland (FI): Finnish Health Registries

Universal health insurance is accessible for all citizens and permanent residents in Finland. Wellbeing services counties (n=22) are responsible for arranging health care funded by state. Health services are divided into primary health care and specialised medical care. The data that THL provides access to is most healthcare registries covering the whole population of Finland (around 5.6 million inhabitants). The core data of the Drugs and Pregnancy project (https://thl.fi/en/research-and-development/research-and-projects/drugs-and-pregnancy) includes data from Medical Birth Register, Register of Congenital Malformations and Register of Induced Abortions from 1996 onwards. Drugs and Pregnancy Database also includes following registries maintained by the Kela: Special refund codes and diagnoses three months before pregnancy to three months following delivery or abortion and reimbursed drug refills three months before pregnancy to three months following delivery or abortion also 1996 onwards. Electronic prescriptions and refills linked to pregnancy data is available one year before pregnancy and six months after delivery from 2017 onwards. Drugs and Pregnancy Database currently includes all pregnancies ending in delivery or induced abortion in 1996-2022 the total amount being around 1.7 million pregnancies. Additional data sources maintained or accessed by THL and previously mapped to ConcePTION CDM are Care Register for Health Care (HILMO), Register of Primary Health Care visits (Avohilmo), Cause of Death Registry for infant and maternal deaths. These data sources have

been extensively used in registry-based research.[47-50] Data collection is mandatory by law and does not require informed consent from the recorded subjects. Data is stored on an individual level and can be linked by the personal identification number assigned to all citizens and permanent residents in Finland at birth or upon immigration. The PROMPT stream of ConcePTION pregnancy identification algorithm has been used at THL. The results were reviewed against the subject knowledge from the source tables and good agreement obtained for included pregnancy periods with green and yellow quality.

10.5.6 France (FR): EFEMERIS

EFEMERIS is a cohort of pregnant women covered by the French Health Insurance System in Haute-Garonne (South-west France), built to conduct drug utilisation and medication safety studies in pregnant women (www.efemeris.fr).[51] EFEMERIS data collection started in July 2004. It is ongoing and updated once a year. EFEMERIS comprises data on: all prescriptions redeemed in out-patient pharmacies, prior to and during pregnancy; administrative and medical data about the mother and the child through children's certificates filled in during the compulsory medical examinations at birth, 9 and 24 months; data about Terminations Of Pregnancy for Foetal Anomaly (TOPFAs); and the nature and date of termination of pregnancy (elective termination, stillbirth, and spontaneous abortion).[52]

This was approved by the French Data Protection Agency on 7 April 2005 (authorisation number 05-1140). Everyone requesting data access and doing statistical analyses are signing a confidentiality agreement form. All requests need to include at least one EFEMERIS investigator. Access requests to EFEMERIS for research purpose must be approved by the Steering Committee and data providers. Currently data on 180,458 mother-outcome pairs are recorded in EFEMERIS for the period between mid-2004 to end of 2021. Part of the EFEMERIS dataset (only data from 2004-2013) has been linked with the RHE31 dataset (Haute-Garonne Child Disability Registry), providing exhaustive data about validated medical diagnosis of severe NDD at the age of 5 and/or 8 years. The disabilities registered in the REH31 include autism spectrum disorders (ASD), pervasive developmental disorders (PDD), severe sensory impairments, motor disabilities and trisomy 21. The French POMME [PrescriptiOn Médicaments Mères Enfants (Prescription-Drugs-Mothers-Children)] cohorts hold anonymised data on children from conception and during their childhood. POMME cohorts are subsets of EFEMERIS data where the children are followed up over time, it includes children born between 1 July 2010 and 30 June 2011 (POMME-2010) and between 1 July 2015 and 20 June 2016 (POMME-2015). POMME-2010 includes more than 8000 children and POMME-2015 more than 10,000 children. The cohorts are updated annually. Currently, available data concern children until 10 years of age for the POMME-2010 cohort and until 5 years of age for the POMME-2015 cohort. In addition to data already collected in EFEMERIS, POMMEs records data on medicines and medical care prescribed and reimbursed to the children during childhood. (http://www.efemeris.fr/communications.html). The datasets that will be used in this project have already been mapped onto the ConcePTION CDM, passed Data characterisation (quality checks). Moreover, the ConcePTION pregnancy algorithm has been quality assured on this data set.

10.5.7 Italy (IT): VAL PADANA LHU

The Val Padana LHU database is a claims database containing patient-level data from the provinces of Mantova and Cremona, in Lombardy region. The coverage of this database is high: from 2008 to 2024, the catchment area population consists of more than 780,000 persons (7.8% of the Lombardy regional population). The Val Padana linkage database consists of several datasets which are linked through a unique patient identifier: a demographic registry, pharmacy claims database with information on concerning all dispensed drugs reimbursed by the Italian NHS, as well as hospital discharge diagnose databases, emergency department admissions database, claims for diagnostic and laboratory tests ordered, and a registry of patients exempt from healthcare service co-payment (e.g. diabetes mellitus, dementia, and other chronic diseases). Birth registry is also available; it provides mother-child linkage and information on child and maternal healthcare as well as sociodemographic data and risk factors. Moreover, all ADRs registered at birth are traceable from the birth registry. There is no algorithm to

identify the beginning of a pregnancy. Val Padana LHU is full member of the European network of population-based registries for the epidemiological surveillance of congenital anomalies (EUROCAT). Val Padana Registry includes cases of congenital anomalies in live births, stillbirths and TOPFA (Terminations of Pregnancy for Foetal Anomaly) that occurred in the first year of life since 2002 (Mantova province) and 2008 (Cremona province). Data is updated to 2020. Patient level data from these claims databases, including other drugs reimbursed by the NHS and dispensed by community pharmacies, can be linked together, using a unique patient identifier. The healthcare information in the databases is coded using international coding systems, such as ICD-9-CM for diagnoses and ATC classification for drugs.

10.5.8 SPAIN (ES): BIFAP

BIFAP (Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público), a computerised database of medical records of primary care (www.bifap.aemps.es),[53,54] is a non-profit research project funded by the Spanish Agency for Medicines and Medical Devices (AEMPS). BIFAP is listed under the ENCePP resources databases (Data source ID 21501). The project started in 2001 and currently includes anonymised clinical and prescription/dispensing data on 22 million (17 active population) patients with clinical information from 15,373 physicians (GPs and paediatricians) from nine participant Autonomous Regions. Those patients represent 94% of the population in participating regions, and 37% of the total Spanish population. Mean duration of follow up in the database is 10 years. Information collected by PCPs includes administrative, socio-demographic, lifestyle, and other general data, clinical diagnosis and health problems, results of diagnostic procedures, interventions, and prescriptions/dispensations. Diagnoses are classified according to the International Classification of Primary Care (ICPC)-2, ICD-9CM and SNOMEDCT system, and a variable proportion of clinical information is registered in "medical notes" in free text fields in the EMR. Additionally, information on hospital discharge diagnoses coded in ICD-10 terminology as well as public specialist prescribing are linked to patients included in BIFAP for a subset of periods and regions participating in the database. All information on prescriptions of medicines by the PCP is incorporated and linked by the PCP to a health problem (episode of care), and information on the dispensing of medicines at pharmacies is extracted from the e-prescription system that is widely implemented in Spain. A mother-child linkage has not been established so far and several options are being exploring with the regional data providers to research in the medium-term. Therefore, BIFAP will participate in specific objectives only.

In BIFAP, two different pregnancy algorithms have been developed and tested: 1) the ConcePTION algorithm retrieved almost 2 million pregnancies between 2008-2021 from primary and hospital medical records. Pregnancy episodes including ongoing pregnancies and pregnancies with and without (may include early spontaneous abortions) unknown outcomes, could be identified; 2) Furthermore, a previous study has demonstrated the usefulness of BIFAP database for studies on drug utilisation during pregnancy (regardless the outcome) using an in-house developed pregnancy-algorithm with the collaboration of experts in the field.[55]

10.5.9 The Netherlands (NL): PHARMO Data Network

The PHARMO Data Network is a population-based network of electronic health records databases.[56] It combines data from different primary and secondary healthcare settings in the Netherlands. These data sources include data from general practices, in- and out-patient pharmacies, clinical laboratories, hospitals, the cancer registry, the pathology registry, and the perinatal registry. These data sources are linked on a patient level through validated algorithms. The longitudinal nature of the PHARMO Data Network enables to follow-up more than 4 million (25%) residents of a well-defined population in the Netherlands for an average of 10 years.[57]

PHARMO established the PHARMO Perinatal Research Network (PPRN) which is set up as a resource for life course perinatal and paediatric research by linking population-based data from existing registrations.[58] The PPRN is a unique linkage of the Netherlands Perinatal Registry (Perined) and the

PHARMO Data Network. With data collection starting in 1999, the linkage of these population-based data sources facilitates large-scale observational pharmacoepidemiological perinatal research. It contains pre-conceptional information on maternal healthcare extending into long-term follow-up and outcomes after birth for both mother and child, with ongoing annual updates of the routinely collected data. Perined is a nationwide registry in which medical data around pregnancy and birth are included from pregnancies with a gestational age of at least 16 weeks (including terminated pregnancies and stillborn). Among the items reported are maternal demographics and medical conditions, pregnancy complications and details concerning labour, birth and neonatal outcomes.

10.6 Study size

The study comprises information on over 63 million active subjects as source population, among those the majority will be part of the base population of women of childbearing potential and men. For different sub-objectives the size of the population will differ, but we have no specific hypothesis to test and therefore no specific sample size calculation is required.

10.7 Data management

The study will be conducted in a distributed manner using the EU PE&PV, ConcepTION, UMCU, ARS and VAC4EU tools, procedures, and pipeline. Figure 4 **Error! Reference source not found.**depicts this pipeline from a programming perspective, specifying the data sets (D) and transformation processes (T). Programming follows this pipeline, with involvement of different types of experts.

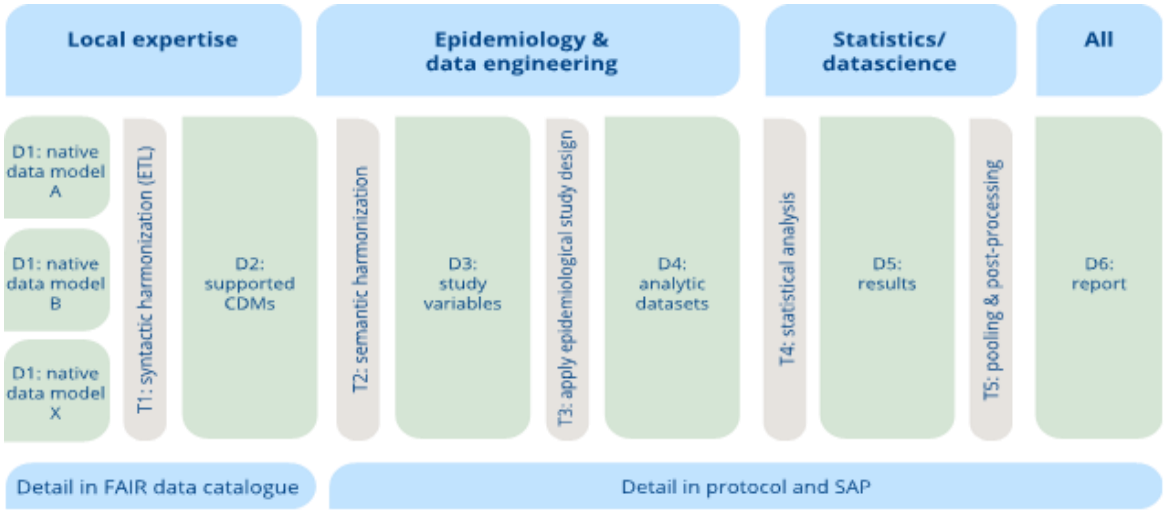

Figure 4. RWE data transformation pipeline from a programming perspective. T: transformation steps, D: data sets.

D1: Original data can be in any native format

The RWD-RWE pipeline used by EU PE&PV, ConcePTION, and VAC4EU starts with data banks that are controlled by DAPs. These can be in any format and data stays local. The ETL design is shared in a searchable FAIR catalogue. The ConcePTION Molgenis data catalogue is a metadata management tool designed to contain searchable meta-data describing organisations that can provide access to specific data sources.

T1: Syntactic harmonisation (ETL)

Syntactic harmonisation is conducted through an extraction, transformation, and loading (ETL) process of native data into the requested CDM. To harmonise the structure of the data sets stored and maintained by each data partner, a shared syntactic foundation is used. The ETL process has various structured steps as described by Thurin et al.[59] Metadata (descriptive data about the data sources and databanks) & data dictionaries, are uploaded in ConcePTION data catalogue.

D2: Common Data Model

For this project, the CDM (D2) of the ConcePTION pipeline, version v2.2., will be utilised, which is available as an open-source CDM. In this CDM, data are represented in a common structure, but the values of the data remain in their original language (e.g. codes will have either ICD9/10/ICPC/Italian code system for exemptions/SNOMED/Medcode values).

T2: Semantic harmonisation

During the T2 step, many data transformations occur related to the completion of missing features in the data. Based on the relevant diagnostic medical codes and keywords, as well as other relevant concepts (e.g., medications), one or more ***phenotype algorithms*** are constructed (typically one sensitive, or broad, algorithm and one specific, or narrow, algorithm) to operationalise the identification and measurement of each event. In this step we conduct time anchoring (observation periods, look back periods), clean the data, sort on record level, aggregate across multiple records, and combine concepts for implantation of algorithms, and rule-based creation of study variables.

In this phase of creation of study variables, the semantic mapping is conducted. This semantic mapping across different vocabularies is conducted as part of the R-study script using different functionalities. To reconcile differences between different terminologies and native data availability, machine readable code lists are used that comprise the terminologies that are used in the network (e.g. ICD-9, ICD10, SNOMED, ICPC and DAP specific adaptations). This is combined with the BRIDGE metadata file that defines risk windows, look-back periods, and algorithms for each study variable.[60]

D3: Study variables

D3 datasets are interim data sets with information on study variables for each study participant, the unit may be a person, a medicine, or episode of time. The design of these datasets is described in codebooks. Examples of D3 datasets are the outputs of the ConcePTION pregnancy algorithm, functions that define smoking. Multiple functions/packages exist for different study variables.

T3: Application of epidemiological design

In the T3 step epidemiological designs are applied such as sampling, matching (on specific variables and/or propensity scores), and selection based on inclusion and exclusion criteria using the study variables in the D3 datasets. The designs will be implemented for the various study objectives using R-scripts, and these may use the existing functions (R-cran) or functions that have been developed in the VAC4EU and ConcePTION community.

D4: Analytical data set

D4 is an analytical dataset, and multiple D4 data sets may be produced based on the objectives of the study. The format is described initially in a code book for communication between programmers and statisticians.

T4: Statistical analysis

This step in the data transformation pipeline will produce statistical estimates such as descriptives (counts, percentages), distributions (mean, percentiles), rates (prevalence, incidence), regression coefficients, or other relevant estimates. This will be conducted using R.

D5: Results

D5 is the set of estimands, tables or aggregate data that is transferred from the DAPs to the Digital Research Environment (DRE). The aggregated results produced by these scripts at the DAPs site will be uploaded to the UMCU Digital Research Environment (DRE) for post-processing, pooling and visualisation (see Figure 4). The DRE is a cloud-based, globally available research environment where data are stored and organised securely and where researchers can collaborate. The DRE is made available through UMCU (The anDREa consortium 2021). The DRE applies double authentication where researchers can collaborate using data that are stored and organised securely. UMC Utrecht is responsible for data processing and data security.

All researchers who need access to the DRE will be granted access to study-specific secure workspaces by UMCU. Access to the workspaces will be possible only after double authentication using an identification code and password together with the user's mobile phone for authentication.

Uploading of files will be possible for all researchers with access to the workspace within the DRE. Downloading of files will be possible only after requesting and receiving permission from a workspace member with an "owner" role, who will be a UMCU team member.

T5: Post-processing/ pooling

In this step, the result from different DAPs is pooled and converted in tables and figures for reporting.

Scripting and deployment

The analytical R scripts that produce the T2-T4 steps are produced on institutional GitHubs for version control. Links to the latest script will be distributed to DAPs for local deployment. Any issues can be notified on the private GitHub, and the data engineers who are responsible for the R code will work with the local DAP to resolve issues if they occur. After the final report is accepted the script will be made publicly available through GitHub and get a digital object identifier through Zenodo platform.

10.8 Data analysis

All scripts will be coded based on the data transformation pipeline described in Figure 4 in R.

Objective 1.1

Incidence and prevalence rates of ASM use will be calculated in the total population among both women of childbearing potential and men >12-year-old overall (N03A and N02BF), by subgroup, and by

individual generic substance. Annual incidence and prevalence rates of ASM use will be estimated over the study period, for each DAP, and stratified by sex, age group, calendar year. For incidence rates per calendar year, we will use a look-back period of one year of no ASM use. A person will be counted as an incident (or new) user in a specific year if they have a first prescription that year, also considering the 1-year look-back period. Subjects will be counted as prevalent (or current) users of ASMs in a year if they start a prescription or were on a prescription that year. The duration of the prescription should cover at least one day of that year.

Objective 1.2

The duration of ASM use in the ASM user's cohort (i.e., all women of childbearing potential and men who used ASMs during study period) will be estimated based on the constructed treatment episodes for each individual ASM, subgroup, and the overall group (N03A and N02BF). The number of discontinuers of ASMs (individual drugs, subgroups, and overall) will be counted per year, for each DAP, stratified by sex, age group, indication, comorbidities, and calendar year. Annual discontinuation rates will be provided by dividing the number of discontinuers for each ASM and stratum by the total number of prevalent (current) users of the ASM in that stratum (of sex, age, indication and comorbidity) per calendar year, for each DAP. The use of alternative medications in prevalent users of ASMs will be counted during the study period as the yearly number of prescriptions/dispensings, for each DAP, and will be reported separately for each of the indications of ASM. The annual incidence of treatment switches from an ASMs to another ASM or to an alternative medication will be estimated as the number of discontinuers who switch in a year divided by the total number of current ASM users that year, stratified by sex, age group, indication, comorbidities, and calendar year.

Objective 1.3

Here we will assess pre-pregnancy ASM use, initiation of ASMs during pregnancy, and continuous use of ASMs during pregnancy for individual drugs, subgroups, and overall group, among pregnant women. The estimations will be based on the constructed treatment episodes by the CreateDOT and AdhereR functions. Annual rates of pre-pregnancy ASM use will be estimated, where the numerator is the number of pregnant women (unique pregnancies, not women) who had a treatment episode of an ASM in the year before pregnancy, falling within both 12-6 months before pregnancy and 6-0 months before pregnancy, and the denominator is the number of total pregnant women in the data source in a calendar year. Annual rates of initiation of ASMs during pregnancy will be calculated considering the number of pregnancies with an ASM treatment episode starting during any trimester, but no such ASM use (treatment episode) in the 12 months prior to pregnancy start. The annual rate of continuous use of ASMs will be calculated with the number of pregnancies with a pre-pregnancy ASM use that runs into the first, second and third trimester. For both initiation rates of ASMs and continuous use rates of ASM, the dominator will be the total number of pregnancies in that year in the data source.

Objective 1.4

Pre-pregnancy discontinuation rates of ASMs, early and late discontinuation rates during pregnancy, polytherapy rates, and rate of switching from an ASM to another ASM or to an alternative medication among pregnant women will be estimated in all data sources, and stratified by indication. We will estimate annual pre-pregnancy discontinuation rates with the number of pregnant women who had pre-pregnancy ASM use that does not run into the pregnancy period in the numerator. Annual early and late discontinuation rates of ASM will be calculated with the number of pregnant women in each data source and calendar year with pre-pregnancy ASM use that continued to first and second trimesters only, respectively. The denominators for all discontinuation rates will be the total number of pregnant women in that year per each data source, who were using ASM before pregnancy (using numbers of

prevalent ASM users from Obj. 1.1). Annual rates of polytherapy of ASM will be estimated as the number of pregnant women with a treatment episode of ≥2 distinct ASMs in the first trimester that both take ≥3 months, by the total number of pregnant women in each data source and calendar year. Annual rate of switching of ASMs is defined with the number of pregnant women who had a particular ASM treatment episode in the year prior to pregnancy that ends before the pregnancy period, and initiation of a different ASM in one of the three trimesters, by the number of pregnant women who continued using the original ASM during pregnancy. Based on these findings, we will compare discontinuation and switching rates of various ASMs (individual drugs, ATC subgroups, and overall ASMs), per each DAP, and stratified by indications, using line charts, and Sankey diagrams.

Objective 1.5

Finally, we 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. To implement this, we will calculate daily dose in DDDs of the prescribed/dispensed ASMs in the previously estimated treatment episodes, using the number of tablets taken per day, the strength (dose) of the tablet, and the length of treatment. We will then calculate the mean weighted daily dose of ASMs in various time windows before and during pregnancy (3-months before and first, second and third trimesters) for each individual based on the constructed treatment episodes and their contribution to each time window. Then, the calculated mean weighted daily doses of ASMs will be stratified as low (<0.5 DDD), mid (0.5-1.49 DDD), and high (>1.5 DDD) for each individual. Finally, setting the start of pregnancy (from the pregnancy algorithm) as the 'transition point', we 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). This will only be done in data sources with a recorded prescribed dose regimen.

10.9 Quality control

Data sources will be transforming their data instances into the ConcePTION CDM as described above. To verify the correctness of the data instance, the INSIGHT quality checks,[61] will be required to run. Level 1,2 and 3 checks are standardised quality check programs against the ConcePTION CDM that are publicly available with detailed SAPs, below:

• https://github.com/UMC-Utrecht-RWE/INSIGHT-Level1

• https://github.com/UMC-Utrecht-RWE/INSIGHT-Level2

• https://github.com/UMC-Utrecht-RWE/ConcePTION-INSIGHT-Level3

Level 1 - Data completeness (including level 1b)

The purpose of the level 1 check is to verify the completeness of the ETL process and the data in the variables. Examples of tests are:

- Presence of variables in each of the CDM tables in D2
- Checks for misspelling and letter case in variable names in each of the CDM tables
- Verification of vocabularies
- Check date formats
- Check conventions of values
- Missing data analysis
- Frequency tables for categorical variables

Level 2 - Data logic/consistency

Real data is not random but follow certain logical constraints that reflect rules governing real-world situations. Examples of indicators generated by level 2 checks are:

- Event dates before date of birth.
- Event dates after date of death.
- Event dates out of observation periods.
- Subjects having an observation but not present in the PERSONS table.
- Observations associated with a visit id and occurred before/after the visit start/end date.
- Subjects younger than 12 years old reported as parents.
- Age at the observation period older than 115 y old

Level 3 - Data content characterisation

Level 3 checks review patterns of study variables over time, age within and between data sources. We will use 7 modules, which may be used depending on the study variables.

- Source and study population
- Medicines
- Diagnoses
- Pregnancy
- Populations of interest
- Health-seeking behaviour and lifestyle factors.

General approach to quality of R-coding

Data Management will follow standard operating procedures. R programs will be made available by UMC Utrecht (INSIGHT data quality checks), UU (analysis code) and ARS (Pregnancy algorithm). UU will create clear documentation of the data management steps.

Quality of study conduct

This research will be conducted according to the guidelines for Good Pharmacoepidemiology Practice (GPP) (International Society for Pharmacoepidemiology 2008) and according to the ENCePP code of conduct (European Medicines Agency 2018).[62,63] All partners and principal investigators have experience in conducting pharmacovigilance/pharmacoepidemiological research and research is done by researchers trained in pharmacoepidemiology or pharmacovigilance. Utrecht University and University Medical Center Utrecht (data management) work according to a quality management system based on ISO 9001 principles and are certified.

All partners are ENCePP centres. The quality management system is system and process-oriented and based on continuous improvement. The system is based upon standard operating procedures implemented throughout the divisions with regular internal audits as well as external audits that lead to certification. The quality management system is based on national and international external quality requirements where available and pertinent, including the guidelines for Good Pharmacoepidemiological Practices, RECORD-PE, ENCePP Guide on Methodological Standards in Pharmacoepidemiology, Good Clinical Practice, and Good Clinical Data management. Practice as well as national and international guidelines and legislation concerning data-handling and privacy issues. All deliverables will be reviewed by project partners.

10.10 Limitations of the research methods

10.10.1. Limitations related to data sources

This proposal uses 9 available data sources, which capture different databanks and different underlying populations. The EFEMERIS and THL data source are cohorts of pregnancies, whereas other data banks are based on routine care, and record linkage. Although the data sources do not all capture the same type of information we will work with one protocol, a common data model and one script, to minimise heterogeneity. Previous work in CONSIGN has shown that it is possible to overcome the heterogeneity in the systems.[64] Using prescription/dispensing data on exposure drugs can automatically introduce misclassification of exposure bias, as there is no other information on actual use of medications,

although repeated prescriptions may show actual use. This is especially concerning for gabapentinoids and particularly pregabalin, which unlike other ASMs have the potential to misuse, and the illicit drug use is normally not captured in EHDs.

Also, it may happen that misclassification affects the pregnancy cohort in various ways: 1) Persons may be classified as pregnant even if they are not. This is unlikely, because the ConcePTION Pregnancy Algorithm builds pregnancy episodes based on records that imply at face value that the person is pregnant at record date. But, it is not impossible. 2) Start date of the pregnancy may be misclassified. This may be a risk especially in pregnancy color-coded with 'yellow' or 'red', because start date has been imputed in such pregnancies, possibly based on a predictive model. The performance of the model will be assessed to evaluate the extent of misclassification. 3) End date of the pregnancy may be misclassified. This may be a risk especially in pregnancy color-coded with 'yellow' or 'blue', because end date has been imputed in such pregnancies. Moreover, the classification of type of end of pregnancy includes several unspecified types (e.g., 'unknown', 'unfavourable outcome unspecified'). In data sources where pregnancies are detected at very early stages (namely, before the end of the first trimester) many pregnancies with unspecified outcome and color-coded as red may be interpreted as early pregnancy losses that did not need urgent medical attention (it is estimated that 80% of pregnancy losses occurs before the end of the first trimester.[65] To mitigate the risk of misclassification, samples of pregnancies included in the ConcePTION Pregnancy Algorithm output are manually verified by experts in the DAP's organisation.

Additionally, not all data sources will capture details on prescribed dose of ASM, which means that prescription duration need to be based on a fixed duration or DDD based approach. These data sources cannot be used to look at dose changes. Another limitation could be data recency and data update times in different data sources that were included. However, a long study period (i.e., since 2000) would enable us to observe the trends in ASM use across almost two decades in all centres. The PHARMO Data Network's PPRN brings together data from various sources, with different data collection periods and catchment areas. Therefore, the final size and coverage of the study population for the Netherlands will depend on the databases included.

10.10.2. Limitations in proposed methodology

Our operational definitions of treatment episodes with a grace period of 30 days, temporary break (between 30-120 days of no new prescription/dispensing), ASM discontinuation (no new record after 90 days), and switching from an ASM to another ASM or an alternative medicine might not reflect the exact clinical scenarios in case of all ASMs, especially when using data from diverse EHDs. One especial case would be misclassification of prevalent users as incident users due to considering not long enough look-back periods. Due to this, we will not estimate incident use of ASMs among women and men of childbearing potential and initiation of ASM during pregnancy in data sources EFEMERIS and THL that we only have 2.5 or 3-months look-back data for medications. But the overall approach is based on prior drug utilisation studies on the same topic,[8,36] and same definitions for all ASMs across all centres, which considering the limitations and data quality will assist in comparability of findings.

Another limitation could be operational definitions for high, medium, and low daily doses of ASMs based on DDD data, which might not always reflect the actual clinical situation. But considering the diversity of data sources and healthcare systems involved, this seems the only feasible option in such a multi-database study. Also, capturing the right doses would be difficult when prescriptions are not renewed but patients were using the old prescription with new instructions from clinician, which is not visible in all our included data sources. This will be accounted for when interpreting findings from the dose analyses.

11 Protection of Human Subjects

This is a non-interventional study using secondary data collection and poses only very limited risks for individuals. Each research partner will apply for an independent ethical and/or institutional board review according to local regulations. Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

Patient information

This study involves data that exists in a pseudonymized structured format locally and aggregated data centrally and contains no patient personal information. All parties will comply with all applicable laws, including laws regarding the implementation of organisational and technical measures to ensure the protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws. Patient personal data will be stored at DAPs in encrypted electronic form and will be password protected to ensure that only authorised study staff have access. DAPs will implement appropriate technical and organisational measures to ensure that personal data can be recovered in the event of a disaster. In the event of a potential personal data breach, DAPs shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

Patient consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from individuals is not required.

12 Management and Reporting of Adverse Events/Reactions

This study is a retrospective drug utilisation study of ASMs, and not a prospective clinical trial or cohort study. Thus, management and reporting of adverse events/reactions will not be relevant and not feasible within the scope of our used methodologies.

For studies in which the research team uses only data from automated EHDs, according to the International Society for Pharmacoepidemiology Guidelines for GPP:

"Aggregate analysis of database studies can identify an unexpected increase in risk associated with a particular exposure. Such studies may be reportable as study reports, but typically do not require reporting of individual cases. Moreover, access to automated databases does not confer a special obligation to assess and/or report any individual events contained in the databases. Formal studies conducted using these databases should adhere to these guidelines."

For non-interventional study designs that are based on secondary use of data, such as studies based on medical chart reviews or electronic health records, systematic reviews, or meta-analyses, reporting of adverse events/adverse drug reactions is not required. Reports of adverse events/adverse drug reactions should only be summarized in the study report, where applicable.

According to the EMA Guideline on GVP, Module VI – Management and Reporting of Adverse Reactions to Medicinal Products,

"All adverse events/reactions collected as part of [non-interventional post-authorization studies with a design based on secondary use of data], the submission of suspected adverse reactions in the form of

[individual case safety reports] is not required. All adverse events/reactions collected for the study should be recorded and summarized in the interim safety analysis and in the final study report."

Module VIII – Post-Authorization Safety Studies echoes this approach. Legislation in the EU further states that for certain study designs such as retrospective cohort studies, particularly those involving electronic health records, it may not be feasible to make a causality assessment at the individual case level.

13 Plans for Disseminating and Communicating Study Results

As per EMA Good Pharmacovigilance Practices (GVP) Module VIII, the study and its protocol has been registered in the HMA-EMA Catalogues of RWD studies prior to the start of data collection.[66] Results of analyses and interpretation will be delivered in report form. Study results will be published following guidelines, including those for authorship, established by the ICMJE. When reporting the results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist and the RECORD-PE extension will be followed. Independent publication rights will be granted to the research team in line with Section VIII.B.5. Publication of study results, of the EMA GVP Module VIII: Post-Authorisation Safety Studies. Upon study completion and finalisation of the study report, the results of this study will be submitted for publication, preferably in a relevant peer-reviewed journal and posted in the HMA-EMA Catalogues of RWD studies. Also, study findings will be presented in national, regional and international conferences, when applicable. Analytical programs will be posted in a public GitHub & Zenodo repository after acceptance of the report. The study report will also be publicly posted on Zenodo (VAC4EU, EU PE&PV) and cross-linked to the HMA-EMA Catalogues of RWD studies.

14 References

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