



Study Protocol

P5-C1-012

DARWIN EU® - Sex differences in prescribing of benzodiazepines and benzodiazepine-related medicines over time in adolescents and young adults

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Version 5.0

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Public

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Study title	DARWIN EU® - Sex differences in prescribing of benzodiazepines and benzodiazepine-related medicines over time in adolescents and young adults	
Protocol version	V5.0	
Date	28/09/2026	
EUPAS number	EUPAS1000001096	
Active Substance	Drug class	WHO ATC code
	Anxiolytic benzodiazepines	N05BA
	Hypnotic benzodiazepines	N05CD
	Antiepileptic benzodiazepines	N03AE
	Benzodiazepine-related drugs	N05CF
	Ingredient	WHO ATC code
	Diazepam	N05BA01
	Alprazolam	N05BA12
Medicinal Product	Not applicable	
Research question and objectives	<u>Research question:</u>	
	What are the sex-related prescribing patterns of benzodiazepines and benzodiazepine-related medicines over time in adolescents and young adults?	
	<u>Study objectives:</u> 1) To estimate the incidence and prevalence of prescriptions of benzodiazepines and benzodiazepine-related medicines over time, overall and by type of benzodiazepine at treatment initiation. 2) To describe demographic and clinical characteristics of individuals prescribed with benzodiazepines and benzodiazepine-related medicines. 3) To estimate the duration of benzodiazepine and benzodiazepine-related medicines use. All analyses will be presented by pre-specified drug classes and selected ingredients. Analyses for <i>objective 1</i> will be stratified by calendar year, sex, and age group, whereas analyses for <i>objective 2</i> and <i>3</i> will be stratified by sex and age group.	
Countries of study	Denmark, Finland, Germany, Spain, the Netherlands, the United Kingdom	
Authors	Ellen Gerritsen, e.gerritsen@darwin-eu.org Dina Vojinovic, d.vojinovic@darwin-eu.org	

LIST OF ABBREVIATIONS

Acronyms/terms	Description
ATC	Anatomical Therapeutic Chemical
CC	Coordination Centre
CDM	Common Data Model
CI	Confidence Interval
CPRD GOLD	Clinical Practice Research Datalink GOLD
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DK-DHR	Danish Data Health Registries
DKMA	Danish Medicines Agency
DRE	Digital Research Environment
DTZ	Data Transfer Zone
EHR	Electronic Health Records
EMA	European Medicines Agency
EMC	Erasmus University Medical Center
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ETL	Extract, Transform, Load
EU	European Union
EUPAS	EU Post-Authorisation Studies Register
FinOMOP-THL	Finnish Care Register for Health Care
GDPR	General Data Protection Regulation
GP	General Practitioner
LOINC	Logical Observation Identifiers Names and Codes
ICD	International Classification of Diseases
IDIAPJGol	Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina
IPCI	Integrated Primary Care Information
IQR	Interquartile range
IQVIA DA Germany	IQVIA Disease Analyzer Germany
IRB	Institutional Review Board
N	Number of individuals
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
Oxford NDORMS	University of Oxford - Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences
RxNorm	Medical prescription normalised
SIDIAP	The Information System for Research in Primary Care
SNOMED	Systematized Nomenclature of Medicine
WHO	World Health Organization

1. TITLE

DARWIN EU® - Sex differences in prescribing of benzodiazepines and benzodiazepine-related medicines over time in adolescents and young adults.

2. DESCRIPTION OF THE STUDY TEAM

Study team role	Names	Organisation
Principal Investigator	Ellen Gerritsen Dina Vojinovic	IQVIA
Data Scientist	Akram Mendez Gargi Jadhav	IQVIA
Study Manager	Natasha Yefimenko	Erasmus MC
Data source	Names	Data Partner Organisation*
Danish Data Health Registries (DK-DHR)	Elvira Bräuner Susanne Bruun	Danish Medicines Agency (DKMA)
Finnish Care Register for Health Care (FinOMOP-THL)	Toni Lehtonen Tiina Wahlfors Petteri Hovi Gustav Klingstedt Tuomo Susi Terhi Kilpi Miia Ryhänen-Tompuri Laura Salonen	FinOMOP
IQVIA Disease Analyzer Germany (IQVIA DA Germany)	James Brash	IQVIA
The Information System for Research in Primary Care (SIDIAP)	Laura Granés González Agustina Giuliodori Picco Talita Duarte Salles Elena Roel Herranz	Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol)
Integrated Primary Care Information (IPCI)	Katia Verhamme Marcel de Wilde Guido van Leeuwen Mees Mosseveld	Erasmus University Medical Center (EMC)
Clinical Practice Research Datalink GOLD (CPRD GOLD)	Antonella Delmestri Marta Pineda Moncusí Mandickel Kamtengeni Hezekiah Omulo	University of Oxford - Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences (Oxford NDORMS)

*Data Partners do not have an investigator role. The role of the Data Partners is to execute analytical code and review and approve outputs using their expert knowledge about their respective data sources.

3. ABSTRACT

Title

DARWIN EU® - Sex differences in prescribing of benzodiazepines and benzodiazepine-related medicines over time in adolescents and young adults

Rationale and background

The widespread prescribing of benzodiazepines and related medicines has raised ongoing public health concerns due to risks, such as tolerance, dependence, withdrawal, and serious side effects. Evidence on use of benzodiazepines in younger populations is limited. Given the prevalence of off-label prescribing and the unclear balance of risks and benefits in younger populations, there is a need to better understand prescribing patterns.

In addition, the COVID-19 pandemic has had a large impact on mental health, particularly among young females. However, its potential influence on prescribing patterns of anxiolytics, including benzodiazepines, remains unclear.

To address these gaps, this study aims to examine patterns in prescribing of benzodiazepines over time among adolescents and young adults and to assess differences in prescribing patterns between females and males, including changes during the COVID-19 pandemic period.

Research question and objectives

Research question

What are the sex-related prescribing patterns of benzodiazepines and benzodiazepine-related medicines over time in adolescents and young adults?

Objectives

The specific objectives of this study are:

1. To estimate the incidence and prevalence of prescriptions of benzodiazepines and benzodiazepine-related medicines over time, overall and by type of benzodiazepine at treatment initiation.
2. To describe demographic and clinical characteristics of individuals prescribed with benzodiazepines and benzodiazepine-related medicines.
3. To estimate the duration of benzodiazepine and benzodiazepine-related medicines use.

All analyses will be presented by pre-specified drug classes and selected ingredients. Analyses for *objective 1* will be stratified by calendar year, sex, and age group, whereas analyses for *objective 2* and *3* will be stratified by sex and age group.

Methods

Study design

This will be a descriptive retrospective cohort study.

Population

For *objective 1*, the study population will include all adolescents and young adults aged ≥ 12 to ≤ 25 years present in the data source within the study period from 01/01/2015 to 31/12/2025 (or the end of available data, if earlier). For the incidence analysis, individuals are also required to have at least 365 days of data visibility, and no recorded benzodiazepine use during the 365 days prior to the index date.

For *objectives 2* and *3*, the study population will include all adolescents and young adults aged ≥ 12 to ≤ 25 years with a first prescription for a benzodiazepine product recorded within the study period from

01/01/2015 to 31/12/2025 (or the end of available data, if earlier). Eligible individuals are required to have at least 365 days of data visibility prior to the date of treatment initiation and no recorded benzodiazepine use in the 365 days preceding treatment initiation.

Variables

Exposure: Benzodiazepines and benzodiazepine-related medicines presented by:

- Drug classes (anxiolytic benzodiazepines (WHO ATC code N05BA), hypnotic benzodiazepines (WHO ATC code N05CD), antiepileptic benzodiazepines (WHO ATC code N03AE), and benzodiazepine-related drugs (WHO ATC code N05CF).
- Selected ingredients: diazepam (WHO ATC code N05BA01) and alprazolam (WHO ATC code N05BA12).

Relevant covariates and other variables: Demographics, pre-specified indication for use, co-prescribing of other psychotropic medications, type of healthcare provider (*if feasible*), and comorbidities.

Data sources

1. Denmark: Danish Data Health Registries (DK-DHR)
2. Finland: Finnish Care Register for Health Care (FinOMOP-THL)
3. Germany: IQVIA Disease Analyzer Germany (IQVIA DA Germany)
4. Spain: The Information System for Research in Primary Care (SIDIAP)
5. The Netherlands: Integrated Primary Care Information (IPCI)
6. The United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

Study size

No sample size has been calculated, as this is an exploratory study which will not test a specific hypothesis.

Statistical analysis

Incidence and prevalence of benzodiazepine and benzodiazepine-related medicines (objective 1): Incidence rates per 100,000 person-years and period prevalence of benzodiazepines and benzodiazepine-related medicines will be estimated in adolescents and young adults, overall and stratified by drug class, selected ingredients, calendar year, sex, and age groups. Incidence rates will be reported together with 95% Poisson confidence intervals. Prevalence will be expressed as proportions together with binomial 95% confidence intervals. The impact of the COVID-19 pandemic on prescribing patterns will be assessed descriptively through graphical presentations.

Characterisation and treatment utilisation (objectives 2 and 3): Demographics (age, sex) will be assessed at the date of the first recorded benzodiazepine prescription during the study period (index date). Indication for use (inferred from diagnosis codes), co-prescribing of other pre-specified psychotropic medications, top 10 recorded comorbidities, and type of healthcare provider (*if feasible*) will be assessed within specific predefined time windows around the index date. Total treatment duration during the study period will also be described. Categorical variables will be summarised as counts and proportions, while continuous variables will be reported as medians with interquartile ranges (IQR). All analyses will be presented by pre-specified drug classes and selected ingredients and stratified by sex and age group.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Study milestones and deliverables	Planned dates*
Final Study Protocol	28 August 2026
Creation of Analytical code	August/September 2026
Execution of Analytical Code on the data	September 2026
Draft Study Report	02 November 2026
Final Study Report	30 November 2026

*Planned dates are dependent on obtaining approval from the internal review boards of the data sources, code execution by the data sources, and deliverable review cycles.

6. RATIONALE AND BACKGROUND

The widespread prescribing of benzodiazepines and benzodiazepine-related medicines has raised ongoing public health concerns due to risks, such as tolerance, dependence, withdrawal, and serious side effects, particularly with prolonged use. Most research focuses on adults and older populations, where these medicines are frequently used for the management of anxiety and insomnia. While guidelines recommend limiting treatment duration to 2 – 4 weeks, it has been shown that long-term use remains common despite limited evidence on long-term benefits.[1, 2]

In contrast, evidence on use of benzodiazepines and benzodiazepine-related medicines in younger populations is more limited. The use of these medicines is generally not recommended for individuals under 18 years, except for specific indications, such as seizures and status epilepticus.[1, 2] While prescription rates among children and adolescents are generally reported to be low, trends vary across countries, with some studies reporting increasing use over time. Furthermore, although the incident use appears to be declining, stable, or rising, prevalent use suggests a potential shift toward longer-term treatment.[1-3]

Existing studies have also raised concerns regarding potentially inappropriate prescribing of benzodiazepines and benzodiazepine-related medicines, frequent co-prescription with other psychotropic medications, increasing involvement of non-specialists, and prolonged use among adolescent and young adult populations.[2-9] Given the prevalence of off-label prescribing and the unclear balance of risks and benefits in younger populations, a better understanding of prescribing patterns in this age group is needed.

In addition, recent studies show that the COVID-19 pandemic has had a large impact on mental health, particularly among adolescents and young adults.[10, 11] Evidence suggests that this impact may have been more pronounced among females, especially with respect to anxiety-related conditions.[10-12] However, the extent to which these changes have influenced prescribing patterns of benzodiazepines and benzodiazepine-related medicines remains unclear.

To address these gaps, this study aims to examine the prescribing patterns of benzodiazepines and benzodiazepine-related medicines among adolescents and young adults, including changes over time before and after COVID-19 pandemic. This study will also examine differences in prescribing patterns by sex.

7. RESEARCH QUESTION AND OBJECTIVES

Research questions

What are the sex-related prescribing patterns of benzodiazepines and benzodiazepine-related medicines over time in adolescents and young adults?

Research objectives

The specific objectives of this study are:

1. To estimate the incidence and prevalence of prescriptions of benzodiazepines and benzodiazepine-related medicines over time, overall and by type of benzodiazepine at treatment initiation.
2. To describe demographic and clinical characteristics of individuals prescribed with benzodiazepines and benzodiazepine-related medicines.
3. To estimate the duration of benzodiazepine and benzodiazepine-related medicines use.

All analyses will be presented by pre-specified drug classes and selected ingredients. Analyses for *objective 1* will be stratified by calendar year, sex, and age group, whereas analyses for *objective 2* and *3* will be stratified by sex and age group.

8. RESEARCH METHODS

8.1. Study design

A cohort study will be conducted using routinely collected health data from 6 data sources from 6 countries across Europe. The study will comprise:

- A population-level drug utilisation study, which will be conducted to address *objective 1*, estimating the incidence and prevalence of recorded prescriptions of benzodiazepines and benzodiazepine-related medicines among young adults and adolescents (**Figure 1**).
- A patient-level characterisation and drug utilisation study, which will be conducted to address *objectives 2 and 3*, assessing demographics, clinical characteristics, and treatment characteristics of patients prescribed with benzodiazepines, including age, sex, indication for use, co-prescribing of other psychotropic medications, type of healthcare provider (*if feasible*), comorbidities, and treatment duration (**Figure 2**).

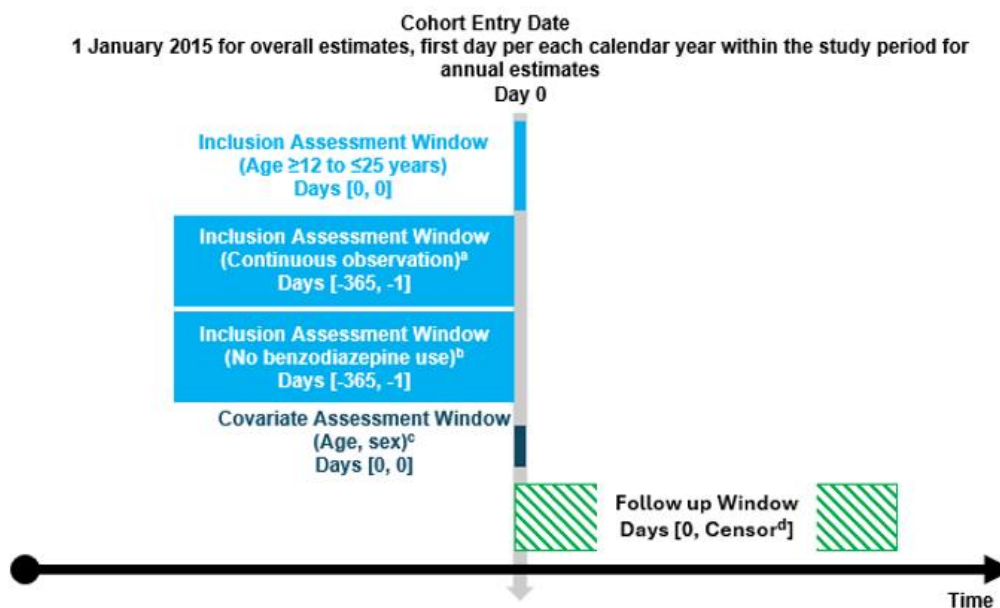


Figure 1. Graphical depiction of the study design (*objective 1*).

- Prior data availability criterion is only applicable for the estimation of incidence rates and is not required for prevalence analyses.
- Washout window (no benzodiazepine use 365 days before Day 0 or index date) is only applicable for the estimation of incidence rates and is not required for prevalence analyses.
- Results will be presented overall and stratified by age group or sex.
- Follow-up will continue until earliest of: reaching 26 years of age, loss to follow-up, death, end of observation period (the latest available data), or end of the study period (31/12/2025). For the incidence analysis, individuals will additionally be censored at the first recorded prescription/dispensing of benzodiazepine class or ingredient of interest, after which they are no longer considered at risk of incident use.

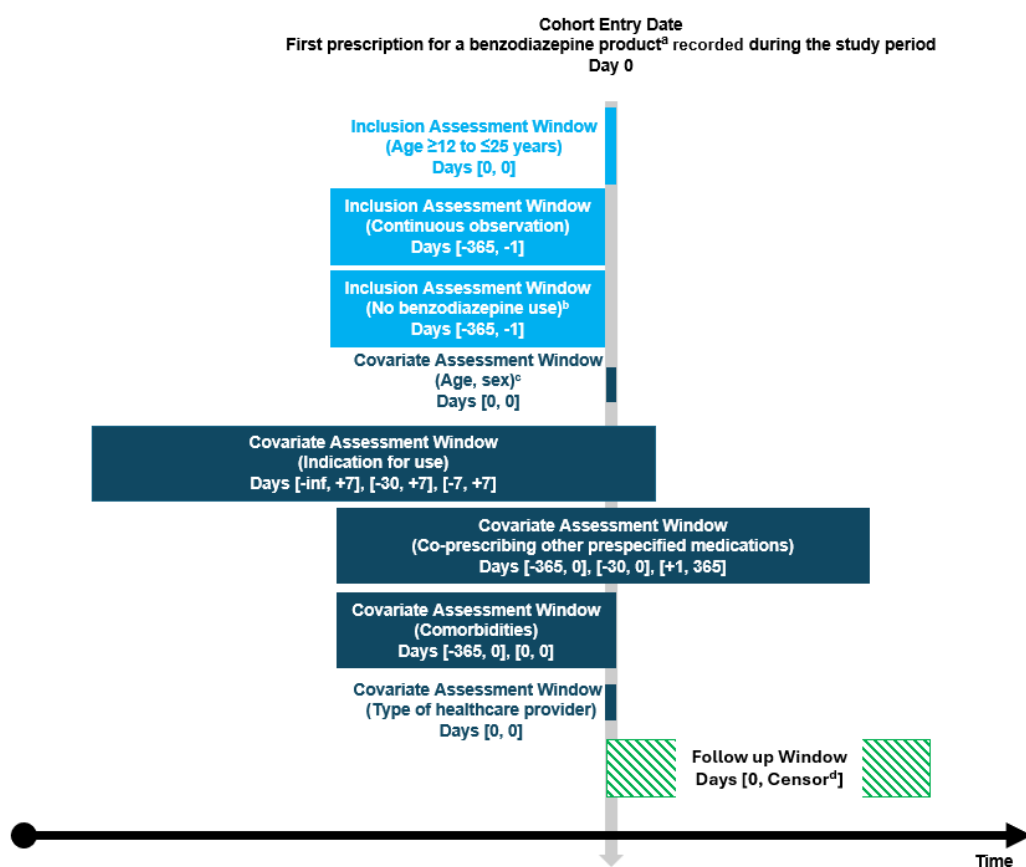


Figure 2. Graphical depiction of the study design (*objectives 2 and 3*).

- Analyses will be presented by pre-specified drug classes and selected ingredients.
- Prior to the first prescription recorded during the study period.
- Results will be presented overall and stratified by age- and sex-specific population strata (*objective 2*) or by age group or sex (*objective 3*).
- Follow-up will continue until earliest of: reaching 26 years of age, loss to follow-up, death, end of observation period (the latest available data), or end of the study period (31/12/2025).

8.2. Follow-up

For the calculation of incidence rates of individuals prescribed with benzodiazepines and benzodiazepine-related medicines (*objective 1*), follow-up will start on the respective date of the latest of the following: i) study start date (01/01/2015), ii) date at which individuals reach 365 days of prior history, or iii) date at which individuals meet the washout period criterion of 365 days, while aged ≥ 12 to ≤ 25 years. For prevalence estimations of individuals with recorded prescriptions of benzodiazepines and benzodiazepine-related medicines (*objective 1*), follow-up will start on the earliest date within the study period (01/01/2015 – 31/12/2025) when an individual is recorded in the data source while aged ≥ 12 to ≤ 25 years.

For patient-level characterisation of individuals prescribed with benzodiazepines (*objective 2*) and estimation of drug utilisation (*objective 3*), follow-up will start on the date of a first recorded benzodiazepine prescription between 01/01/2015 and 31/12/2025 (or latest date available) while aged ≥ 12 to ≤ 25 years. Eligible individuals are required to have at least 365 days of data visibility prior to the date of treatment initiation and no recorded benzodiazepine use in the 365 days preceding treatment initiation.

Follow-up will end on the earliest of: reaching 26 years of age, loss to follow-up, death, end of the observation period (the latest available data), or the study end date (31/12/2025). For incidence analysis (*objective 1*), individuals will additionally be censored at the first recorded prescription/dispensing of

benzodiazepine class or ingredient of interest, after which they are no longer considered at risk of incident use.

Study participants contribute person-time-at-risk from the index date until the earliest censoring event, as described above in [Section 8.2](#). Illustrative examples of denominator population entry, follow-up, person-time contribution, and censoring for incidence and prevalence analyses are provided in [ANNEX V](#).

8.3. Study population with inclusion and exclusion criteria

For the calculation of incidence rates or prevalence of benzodiazepine or benzodiazepine-related product use (*objective 1*), the study population will include:

Inclusion criteria

- All individuals present in the data source during the study period (01/01/2015 to 31/12/2025 (or latest available date)).
- Individuals aged ≥ 12 to ≤ 25 years.
- At least 365 days of data visibility prior to the index date (only for incidence estimations).
- No use of benzodiazepines or benzodiazepine-related products in the previous 365 days (washout window, only for incidence estimations).

For the characterisation of individuals prescribed with benzodiazepines (*objective 2*) and estimation of drug utilisation (*objective 3*), the study population will include:

Inclusion criteria:

- All individuals with a first record of a benzodiazepine or benzodiazepine-related prescription during the study period (01/01/2015 to 31/12/2025 (or latest available date, if earlier)).
- Individuals aged ≥ 12 to ≤ 25 years.
- At least 365 days of data visibility prior to the index date.
- No use of benzodiazepines or benzodiazepine-related products in the previous 365 days (washout window).

8.4. Study setting and data sources

This study will be conducted using routinely collected data from 6 primary care and registry data sources in the DARWIN EU® Network of Data Partners from 6 European countries ([Table 1](#), [ANNEX I](#)). All data were *a priori* mapped to the Observational Medical Outcomes Partnership Common Data Model (OMOP CDM).

Data sources

1. Denmark: Danish Data Health Registries (DK-DHR)
2. Finland: Finnish Care Register for Health Care (FinOMOP-THL)
3. Germany: IQVIA Disease Analyzer Germany (IQVIA DA Germany)
4. Spain: The Information System for Research in Primary Care (SIDIAP)
5. The Netherlands: Integrated Primary Care Information (IPCI)
6. The United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

Table 1. Data sources.

Country	Name of Data source	Health Care setting	Type of Data	Number of active individuals*	Calendar period covered by each data source	Contributing to **
Denmark	DK-DHR	Registry	EHR, registries	6,015,500	1995 – 11/2025	All objectives
Finland	FinOMOP-THL	Registry	EHR, registries	6,154,220	2011 – 12/2025 (prescription drug data available until 12/2023)	Objectives 1 – 2 ^a
Germany	IQVIA DA Germany	Outpatient General Practitioner Care	EHR	4,715,400	1989 – 06/2025	All objectives
Spain	SIDIAP	Outpatient General Practitioner Care	EHR	6,068,000	2006 – 12/2024	All objectives
The Netherlands	IPCI	Outpatient General Practitioner Care	EHR	1,339,300	2006 – 12/2025	All objectives
The United Kingdom	CPRD GOLD	Outpatient General Practitioner Care	EHR	2,371,680	1987 – 11/2025	All objectives

*Number of active individuals is defined as the number of individuals present in the last six months of the respective data source.

**Due to the absence of meaningful drug exposure end dates and days of supply in the OMOP CDM, FinOMOP-THL will not contribute to analyses requiring estimation of treatment duration (*objective 3*).

CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; EHR = Electronic Health Records; FinOMOP-THL = Finnish Care Register for Health Care; IPCI = Integrated Primary Care Information; IQVIA DA Germany = IQVIA Disease Analyzer Germany; SIDIAP = The Information System for Research in Primary Care.

Data sources selection

These data sources fulfil the criteria required in terms of data quality, completeness, timeliness, and representativeness for a drug utilisation and characterisation study while covering different regions of Europe ([ANNEX II](#)).

8.5. Study period

The study period will be from 01/01/2015 to 31/12/2025 or the most recent data available for each contributing data source, if earlier.

It should be noted that the period of available data varied across data sources and did not extend to the end of the study period for several data sources. Detailed information about the study period covered per data source can be found in [Section 8.4.](#) and [Table 1.](#)

8.6. Variables

8.6.1. Exposure

For *objectives 2 and 3*, exposure will be identified as the first recorded prescription or dispensing record of benzodiazepines and benzodiazepine-related medicines during the study period. Individuals will be required to have no recorded benzodiazepine use in the 365 days prior to the index date (washout window).

Treatment episodes will be generated by grouping sequential prescriptions (i.e. drug era) that have a maximum of 30 days between the end date of one prescription and the start date of the next prescription (i.e. definition of gap). The exposed risk window will therefore account for all periods when the individual is likely to be using benzodiazepines and benzodiazepine-related medicines.

For all objectives, results will be provided per pre-specified benzodiazepine WHO Anatomical Therapeutic Chemical (ATC) classes and selected ingredients as follows:

WHO ATC classes

- N05BA, Anxiolytic benzodiazepines
- N05CD, Hypnotic benzodiazepines
- N03AE, Antiepileptic benzodiazepines
- N05CF, Benzodiazepine-related drugs

Selected ingredients

- N05BA01, Diazepam
- N05BA12, Alprazolam

The preliminary concept sets used for the identification of exposures are described in ANNEX IV. These codes will be refined during study execution, following the standard DARWIN EU® phenotyping processes, which involve the review of code lists and the review of phenotypes after their execution in the participating data sources.

8.6.2. Outcome

Not applicable.

8.6.3. Covariates, including confounders, effect modifiers, and other variables

The variables for stratification of incidence rates and prevalence of benzodiazepines and benzodiazepine-related medicines (*objective 1*) and treatment duration of benzodiazepine use (*objective 3*) will be as follows:

- Calendar year (*only objective 1*)
- Age groups (overall, adolescents aged ≥ 12 to ≤ 18 years, young adults aged ≥ 19 to ≤ 25 years)
- Sex (overall, females, males)

The variables for characterisation of individuals prescribed with benzodiazepines (*objective 2*) will be as follows:

- Demographics, defined at the index date:
 - Sex: Female/Male
 - Age

- Indication for use will be identified based on pre-specified conditions recorded around the index date, assessment window any time before to 7 days after index date [-inf, +7], 30 days before to 7 days after index date [-30, +7], and 7 days before to 7 days after index date [-7, +7]:
 - Anxiety
 - Delirium
 - Dementia
 - Epilepsy
 - Febrile convulsions
 - Psychotic disorder
 - Sleep disorder
 - Withdrawal syndrome (alcohol-, drug-, and medication-related)
 - Unknown (other)
 - None
- Co-prescribing of other pre-specified psychotropic and antiseizure medications, assessment window one year before the index date [-365, 0], 30 days before the index date [-30, 0], and one year following the index date [+1, +365]
 - Antidepressants (N06A)
 - Antipsychotics (N05A)
 - Mood stabilisers (N03AF01)
 - Antiseizure medications (N03A)
 - Psychostimulants (N06B)
 - Dementia medications (N06D)
 - Gabapentinoids (N02BF)
- Comorbidities will be described by means of large-scale characterisation identifying the most frequent diagnostic codes (proxy for comorbidities), assessment window one year prior to the index date [-365, 0] and at the index date [0, 0]. Conditions included as indication for use will be excluded from the top 10 comorbidity tables.
- Type of healthcare provider (*if feasible*), assessment window on the index [0, 0]:
 - Primary care
 - Psychiatric care
 - Other specialised care

The variables for stratification of the demographic and clinical characteristics (*objective 2*) will be as follows:

- Age- and sex-specific population strata:
 - Overall adolescent population, aged ≥ 12 to ≤ 18 years
 - Female adolescent population, aged ≥ 12 to ≤ 18 years
 - Male adolescent population, aged ≥ 12 to ≤ 18 years

- Overall young adults, aged ≥ 19 to ≤ 25 years
- Female young adults, aged ≥ 19 to ≤ 25 years
- Male young adults, aged ≥ 19 to ≤ 25 years

The preliminary concept sets used for the identification of covariates are described in [ANNEX IV](#). These codes will be refined during study execution, following the standard DARWIN EU® phenotyping processes, which involve the review of code lists and the review of phenotypes after their execution in the participating data sources.

8.7. Study size

No sample size has been calculated, as this is a drug utilisation study with a descriptive design, which will not test a specific hypothesis. Thus, the sample size is driven by the availability of data for eligible individuals with prescriptions for benzodiazepines and benzodiazepine-related medicines. For example, based on a preliminary feasibility assessment, the expected number of record counts for alprazolam among adolescents and young adults in the data sources included in this study range from 1,900 (CPRD GOLD) to 647,800 (SIDIAP), and from 30,900 (IPCI) to 1,545,200 (CPRD GOLD) for diazepam.

8.8. Analysis

8.8.1. Federated network analyses

All analyses will be conducted separately for each data source and will be carried out in a federated manner, allowing analyses to be run locally without sharing individuals' data.

Before sharing the study package, test runs of the analytics will be performed on a subset of the data sources, and quality control checks will be performed. After all the tests are passed (see [ANNEX III](#)), the final package will be released in a version-controlled study repository for execution against all the participating data sources.

8.8.2. Data privacy protection

The data partners will locally execute the analytics against the OMOP CDM in R Studio and review and approve the default aggregated results. They will then be made available to the Principal Investigators and study team in secure online repository of Data Transfer Zone (DTZ). All results will be locked and timestamped for reproducibility and transparency. The study results of all data sources will be checked, after which they are made available to the team, and the Study Dissemination Phase can start. All analyses will be conducted separately for each data source, and will be carried out in a federated manner, allowing analyses to be run locally without sharing patient-level data. Cell counts < 5 will be suppressed when reporting results to comply with the data source's privacy protection regulations.

8.8.3. Statistical model specification and assumptions of the analytical approach considered

Objective 1

The incidence and prevalence of benzodiazepine or benzodiazepine-related product use will be estimated based on OMOP CDM mapped data using the *IncidencePrevalence* R package (<https://darwin-eu.github.io/IncidencePrevalence/>), developed by DARWIN EU®.

Incidence rates of benzodiazepine or benzodiazepine-related product use among adolescents and young adults will be calculated as the number of treatment initiations per 100,000 person-years, among individuals fulfilling the inclusion criteria. Incident users are defined as individuals whose first benzodiazepine record during the study period was preceded by at least 365 days without benzodiazepine use (washout window). Consequently, individuals with benzodiazepine use prior to the study period will only become eligible to contribute person-time once ≥ 365 consecutive days without benzodiazepine use

have elapsed. Incidence rates will be reported together with 95% Poisson confidence intervals. Individuals who enter the denominator population will contribute time-at-risk from cohort entry until the earliest of the following: reaching 26 years of age, the first recorded prescription record/dispensing of the benzodiazepine class or ingredient of interest, loss to follow-up, death, end of the observation period (the latest available data), or the study end date (31/12/2025). Participants who do not initiate benzodiazepine treatment during the study period are administratively censored at the end of follow-up.

Prevalence of benzodiazepine or benzodiazepine-related product use among adolescents and young adults will be calculated as period prevalence, which summarises the total number of individuals with a benzodiazepine-related product prescription during a given period divided by the population at risk of exposure during that period. Therefore, period prevalence gives the proportion of individuals exposed at any time during a specified interval. Binomial 95% confidence intervals will be calculated.

Incidence rates and prevalence will be presented overall and by pre-specified drug class and selected ingredients, and stratified by calendar year, sex, and age groups. The impact of the COVID-19 pandemic on prescribing patterns will be assessed descriptively through graphical presentations to facilitate the visual assessment of potential changes in prescribing prior to, during, and following the COVID-19 pandemic period.

An illustration of the calculation of the incidence of benzodiazepine or benzodiazepine-related product use is shown below in **Figure 3**. Person IDs 1 and 4 will contribute time-at-risk up to the point at which they become incident users of selected pre-specified medications of interest during the study period. Person IDs 2 and 5 do not use pre-specified medications of interest and so contribute time-at-risk but no incident outcomes. Meanwhile, person ID 3 first will contribute time-at-risk starting at the day when the washout period of a previous exposure (which occurred before the study start) ends, and will continue to contribute time at risk until the start of the next exposure to the pre-specified medication(s) of interest.

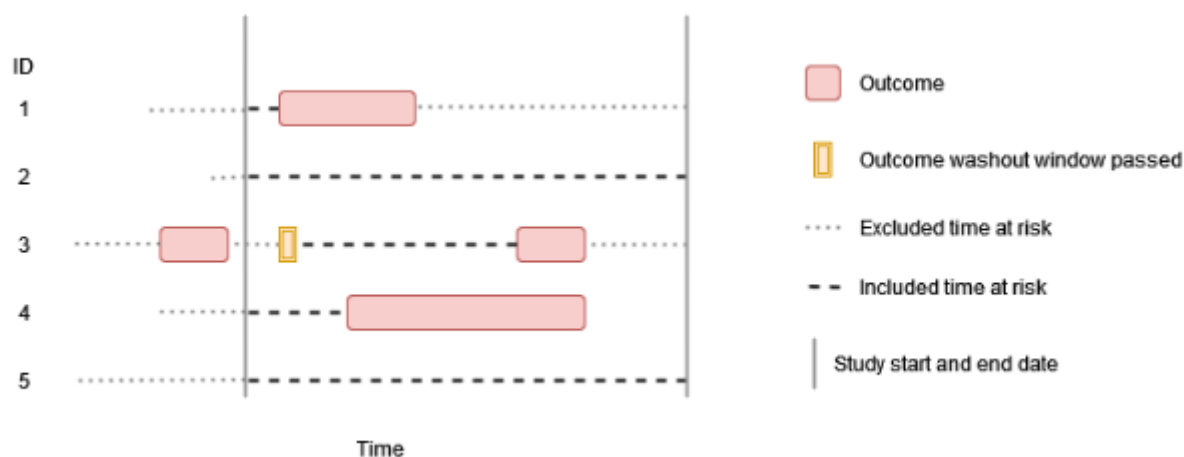


Figure 3. Illustration of incidence assessment.

An illustration of the calculation of period prevalence is shown below in **Figure 4**. Between time $t+2$ and $t+3$, two of the five study participants are users of benzodiazepine or benzodiazepine-related products, resulting in a prevalence of 40%. Meanwhile, for the period t to $t+1$, all five also have some observation time during the year, with one of the five study participants being a user of pre-selected medications of interest (i.e. prevalence of 20%).

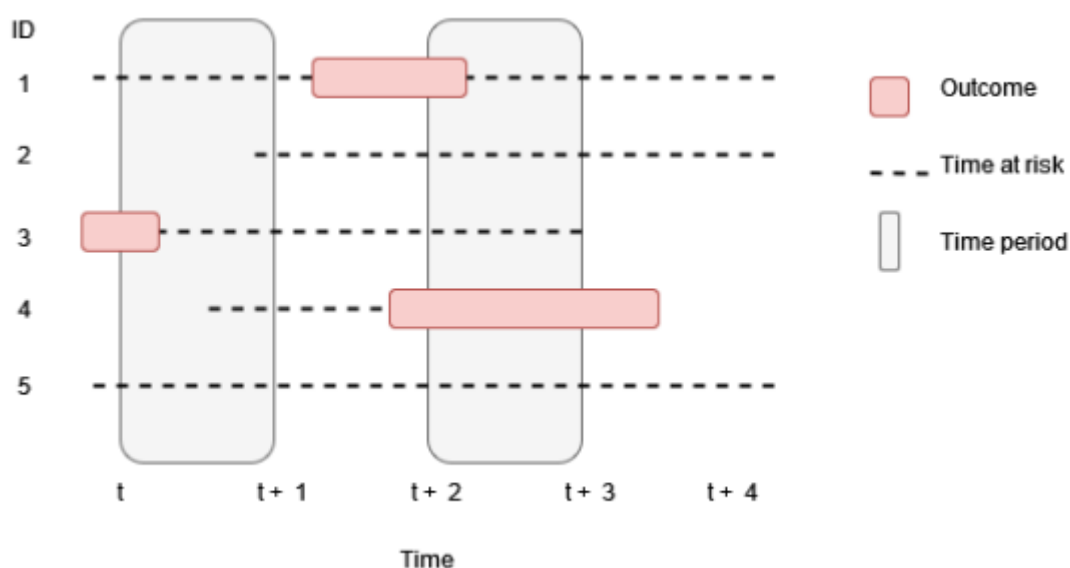


Figure 4. Illustration of period prevalence assessment.

Objective 2

The characterisation of individuals prescribed with benzodiazepines will be estimated based on OMOP CDM mapped data using the *CohortCharacteristics* R package (<https://darwin-eu.github.io/CohortCharacteristics/>), developed by DARWIN EU®.

Individuals prescribed with benzodiazepines who meet the inclusion criteria will be characterised in terms of demographics, pre-specified indication for use, co-prescribing of other psychotropic medications, type of healthcare provider (*if feasible*), and comorbidities. Categorical variables will be summarised as counts and proportions, while continuous variables will be reported as minimum, Q25, median, Q75, and maximum. Analyses will be presented by the following age- and sex-specific population strata:

- Overall adolescent population, aged ≥ 12 to ≤ 18 years
- Female adolescent population, aged ≥ 12 to ≤ 18 years
- Male adolescent population, aged ≥ 12 to ≤ 18 years
- Overall young adults, aged ≥ 19 to ≤ 25 years
- Female young adults, aged ≥ 19 to ≤ 25 years
- Male young adults, aged ≥ 19 to ≤ 25 years

Objective 3

Treatment utilisation will be assessed using the *DrugUtilisation* R package (<https://github.com/darwin-eu/DrugUtilisation>), developed by DARWIN EU®.

The total treatment duration will be calculated for the medications of interest during the study period, provided the treatment initiation meets the washout criteria. Treatment duration will be summarised by providing the minimum, Q25, median, Q75, and maximum duration of the treatment episode. For data sources where duration cannot be calculated, due to e.g. missing information on quantity or dosing, treatment duration will not be provided.

Drug exposure calculations

Drug eras will be defined as follows: exposure will start at the date of a new prescription of benzodiazepines or benzodiazepine-related products during the study period. For each prescription, the estimated duration of use will be retrieved from the corresponding record in the OMOP Drug Exposure Table, using the start and end date of the exposure. The drug exposure end date may be directly recorded in the source data or derived during transformation into the OMOP CDM using source information available and predefined Extract, Transform, Load (ETL) rules. Consecutive prescriptions will be combined into a single continuous exposed episodes (drug eras) if the distance in days between end of the first prescription record/dispensing and start of the second prescription record/dispensing is ≤ 30 days. This process will be applied iteratively such that multiple consecutive prescription records/dispensings separated by gaps of ≤ 30 days will be combined into one continuous drug era.

Methods to deal with missing data

For the drug utilisation analyses, it will be assumed that the absence of a prescription record means that the individual does not receive the respective drug. For indications, it will be assumed that the missingness of a record of the respective condition means that that condition is not the indication for the drug prescription.

8.8.4. Output

Output will consist of a PDF report, including a summary of key study findings and the following tables and figures.

MOCK Table 1. Study attrition of individuals included in the study population, presented by data source (objective 1).

	Data source 1	Data source 2	Data source 3/4/5/6
Qualifying initial records ¹			
Aged ≥ 12 to ≤ 25 years			
Prior observation of ≥ 365 days*			
No prior benzodiazepine use within 365 days prior to index date*			

¹All individuals present in the data source during the study period (01/01/2015 to 31/12/2025 (or latest available date)).

*Applicable for estimations of incidence.

For incidence rate estimations, the index date is defined as the date during the study period (01/01/2015 – 31/12/2025 (or latest available date if earlier) on which an individual satisfies all eligibility criteria, namely being aged ≥ 12 to ≤ 25 years, having at least 365 days of prior history available, and having no benzodiazepine use recorded during the preceding 365 days. For prevalence estimations, the index date is defined as the earliest date within the study period (01/01/2015 – 31/12/2025) on which an individual is recorded in the data source while aged ≥ 12 to ≤ 25 years. Illustrative examples are provided in [ANNEX V](#).

MOCK Table 2. Study attrition of individuals with a first recorded benzodiazepine prescription during the study period, presented by data source (*objectives 2 and 3*).

	Data source 1	Data source 2	Data source 3/4/5/6
Qualifying initial records ¹			
First record of benzodiazepine or benzodiazepine-related prescription (index date) ²			
Aged ≥12 to ≤25 years			
Prior observation of ≥365 days			
No prior benzodiazepine use within 365 days prior to index date			

¹All individuals present in the data source during the study period (01/01/2015 to 31/12/2025 (or latest available date)).

²First record of a benzodiazepine or benzodiazepine-related prescription during the study period (01/01/2015 to 31/12/2025 (or latest available date, if earlier)).

MOCK Table 3. Overall incidence rates of prescriptions for benzodiazepines and benzodiazepine-related medicines (*objective 1*).

Age group	Data source	Denominator (N)	Person-years	Outcome (N)	Incidence 100,000 person-years [95% CI]
Anxiolytic benzodiazepines*					
Overall	DK-DHR				
	FinOMOP-THL				
	IQVIA DA Germany				
	SIDIAP				
	IPCI				
	CPRD GOLD				
Adolescents aged ≥12 to ≤18 years	DK-DHR				
	FinOMOP-THL				
	IQVIA DA Germany				
	SIDIAP				
	IPCI				
	CPRD GOLD				
Young adults aged ≥19 to ≤25 years	DK-DHR				
	FinOMOP-THL				

Age group	Data source	Denominator (N)	Person-years	Outcome (N)	Incidence 100,000 person-years [95% CI]
	IQVIA DA Germany				
	SIDIAP				
	IPCI				
	CPRD GOLD				
...					

CI = confidence interval; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; EHR = Electronic Health Records; FinOMOP-THL = Finnish Care Register for Health Care; IPCI = Integrated Primary Care Information; IQVIA DA Germany = IQVIA Disease Analyzer Germany; SIDIAP = The Information System for Research in Primary Care; N = number of individuals.

*The same table structure will be applied to all other benzodiazepine classes and selected ingredients, including hypnotic benzodiazepines, antiepileptic benzodiazepines, benzodiazepine-related medicines, diazepam, and alprazolam.

MOCK Table 4. Overall prevalence of prescriptions for benzodiazepines and benzodiazepine-related medicines, overall and per type of benzodiazepine (*objective 1*).

Age group	Data source	Denominator (N)	Outcome (N)	Prevalence [95% CI]
Anxiolytic benzodiazepines*				
Overall	DK-DHR			
	FinOMOP-THL			
	IQVIA DA Germany			
	SIDIAP			
	IPCI			
	CPRD GOLD			
Adolescents aged ≥ 12 to ≤ 18 years	DK-DHR			
	FinOMOP-THL			
	IQVIA DA Germany			
	SIDIAP			
	IPCI			
	CPRD GOLD			
Young adults aged ≥ 19 to ≤ 25 years	DK-DHR			
	FinOMOP-THL			
	IQVIA DA Germany			
	SIDIAP			
	IPCI			
	CPRD GOLD			

CI = confidence interval; CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; EHR = Electronic Health Records; FinOMOP-THL = Finnish Care Register for Health Care; IPCI = Integrated Primary Care Information; IQVIA DA Germany = IQVIA Disease Analyzer Germany; SIDIAP = The Information System for Research in Primary Care; N = number of individuals.

*The same table structure will be applied to all other benzodiazepine classes and selected ingredients, including hypnotic benzodiazepines, antiepileptic benzodiazepines, benzodiazepine-related medicines, diazepam, and alprazolam.

MOCK Table 5. Overall demographic characteristics of individuals prescribed benzodiazepines or benzodiazepine-related medicines during the study period (*objective 2*).

Variable name	Data source name											
	DK-DHR		FinOMOP-THL		IQVIA DA Germany		SIDIAP		IPCI		CPRD GOLD	
	≥12 to ≤18 years	≥19 to ≤25 years	≥12 to ≤18 years	≥19 to ≤25 years	≥12 to ≤18 years	≥19 to ≤25 years	≥12 to ≤18 years	≥19 to ≤25 years	≥12 to ≤18 years	≥19 to ≤25 years	≥12 to ≤18 years	≥19 to ≤25 years
Number of subjects												
Age (years), median [Q25–Q75]												
Age (years), range (min–max)												
Condition 1												
Condition 2												
Condition 3												
Condition 4												
Condition 5												
Condition 6												
Condition 7												
Condition 8												
Condition 9												
Condition 10												
Co-prescribing 1												
Co-prescribing 2												
Co-prescribing 3												
Co-prescribing 4												

Variable name	Data source name											
	DK-DHR		FinOMOP-THL		IQVIA DA Germany		SIDIAP		IPCI		CPRD GOLD	
	≥12 to ≤18 years	≥19 to ≤25 years	≥12 to ≤18 years	≥19 to ≤25 years	≥12 to ≤18 years	≥19 to ≤25 years	≥12 to ≤18 years	≥19 to ≤25 years	≥12 to ≤18 years	≥19 to ≤25 years	≥12 to ≤18 years	≥19 to ≤25 years
Co-prescribing 5												
Comorbidities 1												
Comorbidities 2												
Comorbidities 3												
Comorbidities 4												
Comorbidities 5												
Comorbidities 6												
Comorbidities 7												
Comorbidities 8												
Comorbidities 9												
Comorbidities 10												
Healthcare provider 1												
Healthcare provider 2												
Healthcare provider 3												

CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; EHR = Electronic Health Records; FinOMOP-THL = Finnish Care Register for Health Care; IPCI = Integrated Primary Care Information; IQVIA DA Germany = IQVIA Disease Analyzer Germany; SIDIAP = The Information System for Research in Primary Care; N = number of individuals.

MOCK Table 6. Demographic characteristics of individuals prescribed benzodiazepines or benzodiazepine-related medicines during the study period (*objective 2*).

Analysis population*	Variable name	Data source name											
		DK-DHR		FinOMOP-THL		IQVIA DA Germany		SIDIAP		IPCI		CPRD GOLD	
		Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Anxiolytic benzodiazepines													
Adolescent population, aged ≥12 to ≤18 years	Number of subjects												
	Age (years), median [Q25–Q75]												
	Age (years), range (min–max)												
Young adults, aged ≥19 to ≤25 years	Number of subjects												
	Age (years), median [Q25–Q75]												
	Age (years), range (min–max)												

CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; EHR = Electronic Health Records; FinOMOP-THL = Finnish Care Register for Health Care; IPCI = Integrated Primary Care Information; IQVIA DA Germany = IQVIA Disease Analyzer Germany; SIDIAP = The Information System for Research in Primary Care; N = number of individuals.

*The same table structure will be applied to all other benzodiazepine classes and selected ingredients, including hypnotic benzodiazepines, antiepileptic benzodiazepines, benzodiazepine-related medicines, diazepam, and alprazolam.

MOCK Table 7. Indication for use of individuals prescribed benzodiazepine, reported per type of benzodiazepine and stratified by sex, recorded any time before to 7 days following the index date (*objective 2*).

Analysis population	Variable name	Data source name											
		DK-DHR		FinOMOP-THL		IQVIA DA Germany		SIDIAP		IPCI		CPRD GOLD	
		Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Anxiolytic benzodiazepines													
Adolescent population, aged ≥12 to ≤18 years	Condition 1												
	Condition 2												
	Condition 3/4/5/												
Young adults, aged ≥19 to ≤25 years	Condition 1												
	Condition 2												
	Condition 3/4/5/												
Hypnotic benzodiazepines / Antiepileptic benzodiazepines / Benzodiazepine-related medicines / Diazepam / Alprazolam													
adolescent population, aged ≥12 to ≤18 years/ young adults, aged ≥19 to ≤25	Condition 1												
	Condition 2												

Analysis population	Variable name	Data source name											
		DK-DHR		FinOMOP-THL		IQVIA DA Germany		SIDIAP		IPCI		CPRD GOLD	
		Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
	Condition 3/4/5/												

CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; EHR = Electronic Health Records; FinOMOP-THL = Finnish Care Register for Health Care; IPCI = Integrated Primary Care Information; IQVIA DA Germany = IQVIA Disease Analyzer Germany; SIDIAP = The Information System for Research in Primary Care; N = number of individuals.

The same table structure will be applied for the other time windows (MOCK Tables 7–8):

MOCK Table 8. Indication for use of individuals prescribed benzodiazepine, reported per type of benzodiazepine, and stratified by sex, recorded 30 days prior to 7 days following the index date (objective 2).

MOCK Table 9. Indication for use of individuals prescribed benzodiazepine, reported per type of benzodiazepine, and stratified by sex, recorded 7 days prior to 7 days following the index date (objective 2).

MOCK Table 10. Co-prescribing of other pre-specified psychotropic medications of individuals prescribed anxiolytic benzodiazepines during the study period (objective 2).

		Data source name					
	Variable name	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	IPCI	CPRD GOLD
Time window 1							
Overall adolescent population, aged ≥ 12 to ≤ 18 years	Antidepressants, n (%)						
	Antipsychotics n (%)						
	Mood stabilisers, n (%)						

		Data source name					
	Variable name	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	IPCI	CPRD GOLD
	Psychostimulants, n (%)						
	Dementia medications, n (%)						
Female adolescent population, aged ≥ 12 to ≤ 18 years	Antidepressants, n (%)						
	Antipsychotics n (%)						
	Mood stabilisers, n (%)						
	Psychostimulants, n (%)						
	Dementia medications, n (%)						
Male adolescent population, aged ≥ 12 to ≤ 18 years	Antidepressants, n (%)						
	Antipsychotics n (%)						
	Mood stabilisers, n (%)						
	Psychostimulants, n (%)						
	Dementia medications, n (%)						
Overall young adults, aged ≥ 19 to ≤ 25 years	Antidepressants, n (%)						

		Data source name					
	Variable name	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	IPCI	CPRD GOLD
	Antipsychotics n (%)						
	Mood stabilisers, n (%)						
	Psychostimulants, n (%)						
	Dementia medications, n (%)						
Female young adults, aged ≥19 to ≤25 years	Antidepressants, n (%)						
	Antipsychotics n (%)						
	Mood stabilisers, n (%)						
	Psychostimulants, n (%)						
	Dementia medications, n (%)						
Male young adults, aged ≥19 to ≤25 years	Antidepressants, n (%)						
	Antipsychotics n (%)						
	Mood stabilisers, n (%)						
	Psychostimulants, n (%)						
	Dementia medications, n (%)						

		Data source name					
	Variable name	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	IPCI	CPRD GOLD
Time window 2							
Overall adolescent population, aged ≥12 to ≤18 years	Antidepressants, n (%)						
	Antipsychotics n (%)						
	Mood stabilisers, n (%)						
	Psychostimulants, n (%)						
	Dementia medications, n (%)						
Female adolescent population, aged ≥12 to ≤18 years	Antidepressants, n (%)						
	Antipsychotics n (%)						
	Mood stabilisers, n (%)						
	Psychostimulants, n (%)						
	Dementia medications, n (%)						
Male adolescent population, aged ≥12 to ≤18 years	Antidepressants, n (%)						
	Antipsychotics n (%)						
	Mood stabilisers, n (%)						

		Data source name					
	Variable name	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	IPCI	CPRD GOLD
	Psychostimulants, n (%)						
	Dementia medications, n (%)						
Overall young adults, aged ≥ 19 to ≤ 25 years	Antidepressants, n (%)						
	Antipsychotics n (%)						
	Mood stabilisers, n (%)						
	Psychostimulants, n (%)						
	Dementia medications, n (%)						
Female young adults, aged ≥ 19 to ≤ 25 years	Antidepressants, n (%)						
	Antipsychotics n (%)						
	Mood stabilisers, n (%)						
	Psychostimulants, n (%)						
	Dementia medications, n (%)						
Male young adults, aged ≥ 19 to ≤ 25 years	Antidepressants, n (%)						

		Data source name					
	Variable name	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	IPCI	CPRD GOLD
	Antipsychotics n (%)						
	Mood stabilisers, n (%)						
	Psychostimulants, n (%)						
	Dementia medications, n (%)						
Time window 3							
Overall adolescent population, aged ≥12 to ≤18 years	Antidepressants, n (%)						
	Antipsychotics n (%)						
	Mood stabilisers, n (%)						
	Psychostimulants, n (%)						
	Dementia medications, n (%)						
Female adolescent population, aged ≥12 to ≤18 years	Antidepressants, n (%)						
	Antipsychotics n (%)						
	Mood stabilisers, n (%)						
	Psychostimulants, n (%)						

		Data source name					
	Variable name	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	IPCI	CPRD GOLD
	Dementia medications, n (%)						
Male adolescent population, aged ≥ 12 to ≤ 18 years	Antidepressants, n (%)						
	Antipsychotics n (%)						
	Mood stabilisers, n (%)						
	Psychostimulants, n (%)						
	Dementia medications, n (%)						
Overall young adults, aged ≥ 19 to ≤ 25 years	Antidepressants, n (%)						
	Antipsychotics n (%)						
	Mood stabilisers, n (%)						
	Psychostimulants, n (%)						
	Dementia medications, n (%)						
Female young adults, aged ≥ 19 to ≤ 25 years	Antidepressants, n (%)						
	Antipsychotics n (%)						

		Data source name					
	Variable name	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	IPCI	CPRD GOLD
	Mood stabilisers, n (%)						
	Psychostimulants, n (%)						
	Dementia medications, n (%)						
Male young adults, aged ≥19 to ≤25 years	Antidepressants, n (%)						
	Antipsychotics n (%)						
	Mood stabilisers, n (%)						
	Psychostimulants, n (%)						
	Dementia medications, n (%)						

CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; EHR = Electronic Health Records; FinOMOP-THL = Finnish Care Register for Health Care; IPCI = Integrated Primary Care Information; IQVIA DA Germany = IQVIA Disease Analyzer Germany; SIDIAP = The Information System for Research in Primary Care; n = number of individuals.

Note: The same table structure will be produced separately for hypnotic benzodiazepines, antiepileptic benzodiazepines, benzodiazepine-related medicines, diazepam, and alprazolam.

MOCK Table 11. Top 10 conditions recorded among individuals prescribed anxiolytic benzodiazepines during the study period (*objective 2*).

		Data source name					
	Variable name	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	IPCI	CPRD GOLD
Time window 1							
Overall adolescent population, aged ≥12 to ≤18 years	Condition 1, n (%)						
	Condition 2, n (%)						
	Condition 3, n (%)						
	Condition 4, n (%)						
	Condition 5, n (%)						
	Condition 6, n (%)						
	Condition 7, n (%)						
	Condition 8, n (%)						
	Condition 9, n (%)						
	Condition 10, n (%)						
Female adolescent population, aged ≥12 to ≤18 years	Condition 1, n (%)						
	Condition 2, n (%)						
	Condition 3, n (%)						
	Condition 4, n (%)						
	Condition 5, n (%)						
	Condition 6, n (%)						
	Condition 7, n (%)						

		Data source name					
	Variable name	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	IPCI	CPRD GOLD
	Condition 8, n (%)						
	Condition 9, n (%)						
	Condition 10, n (%)						
Male adolescent population, aged ≥12 to ≤18 years	Condition 1, n (%)						
	Condition 2, n (%)						
	Condition 3, n (%)						
	Condition 4, n (%)						
	Condition 5, n (%)						
	Condition 6, n (%)						
	Condition 7, n (%)						
	Condition 8, n (%)						
	Condition 9, n (%)						
	Condition 10, n (%)						
Overall young adults, aged ≥19 to ≤25 years	Condition 1, n (%)						
	Condition 2, n (%)						
	Condition 3, n (%)						
	Condition 4, n (%)						
	Condition 5, n (%)						
	Condition 6, n (%)						
	Condition 7, n (%)						

		Data source name					
	Variable name	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	IPCI	CPRD GOLD
	Condition 8, n (%)						
	Condition 9, n (%)						
	Condition 10, n (%)						
Female young adults, aged ≥19 to ≤25 years	Condition 1, n (%)						
	Condition 2, n (%)						
	Condition 3, n (%)						
	Condition 4, n (%)						
	Condition 5, n (%)						
	Condition 6, n (%)						
	Condition 7, n (%)						
	Condition 8, n (%)						
	Condition 9, n (%)						
	Condition 10, n (%)						
Male young adults, aged ≥19 to ≤25 years	Condition 1, n (%)						
	Condition 2, n (%)						
	Condition 3, n (%)						
	Condition 4, n (%)						
	Condition 5, n (%)						
	Condition 6, n (%)						
	Condition 7, n (%)						
	Condition 8, n (%)						

		Data source name					
	Variable name	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	IPCI	CPRD GOLD
	Condition 9, n (%)						
	Condition 10, n (%)						
Time window 2							
Overall adolescent population, aged ≥12 to ≤18 years	Condition 1, n (%)						
	Condition 2, n (%)						
	Condition 3, n (%)						
	Condition 4, n (%)						
	Condition 5, n (%)						
	Condition 6, n (%)						
	Condition 7, n (%)						
	Condition 8, n (%)						
	Condition 9, n (%)						
	Condition 10, n (%)						
Female adolescent population, aged ≥12 to ≤18 years	Condition 1, n (%)						
	Condition 2, n (%)						
	Condition 3, n (%)						
	Condition 4, n (%)						
	Condition 5, n (%)						
	Condition 6, n (%)						

		Data source name					
	Variable name	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	IPCI	CPRD GOLD
	Condition 7, n (%)						
	Condition 8, n (%)						
	Condition 9, n (%)						
	Condition 10, n (%)						
Male adolescent population, aged ≥12 to ≤18 years	Condition 1, n (%)						
	Condition 2, n (%)						
	Condition 3, n (%)						
	Condition 4, n (%)						
	Condition 5, n (%)						
	Condition 6, n (%)						
	Condition 7, n (%)						
	Condition 8, n (%)						
	Condition 9, n (%)						
	Condition 10, n (%)						
Overall young adults, aged ≥19 to ≤25 years	Condition 1, n (%)						
	Condition 2, n (%)						
	Condition 3, n (%)						
	Condition 4, n (%)						
	Condition 5, n (%)						
	Condition 6, n (%)						

		Data source name					
	Variable name	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	IPCI	CPRD GOLD
	Condition 7, n (%)						
	Condition 8, n (%)						
	Condition 9, n (%)						
	Condition 10, n (%)						
Female young adults, aged ≥19 to ≤25 years	Condition 1, n (%)						
	Condition 2, n (%)						
	Condition 3, n (%)						
	Condition 4, n (%)						
	Condition 5, n (%)						
	Condition 6, n (%)						
	Condition 7, n (%)						
	Condition 8, n (%)						
	Condition 9, n (%)						
	Condition 10, n (%)						
Male young adults, aged ≥19 to ≤25 years	Condition 1, n (%)						
	Condition 2, n (%)						
	Condition 3, n (%)						
	Condition 4, n (%)						
	Condition 5, n (%)						
	Condition 6, n (%)						
	Condition 7, n (%)						

		Data source name					
	Variable name	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	IPCI	CPRD GOLD
	Condition 8, n (%)						
	Condition 9, n (%)						
	Condition 10, n (%)						

CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; EHR = Electronic Health Records; FinOMOP-THL = Finnish Care Register for Health Care; IPCI = Integrated Primary Care Information; IQVIA DA Germany = IQVIA Disease Analyzer Germany; SIDIAP = The Information System for Research in Primary Care; n = number of individuals. Any recorded pre-specified indication for use will be excluded from the table.

Note: The same table structure will be produced separately for hypnotic benzodiazepines, antiepileptic benzodiazepines, benzodiazepine-related medicines, diazepam, and alprazolam.

MOCK Table 12. Type of healthcare provider prescribing anxiolytic benzodiazepines during the study period (*objective 2 (if feasible)*).

		Data source name					
	Variable name	DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	IPCI	CPRD GOLD
Overall adolescent population, aged ≥ 12 to ≤ 18 years	Primary care, n (%)						
	Psychiatric care, n (%)						
	Other specialised care, n (%)						
Female adolescent population, aged ≥ 12 to ≤ 18 years	Primary care, n (%)						
	Psychiatric care, n (%)						
	Other specialised care, n (%)						

Variable name		Data source name					
		DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	IPCI	CPRD GOLD
Male adolescent population, aged ≥12 to ≤18 years	Primary care, n (%)						
	Psychiatric care, n (%)						
	Other specialised care, n (%)						
Overall young adults, aged ≥19 to ≤25 years	Primary care, n (%)						
	Psychiatric care, n (%)						
	Other specialised care, n (%)						
Female young adults, aged ≥19 to ≤25 years	Primary care, n (%)						
	Psychiatric care, n (%)						
	Other specialised care, n (%)						
Male young adults, aged ≥19 to ≤25 years	Primary care, n (%)						
	Psychiatric care, n (%)						
	Other specialised care, n (%)						

CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; EHR = Electronic Health Records; FinOMOP-THL = Finnish Care Register for Health Care; IPCI = Integrated Primary Care Information; IQVIA DA Germany = IQVIA Disease Analyzer Germany; SIDIAP = The Information System for Research in Primary Care; n = number of individuals.

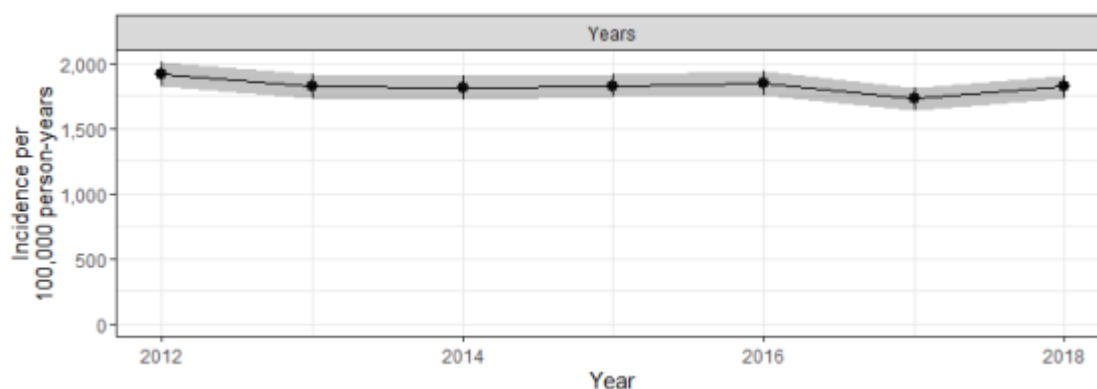
Note: The same table structure will be produced separately for hypnotic benzodiazepines, antiepileptic benzodiazepines, benzodiazepine-related medicines, diazepam, and alprazolam.

MOCK Table 13. Treatment duration of pre-specified benzodiazepines and benzodiazepine-related medicines during the study period and across the data sources (*objective 3*).

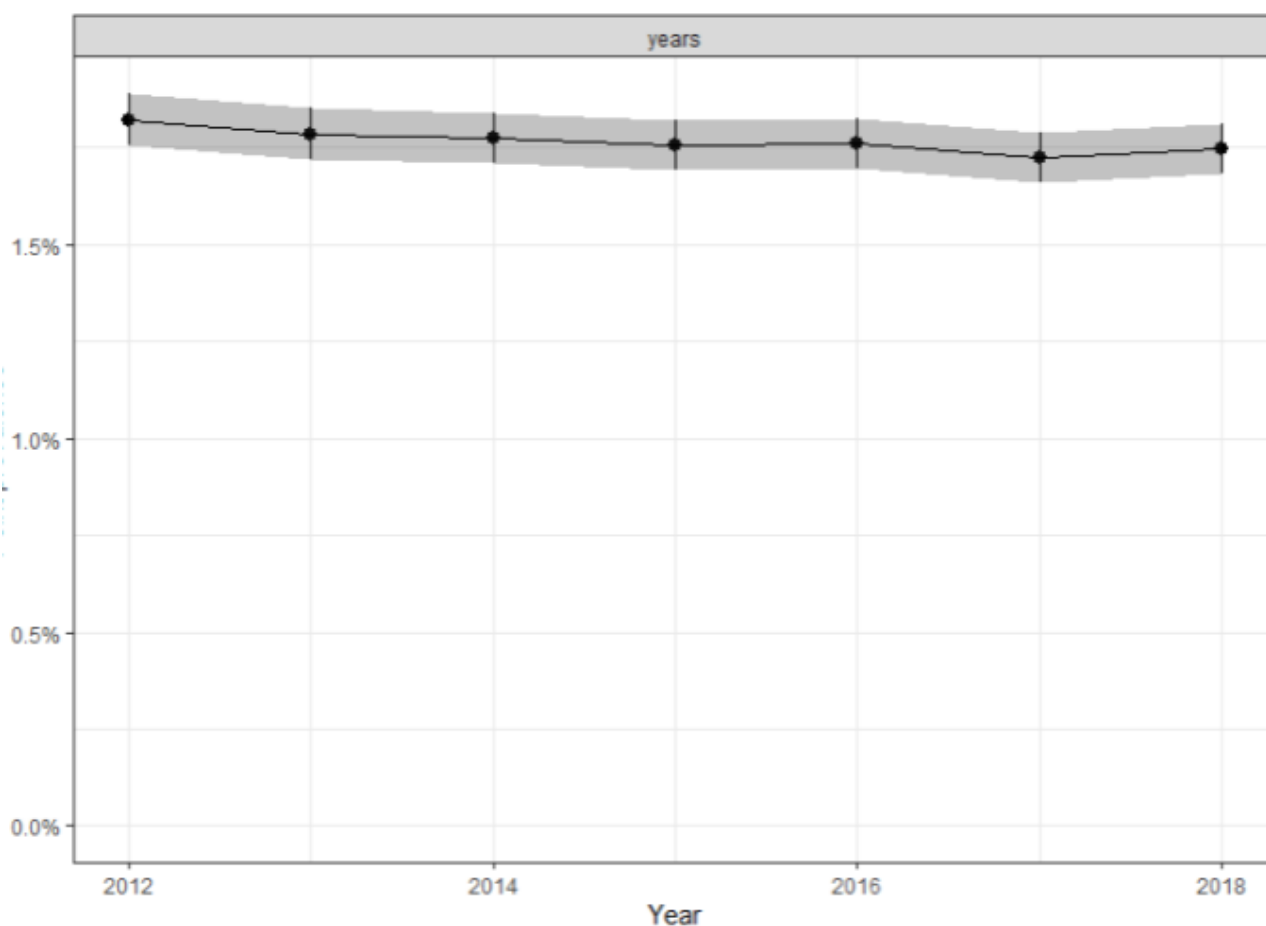
Treatment	Variable name	Estimate name	Data source					
			DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	IPCI	CPRD GOLD
Anxiolytic benzodiazepines	Number subjects	N						
	Days exposed	Median (Q25 – Q75)						
		Min						
		Max						
Hypnotic benzodiazepines	Number subjects	N						
	Days exposed	Median (Q25 – Q75)						
		Min						
		Max						
Antiepileptic benzodiazepines	Number subjects	N						
	Days exposed	Median (Q25 – Q75)						
		Min						
		Max						
Benzodiazepine-related medicines	Number subjects	N						
	Days exposed	Median (Q25 – Q75)						
		Min						
		Max						
Diazepam	Number subjects	N						

Treatment	Variable name	Estimate name	Data source					
			DK-DHR	FinOMOP-THL	IQVIA DA Germany	SIDIAP	IPCI	CPRD GOLD
	Days exposed	Median (Q25 – Q75)						
		Min						
		Max						
Alprazolam	Number subjects	N						
	Days exposed	Median (Q25 – Q75)						
		Min						
		Max						

CPRD GOLD = Clinical Practice Research Datalink GOLD; DK-DHR = Danish Data Health Registries; EHR = Electronic Health Records; FinOMOP-THL = Finnish Care Register for Health Care; IPCI = Integrated Primary Care Information; IQVIA DA Germany = IQVIA Disease Analyzer Germany; SIDIAP = The Information System for Research in Primary Care; N = number of individuals.



MOCK Figure 1. Annual incidence rates of prescriptions for benzodiazepine and benzodiazepine-related medicines, overall (*objective 1*).



MOCK Figure 2. Annual prevalence of prescriptions for benzodiazepines and benzodiazepine-related medicines, overall (*objective 1*).

All results will be provided overall and stratified by calendar year, age, and sex.

An interactive dashboard will be generated by incorporating all the results (tables and figures) included in the PDF report mentioned above.

8.9. Evidence synthesis

Results from analyses described in [Section 8.8](#) will be presented separately for each data source. No meta-analysis of results will be conducted.

9. STRENGTHS AND LIMITATIONS

Strengths

This study leverages several Real-World Data sources from 6 European countries covering primary care and registry data sources. These data sources enable a comprehensive characterisation of adolescents and young adults prescribed benzodiazepines and benzodiazepine-related products, to examine patterns in prescribing of benzodiazepines over time (including pre- and post-COVID-19 pandemic period), and to assess how prescribing patterns differ between sexes across varied healthcare settings. Use of the OMOP CDM ensures standardised data structuring, harmonised variables, and consistent cohort definitions across sources. This facilitates reproducible analyses and enables standardised and consistent characterisation of demographics, clinical variables, prescribing patterns, and treatment characteristics of adolescents and young adults prescribed benzodiazepines and benzodiazepine-related products during the study period.

Limitations

The study will be informed by routinely collected healthcare data, which introduces several important considerations that may influence the interpretation of the findings.

The results from this study will only reflect the populations captured within the six included data sources and may not be generalisable to other countries or healthcare systems. Differences in healthcare systems, coding practices, and data capture may also contribute to heterogeneity across data sources.

Electronic health records are primarily designed for clinical purposes rather than research, and as such, may contain incomplete, inconsistent, or variably recorded information. Therefore, the documentation of clinical characteristics, conditions, and treatment characteristics necessary for patient-level characterisation may vary across data sources. For several variables, analyses rely on the presence of recorded information rather than detailed clinical values or classifications.

The actual clinical indication for prescribing medicines is not directly recorded in the data sources. Instead, proxy measures based on diagnosis codes around the time of benzodiazepine or benzodiazepine-related product prescriptions during the study period are used to assess the indication. Consequently, the estimation of potential indications may be incomplete or imprecise, as relevant diagnoses may not be recorded, may be recorded outside the assessment window, or may not fully reflect the reason for prescribing. To minimise incompleteness of concomitant conditions, a large-scale characterisation will also be performed in different time windows around the index date.

The level of information available on medicine exposure also varies across participating data sources. While most data sources capture prescription records, information on prescribed quantity, treatment duration, or dosing instructions may be incomplete or unavailable. Measures of treatment duration and treatment episodes therefore rely on assumptions regarding prescription timing and permissible gaps between prescriptions and may therefore be subject to misclassification. Treatment history prior to entry into the data source may not be fully captured, and recorded prescriptions do not guarantee that the medications are dispensed or consumed; therefore, assumptions of actual use are made.

The potential impact of COVID-19 on prescribing patterns will be assessed descriptively through graphical presentations. Limited data availability after the pandemic period may impact the assessment of more recent prescribing patterns following the COVID-19 pandemic.

10. REFERENCES

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5. Steffenak, A.K., et al., *Increase in psychotropic drug use between 2006 and 2010 among adolescents in Norway: a nationwide prescription database study*. Clin Epidemiol, 2012. **4**: p. 225-31.
6. Huerta, C., et al., *Exposure to benzodiazepines (anxiolytics, hypnotics and related drugs) in seven European electronic healthcare databases: a cross-national descriptive study from the PROTECT-EU Project*. Pharmacoepidemiol Drug Saf, 2016. **25 Suppl 1**: p. 56-65.
7. Steinhausen, H.C. and C. Bisgaard, *Nationwide time trends in dispensed prescriptions of psychotropic medication for children and adolescents in Denmark*. Acta Psychiatr Scand, 2014. **129**(3): p. 221-31.
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9. Bushnell, G.A., et al., *Drug overdose risk with benzodiazepine treatment in young adults: Comparative analysis in privately and publicly insured individuals*. Addiction, 2024. **119**(2): p. 356-368.
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11. Bosmans, M.W.G., et al., *Impact of the COVID-19 pandemic on long-term trends in youth depression and anxiety*. Discov Ment Health, 2025. **5**(1): p. 210.
12. Kiviruusu, O., et al., *Mental health after the COVID-19 pandemic among Finnish youth: a repeated, cross-sectional, population-based study*. The Lancet Psychiatry, 2024. **11**(6): p. 451-460.

11. ANNEXES

ANNEX I. Description of data sources

Denmark: Danish Data Health Registries (DK-DHR)

#	Section	Description
1	Data source identification and country	DK-DHR (Danish Data Health Registries) Denmark
2	Data partner information section	Danish Medicines Agency (DKMA) Data & Data Analysis (DAD)
3	Coverage and timespan	Data collection since: 1995 Extent: Nation-wide. The data is representative of the entire Danish population.
4	Healthcare setting / type of data	Community pharmacists, and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. The following data elements are collected: diagnosis (including rare diseases and pregnancy data), hospital admissions, discharge and ICU data, Cause of death, Drug prescriptions, dispensing, vaccination and contraception, Procedures (surgical and non-surgical hospital), and Sociodemographic information (sex and age only).
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records, and Registries, and Other. All causes of deaths, all retrieved drug prescriptions, all records of vaccinations, all hospital inpatient and outpatients contacts including disease diagnoses and hospital surgical and non-surgical procedures, histologically confirmed incident cancers, laboratory test results for the entire Danish population from 1/1/1995 onwards.
6	General representativeness	The data is representative of the entire Danish population. Healthcare is free in Denmark, so we do not expect any bias in data collection based on socio-economic status.
7	Data content / source coding	Diagnoses and causes of death are collected using the ICD-10 vocabulary. ATC and RxNorm are used for Drugs. SNOMED codes are used for Procedures.
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5 and the OMOP standard vocabularies. The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Patients have unique identifiers used to link datasets.
9	Quality control (data source specific)	The data we have received relating to nationwide Danish Health Data registries offer an opportunity for large-scale, population-based studies with several advantages 1) Their large size improves the precision of estimates and enables the study of rare exposures and outcomes with long-term latency, 2) Inclusion of nearly all individuals in the target population ensures that the data reflect routine clinical care and all clinical segments of the source population, 3) Data are collected independently of each research study, thus minimising certain types of bias, e.g., non-response, and the influence from attention to the research question on the diagnostic process. Before the source data is sent to us, the Danish Health Data Authority runs and does comprehensive checks of the registry table data validity of the variables, breaks in data, changes in variable coding, missingness, etc. We perform checks of missingness/completeness in relation to requested variables. In essence, we are receiving a dump of a mirror of the data that is controlled by the SDS. The documentation performed by SDS is available online, in Danish primarily https://www.esundhed.dk/Dokumentation (all variables), but also in English https://sundhedsdatastyrelsen.dk/da/english/health_data_and_registers/national_health_registers
10	Linkage	There is no linkage in this data source.
11	Vital status	The Cause of Death registry (DAR) is used, the cause of death is collected using ICD-10 codes.

#	Section	Description
12	Limitations	- Lifestyle factors (such as smoking status and weight) are only complete for pregnant women. - Stillborn children will not have any records in our CDM. This means that e.g. birth weight and birth length of stillborns is not recorded. - There is no information on key socio-economic status (SES) factors, such as occupation, education, and income. - Patient contacts in primary care (visits to the GP) are not included. Consequently, the incidence of chronic diseases like Type 2 Diabetes (T2D) and asthma must be determined using drug prescriptions as a proxy.
13	Main references	Schmidt M, Schmidt SAJ, Adelborg K, Sundbøll J, Laugesen K, Ehrenstein V, Sørensen HT "The Danish health care system and epidemiological research: from health care contacts to database records." Clinical epidemiology (2019): 31372058
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111217 Website: https://sundhedsdatastyrelsen.dk/da/english/health_data_and_registers/healthdatadenmark

Finland: Finnish Care Register for Health Care (FinOMOP-THL)

#	Section	Description
1	Data source identification and country	FinOMOP-THL (Finnish Care Register for Health Care) Finland
2	Data partner information section	FinOMOP (FinOMOP) The Department of Data and Analytics
3	Coverage and timespan	Data collection since: 1998 Extent: Nation-wide. The current CDM population comprises all persons having been alive and residing in Finland since the beginning of 2011.
4	Healthcare setting / type of data	Primary care – General Practitioner, and primary care specialists (e.g. paediatricians), and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care, and other (specify). THL maintains health registers that cover both public and private, primary, and specialised inpatient, urgent and outpatient health care encounters in Finland, starting from 2011. The entire public sector and private inpatient encounters have been included since 2011, while private outpatient encounters, including occupational care, are included since 2020. Since 1998, the Care Register for Health Care (TerveysHilmo) has covered both public outpatient and inpatient specialized care and private inpatient care. Since 2009, the Finnish National Vaccination Register has covered all vaccinations from the public sector and from a large part of private vaccination providers, with the data coverage from both sections being very good to complete from 2020 onwards. Since 2011, the Register of Primary Health Care Visits (AvoHilmo) has covered public primary care. Since 2020, the register has also covered private outpatient care and occupational care. In addition, the CDM also contains positive COVID-19 test results from the Finnish National Infectious Diseases Register. The register itself covers all laboratory confirmations for around 70 specific microbes from 1995 onwards, but only COVID-19 has currently been mapped to the CDM. The CDM also includes prescription records from multiple different sources. Both Care Register for Health Care and Register of Primary Health Care Visits contain very basic prescription data recorded during health care encounters that include just the ATC-code and trade name of medication. More comprehensive prescription data from Kanta Prescription Centre, maintained by Social Insurance Institution of Finland (Kela), has been integrated into the CDM since its 2024 release. The Kanta Prescription records are based electronic prescriptions, which were adopted by most public health care providers in 2010 and by most private providers by 2017.
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records, and Registries. Data is entered by clinicians upon healthcare contact and processed by THL (Kela in the case of Kanta Prescription Centre).

#	Section	Description
6	General representativeness	The THL data has national coverage and is therefore well representative of the Finnish population. Using the complete population as a basis for the person table also serves to facilitate calculations on a population level, e.g. incidence rates.
7	Data content / source coding	The following coding systems have been OMOP-mapped, typically to a good level of completeness: ICD10fi Finnish Extension, ICPC-2, ATC, Toimenpideluokitus (procedure classification adapted from the Nordic Classification of Surgical Procedures (NCSP)), Terveystieteiden tutkimuskeskusten erikoissalat (Hilmo specific provider speciality), Rokotustapa (AR/YDIN National classification for vaccine administration), Tupakointistatus (AR/YDIN National classification for smoking status). Vaccinations are identified on product level based on batch number, trade name, vaccine title, and ATC-code. This is mapped on brand and type in the OMOP CDM.
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5 and the OMOP standard vocabularies. The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Each patient in THL has a unique identifier.
9	Quality control (data source specific)	The source data collection undergoes a structural and semantic validation before entry into the source database. Additionally, some coded variables undergo quality assessment against the respective code systems post entry into the database. The source registers are also assessed for completeness and coverage, with the aim of improving future collection in the areas where data is lacking.
10	Linkage	THL is already a linkage of multiple Finnish registries (see above).
11	Vital status	The National Population registry data forms the basis for forming the patient population. This ensures an up-to-date location (municipality of residence) of patients, as well as complete death occurrences (although not the cause of death).
12	Limitations	All drug records in the CDM are currently based on prescriptions. Kanta Prescription Centre also includes information on drug dispensings, but these have not currently been converted into OMOP CDM. Depending on the type of the medication, a single prescription can be for up to two years dosage of the drug. This means a patient can have up to two-year breaks between observations while actively using the drug. Observation of a prescription also does not mean that the patient necessarily bought or used the medication. The CDM does not currently have meaningful end dates or days of supply for drug exposure. This information is not available for Care Register for Health Care or Register of Primary Health Care Visits, and for Kanta Prescription Centre it is only available in unstructured, free-form format that has not been converted into OMOP CDM. The source system for prescription drug data is only available to the DP until Dec-2023, therefore drug_exposure records from this source are only available in that time range. Some vital signs, like height and weight measurements, are recorded even if the person has not been actually measured, just that the measurement is deemed relevant to the condition or it's treatment. This may lead to duplicate measurements as the value from previous visit might be taken. Not all private health care records are covered for the CDM's entire follow-up time from 2011 onwards. For Register of Primary Health Care Visits and Finnish National Vaccination Register, records from private health care have been available from 2020 onwards. For Kanta Prescription Centre, the coverage of private health care records has been good from 2017 onwards. The inclusion of private health care mainly presents itself as an increase in the number of observations, meaning that it has to be accounted for when interpreting any time series data from the CDM.
13	Main references	Häkkinen, Pirjo; Mölläri, Kaisa; Saukkonen, Sanna-Mari; Väyrynen, Riikka; Mielikäinen, Lasse; Järvelin, Jutta "Hilmo - Sosiaali- ja terveydenhuollon hoitoilmoitus 2020 : Määrittelyt ja ohjeistus : Voimassa 1.1.2020 alkaen" Terveystieteiden tutkimuskeskusten erikoissalat (2019):
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111187 ; https://catalogues.ema.europa.eu/data-source/1111191 Website: https://thl.fi/en/statistics-and-data/data-and-services/register-descriptions ; https://www.kanta.fi/en/research-and-knowledge-management

Germany: IQVIA Disease Analyzer Germany (IQVIA DA Germany)

#	Section	Description
1	Data source identification and country	IQVIA DA Germany (IQVIA Disease Analyzer Germany) Germany
2	Data partner information section	IQVIA (IQVIA)
3	Coverage and timespan	Data collection since: 1989 Extent: Nation-wide. GP and specialists in Germany using specific patient management software.
4	Healthcare setting / type of data	Primary care – General Practitioner, and primary care specialists (e.g. paediatricians). Diagnoses, medication, and procedures from an ambulatory setting. Medications are recorded as prescriptions of marketed products.
5	Data collection process	Outpatient electronic health records. By clinicians at healthcare contact.
6	General representativeness	No specific details on general representativeness given.
7	Data content / source coding	Prescription is on product code level (German PZN), ICD10, NFC, Local lab coding.
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5 and the OMOP standard vocabularies. The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. There can be patients registered under different ID numbers, because there is no linkage between different GPs.
9	Quality control (data source specific)	Data is quality checked on plausibility.
10	Linkage	No.
11	Vital status	Death information is derived from medical events.
12	Limitations	Observation period is defined from first to last visit, causing a drop in 'healthy' persons at the end of the interval. This creates an artefactual increase in incidence and prevalence ratios.
13	Main references	No main reference provided.
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/104282 Website: https://www.iqvia.com/

Spain: The Information System for Research in Primary Care (SIDIAP)

#	Section	Description
1	Data source identification and country	SIDIAP (The Information System for Research in Primary Care) Catalunya, Spain
2	Data partner information section	Fundació Institut Universitari per a la recerca a l'Atenció Primària de Salut Jordi Gol i Gurina (IDIAPJGol)
3	Coverage and timespan	Data collection since: 2006 Extent: Regional. SIDIAP is a database of primary care electronic health records of the population of Catalonia, North-East Spain. It contains pseudo-anonymised records of more than 8 million people , of which 6.1 million are active as of 2022, representing around 76% of the Catalan population.

#	Section	Description
4	Healthcare setting / type of data	Primary care – General Practitioner, and hospital inpatient care. SIDIAP captured data includes routine visits, socio-demographics, diagnoses, laboratory tests, drugs (prescribed and dispensed), referrals, sick leaves and lifestyle information.
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records. Data is entered by primary care physicians upon healthcare contact, supplemented with hospital discharge records. The Institut Catala de la Salut (Catalan Health Institute) is the data controller.
6	General representativeness	It was previously shown that the captured SIDIAP population is highly representative of the entire Catalan region in terms of geographic, age, and sex distributions.
7	Data content / source coding	SIDIAP data covers all services that occur at the Primary Care Centres, as well as support services, such as sexual and reproductive health or home end-of-life care. Drugs are coded in ATC-WHO terminology in the source data. Health outcomes are captured in ICD-10CM codes. The SIDIAP contains all laboratory tests and results performed in primary health centres. Demographics, geographical, as well as socio-economic factors are recorded for each patient.
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5 and the OMOP standard vocabularies. The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. A patient has a unique id, also upon changing practice or re-registration.
9	Quality control (data source specific)	Internal and external validation processes are carried out to determine the data quality of the SIDIAP information at each data update. These include stratifying the data by geographical regions and year in order to identify differences in data collection that need to be harmonized (e.g. recording of specific information under different codes). The measurement units of variables measuring one characteristic are also homogenized (e.g. transformation of the data from every laboratory that measures haemoglobin to grams per decilitre). Visual inspection of all data included in the database by week is also conducted, allowing one to see temporal patterns in the registry of a certain variable. With this information, the SIDIAP team can issue recommendations to researchers about the most common variable(s) where certain information is recorded (e.g., there are several variables with information concerning the women's menopausal status and with these visual inspection tools the SIDIAP team can inform the researchers about which related variables have the largest number of records and could be more helpful to capture menopause). Data availability (longitudinally and reliability), plausibility (range checks and unusual values), and consistency are inspected through visualisation tools. In addition, before accessing the data for a requested project, research teams have access to a quality-control report. This document contains counts, years, percentiles, maximums and minimums, incidences, and prevalence of the data requested for the project, allowing detection of inconsistencies in the data extraction prior to data delivery. External validation processes of the SIDIAP database mainly include assessing the data recorded in SIDIAP through linkage to external gold standard data sources, by analysing free text, or by sending questionnaires to health professionals.
10	Linkage	SIDIAP is linked to a hospital discharge database, pharmacy dispensation, and primary care laboratories. It can also be linked to other registries in Catalonia on a project by project basis.
11	Vital status	Mortality is fully captured in SIDIAP. The cause of death is not available, but can be linked to the Spanish death registry on a project by project basis.
12	Limitations	The SIDIAP data is not representative of individuals not using public primary care, and conditions that are usually followed by specialist care might not be properly captured. In addition, there is limited information on lifestyle variables. Patients are followed until Death or when transferring to another primary health care centre that does not contribute to SIDIAP.
13	Main references	Recalde M, Rodríguez C, Burn E, Far M, García D, Carrere-Molina J, Benítez M, Moleras A, Pistillo A, Bolívar B, Aragón M, Duarte-Salles T "Data Resource Profile: The Information System for Research in Primary Care (SIDIAP)." International journal of epidemiology (2022): 35415748

#	Section	Description
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/50190 Website: https://www.sidiap.org/index.php/en

The Netherlands: Integrated Primary Care Information (IPCI)

#	Section	Description
1	Data source identification and country	IPCI (Integrated Primary Care Information) the Netherlands
2	Data partner information section	Erasmus University Medical Center (EMC) Department of Medical Informatics
3	Coverage and timespan	Data collection since: 2006 Extent: Nation-wide. IPCI is a Dutch database that contains patient records from 2006 onwards. However, it mainly covers the central part of the country, including the most densely populated area (the 'Randstad') and non-urban areas. IPCI contains information on all patients registered with GPs responsible for non-emergency care and referrals. A patient is registered at birth or at first encounter with the GP.
4	Healthcare setting / type of data	Primary care – General Practitioner. Data is collected from primary care EHR. This includes demographic information, complaints and symptoms, diagnoses, laboratory test results, lifestyle factors (in limited amount), and correspondence with secondary care, such as referral and discharge letters.
5	Data collection process	Outpatient electronic health records. Data is entered into the EHR system by the GPs, during or after the visit. The patient dossiers are collected by Erasmus MC data managers and combined in one harmonized database. Several checks are done on this database to ensure correct data processing. Persons can have dossiers at multiple GPs.
6	General representativeness	More than 99% of the Dutch population has health insurance, and almost all citizens are registered with a general practitioner. Over 12 months, around 78% of the population has at least one contact with their GP. IPCI included around 350 GP practices out of around 5000 in the country (~ 7%). The demographic composition of the IPCI population mirrors that of the general Dutch population in terms of age and sex.
7	Data content / source coding	Dutch GPs use mainly Dutch standard codes, like ICPC-1 and Diagnostische Bepalingen maintained by NHG. And for therapy the G-Standard is used, maintained by ZIndex.
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5 and the OMOP standard vocabularies. The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. Patients can be registered under different IDs, but since a patient can only be registered at one GP at a time, the observations periods will not overlap.
9	Quality control (data source specific)	Prior to each data release, extensive quality control steps are performed, e.g., comparison of patient characteristics between practices, and checks to identify abnormal temporal data patterns in practices. For each practice, around 200 quality indicators are obtained. Of these indicators, a quarter refer to population characteristics, e.g. number of birth and mortalities relative to practice size, temporal consistency. The other indicators are based on medical data, e.g. distribution of measurement values, frequencies of diagnoses and procedures relative to age, completeness of data. The indicators are combined in a couple of quality scores for each practice. For these scores, cut-off values for acceptable quality have been defined. Practices with a score below a cut-off are excluded for research. This approach has shown to be very important, for example to check if data from practices that just joined the database are at an acceptable level of quality. The details of the approach, like the cut-off values for acceptance, are based on years of experience. In addition, trends are compared with the previous database release.

#	Section	Description
		Extensive quality control steps are performed before each data release. These include comparing patient characteristics between practices and checks to identify abnormal temporal data patterns in practices. Additional checks include over 200 indicators related to population characteristics (e.g., reliability of birth and mortality rates) and medical data (e.g., availability of durations of prescriptions and completeness of laboratory results). Records of low quality are excluded from the database.
10	Linkage	Linkage requires additional approval steps and needs to be assessed on a case-by-case basis. IPCI is not routinely linked with other databases.
11	Vital status	Vital status (death date and cause) is collected based on GP records.
12	Limitations	The main limitation comes with the fact that IPCI is limited to GP records, and although it contains information on referrals and discharge letters, it may not fully capture specific hospital information. Capture of oral contraceptives in IPCI is incomplete. The first prescription is recorded within the patient's medical file but not the subsequent prescriptions. If you want to use IPCI data for research questions on oral contraceptives, you can do that but then you need to select those GPs that use MEDICOM as software system (where you have prescribing and dispensing). However, of hormone substitution therapy, the information on prescribing is COMPLETE. IPCI does not include coded/detailed data about medications/procedures/test results from the hospital or other care-providers.
13	Main references	de Ridder MAJ, de Wilde M, de Ben C, Leyba AR, Mosseveld BMT, Verhamme KMC, van der Lei J, Rijnbeek PR "Data Resource Profile: The Integrated Primary Care Information (IPCI) database, The Netherlands." International journal of epidemiology (2022): 35182144
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/42618 Website: http://www.ipci.nl

The United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

#	Section	Description
1	Data source identification and country	CPRD GOLD (Clinical Practice Research Datalink GOLD) the United Kingdom
2	Data partner information section	University of Oxford - Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences (Oxford NDORMS) NDORMS
3	Coverage and timespan	Data collection since: 1987 Extent: Nation-wide. CPRD GOLD consists of patients in contributing practices using Vision software. Historically this covered the whole of the UK, but the number of contributing practices in the England is dropping. In January 2025 only 3 practices from England were a part of CPRD GOLD, while historical patient data were from the whole of the UK, and will continue to be so. In the future, no practices from England will be present, only practices from Scotland, Wales, and Northern Ireland.
4	Healthcare setting / type of data	Primary care – General Practitioner, and primary care specialists (e.g. paediatricians), and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. CPRD GOLD data include patient demographics, biological measurements, clinical symptoms and diagnoses, referrals to specialist/hospital and their outcome, laboratory tests/results, and prescribed medications.
5	Data collection process	Outpatient electronic health records. Data are entered by clinicians into the EHR. Data is processed by CPRD that provides data releases for research.

#	Section	Description
6	General representativeness	In the last 10 years, the CPRD GOLD regional distribution of currently contributing general practitioner (GP) practices has significantly shifted, resulting in many new practices joining from Scotland, Wales, and Northern Ireland, and fewer participating from England. These changes have affected the CPRD GOLD population size, regional coverage, and eligibility for data linkages. CPRD GOLD January 2024 contains >21.3 million historical and current patients (12.9 in England, 3.1 in Wales, 4.7 in Scotland, 0.7 in Northern Ireland). Of these, nearly 3 million are currently registered in a GP practice and represent ~4.3% of the estimated current UK population (0.1% in England, 32.3% in Wales, 28.6% in Scotland, 16.2% in Northern Ireland). Patients currently registered in CPRD GOLD January 2024 are broadly representative of the UK population with respect to age and sex. Reference: https://doi.org/10.1093/ije/dyaf077
7	Data content / source coding	Gemscript, Read, dm+d
8	Data Harmonisation	The data has been mapped to the OMOP CDM v5 and the OMOP standard vocabularies. The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. In GOLD, a patient can be registered under different ID numbers upon changing practice or re-registration. Researchers are not able to identify these patients, as the data are anonymised. However, GOLD covers less than 5% of the current UK GP practices and it is unlikely that an individual who does change GP practice ends up in another GP practice which uses the Vision software and accepts the CPRD data collection agreement. The very small number of duplicated IDs will have different observation periods and should not have an impact on the data analyses.
9	Quality control (data source specific)	CPRD GOLD only includes practices whose data quality is assessed to be up-to-standard (UTS). Each practice is associated to an UTS date set when the data quality standards become satisfactory, and CPRD recommend using only longitudinal data starting from this UTS date. Every time CPRD collect the EHR from a practice, checks are run for the data quality standards, and if they are not adequate, the EHR is not accepted. When the data quality becomes acceptable again, CPRD updates the practice UTS date. CPRD also checks data quality standards at the patient level, and associates each patient with a flag, reporting if its data are acceptable for clinical research. Only patients with acceptable data quality are included in the population to be mapped to CDM.
10	Linkage	CPRD GOLD can be linked to several sources, however our Oxford OMOP CDM is only linked to the CPRD GOLD Ethnicity Record and to the CPRD Townsend Deprivation Index at the Practice Level.
11	Vital status	The date of death in CPRD GOLD has been validated against the Population registry (ONS) mortality data. Reference: https://doi.org/10.1002/pds.4747
12	Limitations	The main limitation is due to the fact that CPRD GOLD is limited to GP records, and although it contains information on referrals and discharge letters, it may not fully capture specific hospital information. Events from hospital and specialist care are not covered.
13	Main references	Sanchez-Santos MT, Axson EL, Dedman D, Delmestri A "Data Resource Profile Update: CPRD GOLD." International journal of epidemiology (2025): 40499193
14	Link to HMA-EMA catalogue and data source webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111113 Website: https://www.cprd.com/data/primary-care-data/cprd-gold

ANNEX II. Fitness for use assessment

Data source justification for inclusion and key characteristics

Denmark: Danish Data Health Registries (DK-DHR)

DK-DHR will be included in this study because it is a registry data source that provides relevant information on benzodiazepine use in the adolescent and young adult population.

Based on a preliminary feasibility assessment, the expected number of record counts for alprazolam will be 186,000 and will be 325,400 for diazepam among adolescents and young adults (all objectives).

Moreover, data availability and follow-up in DK-DHR sufficient, as data availability starts in 1995, and the date of the most recent data extraction (as of July 2026) is 11/2025, which aligns with the study period. The median follow-up of the first observation period is 7,930 days.

There are no study specific limitations present in DK-DHR.

Lastly, DK-DHR has blanket Institutional Review Board (IRB) approval, which makes the execution of this study feasible within the current study timelines.

Finland: Finnish Care Register for Health Care (FinOMOP-THL)

FinOMOP-THL will be included in this study because it is a hospital data source that provides relevant information on benzodiazepine use in the adolescent and young adult population.

Based on a preliminary feasibility assessment, the expected number of record counts for alprazolam will be 147,100 and will be 381,200 for diazepam among adolescents and young adults (all objectives).

Moreover, data availability and follow-up in FinOMOP-THL is sufficient, as data availability starts in 2011, and the date of the most recent data extraction (as of July 2026) is 12/2025, which aligns with the study period. The median follow-up of the first observation period is 4,020 days.

There are some study specific limitations present in FinOMOP-THL, namely: the study period will end in 12/2023, considering the availability of prescription drug data (all objectives). In addition, as drug end dates are not available, FinOMOP-THL will not contribute to objective 3.

Lastly, IRB approval for FinOMOP-THL is estimated to take 1–3 months, which makes the execution of this study feasible within the current study timelines.

Germany: IQVIA Disease Analyzer Germany (IQVIA DA Germany)

IQVIA DA Germany will be included in this study because it is a primary care data source that provides relevant information on benzodiazepine use in the adolescent and young adult population.

Based on a preliminary feasibility assessment, the expected number of record counts for alprazolam will be 14,900 and will be 42,800 for diazepam among adolescents and young adults (all objectives).

Moreover, data availability and follow-up in IQVIA DA Germany is sufficient, as data availability starts in 1989, and the date of the most recent data extraction (as of July 2026) is 06/2025, which aligns with the study period. The median follow-up of the first observation period is 121 days.

There are no study specific limitations present in IQVIA DA Germany.

Lastly, IQVIA DA Germany has blanket IRB approval, which makes the execution of this study feasible within the current study timelines.

Spain: The Information System for Research in Primary Care (SIDIAP)

SIDIAP will be included in this study because it is a primary care data source that provides relevant information on benzodiazepine use in the adolescent and young adult population.

Based on a preliminary feasibility assessment, the expected number of record counts for alprazolam will be 647,800 and will be 987,900 for diazepam among adolescents and young adults (all objectives).

Moreover, data availability and follow-up in SIDIAP is sufficient, as data availability starts in 2006, and the date of the most recent data extraction (as of July 2026) is 12/2024, which aligns with the study period. The median follow-up of the first observation period is 5,760 days.

There are no study specific limitations present in SIDIAP.

Lastly, IRB approval for SIDIAP is estimated to take 1–3 months, which makes the execution of this study feasible within the current study timelines.

The Netherlands: Integrated Primary Care Information (IPCI)

IPCI will be included in this study because it is a primary care data source that provides relevant information on benzodiazepine use in the adolescent and young adult population.

Based on a preliminary feasibility assessment, the expected number of record counts for alprazolam will be 12,200 and will be 30,900 for diazepam among adolescents and young adults (all objectives).

Moreover, data availability and follow-up in IPCI is sufficient, as data availability starts in 2006, and the date of the most recent data extraction (as of July 2026) is 12/2025, which aligns with the study period. The median follow-up of the first observation period is 1,830 days.

There are no study specific limitations present in IPCI.

Lastly, IPCI has blanket IRB approval, which makes the execution of this study feasible within the current study timelines.

The United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

CPRD GOLD will be included in this study because it is a primary care data source that provides relevant information on benzodiazepine use in the adolescent and young adult population.

Based on a preliminary feasibility assessment, the expected number of record counts for alprazolam will be 1,900 and will be 1,545,200 for diazepam among adolescents and young adults (all objectives).

Moreover, data availability and follow-up in CPRD GOLD is sufficient, as data availability starts 1987, and the date of the most recent data extraction (as of July 2026) is 11/2025, which aligns with the study period. The median follow-up of the first observation period is 2,160 days.

There are no study specific limitations present in CPRD GOLD.

Lastly, CPRD GOLD has blanket IRB approval, which makes the execution of this study feasible within the current study timelines.

Table S1. Fitness-for-use assessment of data sources.

Design elements	Operational definition	Data elements for valid capture	Criticality of the quality of the element, including justification where relevant	Suggested extensiveness assessment	Suggested assessment of other quality dimensions	Suggested substantiation by documentation
Study population	Adolescents and young adults (<i>all objectives</i>)	Year of birth	High	100% of included individuals will have year of birth available	N/A	N/A
Treatment/ exposure	Benzodiazepine or benzodiazepine-related drug use (<i>objectives 1 and 3</i>)	Prescription of pre-specified benzodiazepine drug classes and selected ingredients (RxNorm code)	High	100% of included individuals will have a prescription of pre-specified benzodiazepine drug classes and selected ingredients (RxNorm code)	100% of prescriptions have been mapped to RxNorm	N/A
Comparator group (not relevant)	N/A	N/A	N/A	N/A	N/A	N/A
Outcomes	Benzodiazepine or benzodiazepine-related drug use (<i>objective 1</i>)	Prescription of pre-specified benzodiazepine drug classes and selected ingredients (RxNorm code)	Medium	N/A (to be assessed on a research question basis)	N/A	N/A
	Characteristics of benzodiazepine users (<i>objective 2</i>)	Year of birth and concept IDs for sex, and various clinical characteristics, conditions, medication, and type of healthcare provider	Medium	N/A (to be assessed on a research question basis)	N/A	N/A
	Treatment duration (<i>objective 3</i>)	Drug exposure start and end dates	Medium	Only data sources with available drug exposure start and end dates will contribute to this objective	N/A	N/A

Design elements	Operational definition	Data elements for valid capture	Criticality of the quality of the element, including justification where relevant	Suggested extensiveness assessment	Suggested assessment of other quality dimensions	Suggested substantiation by documentation
Covariates	Age and sex strata (<i>all objectives</i>)	Concept IDs for sex, age	Medium	100% of included individuals will have sex and year of birth available	N/A	N/A
Follow-up time (not relevant)	N/A	N/A	N/A	N/A	N/A	N/A

N/A = Not applicable, RxNorm = Medical prescription normalised.

EMA Data Quality Framework for EU medicines regulation: application to Real-World Data for more information

(https://www.ema.europa.eu/system/files/documents/other/data-quality-framework-eu-medicines-regulation-application-real-world-data_en.pdf).

ANNEX III. Operational and reporting considerations

DATA MANAGEMENT

Data management

All data sources have previously mapped their data to the OMOP common data model. This enables the use of standardised analytics and using DARWIN EU® tools across the network, since the structure of the data and the terminology system is harmonised. The OMOP CDM was developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: <https://ohdsi.github.io/CommonDataModel> and in The Book of OHDSI: <http://book.ohdsi.org>.

The analytic code for this study will be written in R and will use standardised analytics wherever possible. Each data partner will execute the study code against their data source containing patient-level data and then return the results (csv files), which will only contain aggregated data. The results from each of the contributing data sites will then be combined in tables and figures for the study report.

Data storage and protection

For this study, participants from various EU member states will process personal data from individuals that is collected in national/regional electronic health record data sources. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All data sources used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate non-identifiable aggregate summary results.

The output files are stored in the DARWIN EU® Digital Research Environment (DRE). These output files do not contain any data that allow identification of subjects included in the study. The DRE implements further security measures to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/2016 in the various member states.

QUALITY CONTROL

Data source quality control

When defining drug cohorts, non-systemic products will be excluded from the list of included codes summarised on the ingredient level.

When defining cohorts for indications, a systematic search of possible codes for inclusion will be identified using the *CodelistGenerator* R package (<https://github.com/darwin-eu/CodelistGenerator>). This package allows the user to define a search strategy and will use this to query the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, the *CohortDiagnostics* (<https://github.com/OHDSI/CohortDiagnostics>) and *DrugExposureDiagnostics* (<https://cran.r-project.org/web/packages/DrugExposureDiagnostics/index.html>) R packages will be run, if needed, to assess the use of different codes across the data sources contributing to the study and identify any codes potentially omitted in error. The *DrugExposureDiagnostics* package evaluates ingredient-specific attributes and patterns in drug exposure records.

The study code will be based on DARWIN EU® R packages: *IncidencePrevalence* to estimate Incidence and Prevalence, *DrugUtilisation* to characterise the drug use, and *CohortCharacteristics* to characterise the cohort by indication. These packages will include numerous automated unit tests to ensure the validity of

the codes, alongside software peer review and user testing. The R package will be made publicly available via GitHub.

PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A PDF report including an executive summary, and the specified tables and/or figures will be submitted to EMA by the DARWIN EU® CC upon completion of the study.

An interactive dashboard incorporating all the results (tables and figures) will be provided alongside the PDF report. The full set of underlying aggregated data used in the dashboard will also be made available, if requested.

ANNEX IV. Lists with concept definitions

Preliminary list of conditions concepts definitions is provided in the table below:

Table S2. Preliminary list of conditions to identify indication for use.

Phenotype	Concept name	Concept ID (including descendants)	Exclude concept ID	Vocabulary
Withdrawal syndrome	Alcohol withdrawal delirium	377830	no	SNOMED
Withdrawal syndrome	Alcohol withdrawal hallucinosis	439277	no	SNOMED
Withdrawal syndrome	Alcohol withdrawal scale	4180457	no	SNOMED
Withdrawal syndrome	Alcohol withdrawal syndrome	36308646	no	LOINC
Withdrawal syndrome	Alcohol withdrawal-induced convulsion	4202330	no	SNOMED
Withdrawal syndrome	Drug or alcohol withdrawal syndrome	36309037	no	LOINC
Withdrawal syndrome	Drug withdrawal headache	4183441	no	SNOMED
Withdrawal syndrome	Perceptual disturbances co-occurrent and due to psychoactive substance withdrawal	37110469	no	SNOMED
Withdrawal syndrome	Psychoactive substance withdrawal	4192127	no	SNOMED
Withdrawal syndrome	Seizure co-occurrent and due to psychoactive substance withdrawal	37110470	no	SNOMED
Withdrawal syndrome	Signs of drug withdrawal	3654825	no	SNOMED
Withdrawal syndrome	Substance use treatment: drug withdrawal	4302387	no	SNOMED
Anxiety	Anxiety	441542	no	SNOMED
Delirium	Delirium	373995	no	SNOMED
Dementia	Amyotrophic lateral sclerosis with dementia	4041685	no	SNOMED
Dementia	Frontotemporal dementia	4043378	no	SNOMED
Dementia	Language disorder of dementia	4044415	no	SNOMED
Dementia	Cerebral degeneration presenting primarily with dementia	4092747	no	SNOMED
Dementia	Dementia	4182210	no	SNOMED
Dementia	Pseudodementia	4187091	no	SNOMED
Dementia	Global deterioration scale finding for assessment of primary degenerative dementia	4250116	no	SNOMED
Dementia	Behavioral and psychological symptoms of dementia	35608576	no	SNOMED
Dementia	Psychological symptom due to dementia	37311890	no	SNOMED
Dementia	Apathetic behavior due to dementia	37312030	no	SNOMED
Dementia	Anxiety due to dementia	37312031	no	SNOMED
Dementia	Agitation due to dementia	37312035	no	SNOMED
Dementia	Aggression due to dementia	37312036	no	SNOMED
Dementia	Wandering due to dementia	37312577	no	SNOMED
Dementia	GRN-related frontotemporal dementia	45765477	no	SNOMED

Phenotype	Concept name	Concept ID (including descendants)	Exclude concept ID	Vocabulary
Dementia	Frontotemporal dementia with parkinsonism-17	45765480	no	SNOMED
Dementia	Inclusion body myopathy with early-onset Paget disease and frontotemporal dementia	45766396	no	SNOMED
Dementia	At increased risk of dementia	44784331	yes	SNOMED
Dementia	Dementia in remission	44782935	yes	SNOMED
Dementia	Primary degenerative dementia of the Alzheimer type, presenile onset in remission	44782941	yes	SNOMED
Dementia	Primary degenerative dementia of the Alzheimer type, senile onset in remission	44782940	yes	SNOMED
Dementia	Vascular dementia in remission	44782934	yes	SNOMED
Epilepsy	Epilepsy	380378	no	SNOMED
Febrile convulsions	Febrile convulsion	444413	no	SNOMED
Psychotic disorder	Psychotic disorder	436073	no	SNOMED
Sleep disorder	Sleep disorder	435524	no	SNOMED

Preliminary list of medicines concepts definitions is provided in the table below:

Table S3. Preliminary list of medicines definitions to identify benzodiazepines and benzodiazepine-related medicines and co-prescribing of other pre-specified psychotropic medications.

Substance Name*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
etizolam	etizolam	Anxiolytic benzodiazepines	N05BA	43009000	Yes
mexazolam	mexazolam	Anxiolytic benzodiazepines	N05BA	43009058	Yes
diazepam	diazepam	Anxiolytic benzodiazepines	N05BA	723013	Yes
Camazepam	Camazepam	Anxiolytic benzodiazepines	N05BA	40798714	Yes
pinazepam	pinazepam	Anxiolytic benzodiazepines	N05BA	2100521	Yes
clorazepate	clorazepate	Anxiolytic benzodiazepines	N05BA	790253	Yes
oxazepam	oxazepam	Anxiolytic benzodiazepines	N05BA	724816	Yes
medazepam	medazepam	Anxiolytic benzodiazepines	N05BA	19125106	Yes
lorazepam	lorazepam	Anxiolytic benzodiazepines	N05BA	791967	Yes
fludiazepam	fludiazepam	Anxiolytic benzodiazepines	N05BA	35198139	Yes
BENTAZEPAM	BENTAZEPAM	Anxiolytic benzodiazepines	N05BA	36852894	Yes
chlordiazepoxide	chlordiazepoxide	Anxiolytic benzodiazepines	N05BA	990678	Yes
ethyl loflazepate	ethyl loflazepate	Anxiolytic benzodiazepines	N05BA	19095467	Yes
bromazepam	bromazepam	Anxiolytic benzodiazepines	N05BA	19030353	Yes
nordazepam	nordazepam	Anxiolytic benzodiazepines	N05BA	19080959	Yes
alprazolam	alprazolam	Anxiolytic benzodiazepines	N05BA	781039	Yes
ADINAZOLAM	ADINAZOLAM	Anxiolytic benzodiazepines	N05BA	36858914	Yes

Substance Name*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
prazepam	prazepam	Anxiolytic benzodiazepines	N05BA	19050461	Yes
clobazam	clobazam	Anxiolytic benzodiazepines	N05BA	19050832	Yes
cloxazolam	cloxazolam	Anxiolytic benzodiazepines	N05BA	19051096	Yes
tofisopam	tofisopam	Anxiolytic benzodiazepines	N05BA	19100773	Yes
clotiazepam	clotiazepam	Anxiolytic benzodiazepines	N05BA	19068821	Yes
halazepam	halazepam	Anxiolytic benzodiazepines	N05BA	801396	Yes
ketazolam	ketazolam	Anxiolytic benzodiazepines	N05BA	19003946	Yes
<u>PHENAZEPAM</u>	PHENAZEPAM	Anxiolytic benzodiazepines	N05BA80	36850946	Yes
triazolam	triazolam	Hypnotic benzodiazepines	N05CD	704599	Yes
flunitrazepam	flunitrazepam	Hypnotic benzodiazepines	N05CD	19055224	Yes
temazepam	temazepam	Hypnotic benzodiazepines	N05CD	836715	Yes
brotizolam	brotizolam	Hypnotic benzodiazepines	N05CD	19039262	Yes
quazepam	quazepam	Hypnotic benzodiazepines	N05CD	731188	Yes
lormetazepam	lormetazepam	Hypnotic benzodiazepines	N05CD	19007977	Yes
estazolam	estazolam	Hypnotic benzodiazepines	N05CD	748010	Yes
flurazepam	flurazepam	Hypnotic benzodiazepines	N05CD	756349	Yes
DOXEFAZEPAM	DOXEFAZEPAM	Hypnotic benzodiazepines	N05CD	36849918	Yes
midazolam	midazolam	Hypnotic benzodiazepines	N05CD	708298	Yes
Triazulenone (loprazolam)	triazulenone	Hypnotic benzodiazepines	N05CD	19042550	Yes
nimetazepam	nimetazepam	Hypnotic benzodiazepines	N05CD	35197946	Yes
CINOLAZEPAM	CINOLAZEPAM	Hypnotic benzodiazepines	N05CD	36852970	Yes
nitrazepam	nitrazepam	Hypnotic benzodiazepines	N05CD	19020021	Yes
remimazolam	remimazolam	Hypnotic benzodiazepines	N05CD	1146633	Yes
clonazepam	clonazepam	Antiepileptic benzodiazepines	N03AE	798874	Yes
zopiclone	zopiclone	Benzodiazepine related drugs	N05CF	19044883	Yes
zolpidem	zolpidem	Benzodiazepine related drugs	N05CF	744740	Yes
eszopiclone	eszopiclone	Benzodiazepine related drugs	N05CF	757352	Yes
zaleplon	zaleplon	Benzodiazepine related drugs	N05CF	720727	Yes
dothiepin	dothiepin	Antidepressants	N06A	19037989	Yes
trazodone	trazodone	Antidepressants	N06A	703547	Yes
amitriptyline	amitriptyline	Antidepressants	N06A	710062	Yes
Hypericum extract	Hypericum extract	Antidepressants	N06A	42899139	Yes
IPROCLOZIDE	IPROCLOZIDE	Antidepressants	N06A	36849601	Yes
desvenlafaxine	desvenlafaxine	Antidepressants	N06A	717607	Yes
imipramine	imipramine	Antidepressants	N06A	778268	Yes

Substance Name*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
levomilnacipran	levomilnacipran	Antidepressants	N06A	43560354	Yes
moclobemide	moclobemide	Antidepressants	N06A	19010652	Yes
tianeptine	tianeptine	Antidepressants	N06A	19041910	Yes
Zimeldine	Zimeldine	Antidepressants	N06A	40799195	Yes
amineptin	amineptin	Antidepressants	N06A	19032424	Yes
iproniazid	iproniazid	Antidepressants	N06A	19122259	Yes
nefazodone	nefazodone	Antidepressants	N06A	714684	Yes
vilazodone	vilazodone	Antidepressants	N06A	40234834	Yes
5-hydroxytryptophan	5-hydroxytryptophan	Antidepressants	N06A	1363516	Yes
Agomelatine	Agomelatine	Antidepressants	N06A	36878783	Yes
fluvoxamine	fluvoxamine	Antidepressants	N06A	751412	Yes
butriptyline	butriptyline	Antidepressants	N06A	19039883	Yes
minaprine	minaprine	Antidepressants	N06A	19072123	Yes
sertraline	sertraline	Antidepressants	N06A	739138	Yes
clomipramine	clomipramine	Antidepressants	N06A	798834	Yes
doxepin	doxepin	Antidepressants	N06A	738156	Yes
esketamine	esketamine	Antidepressants	N06A	1366610	Yes
gepirone	gepirone	Antidepressants	N06A	42608871	Yes
iprindole	iprindole	Antidepressants	N06A	19122204	Yes
milnacipran	milnacipran	Antidepressants	N06A	19080226	Yes
tryptophan	tryptophan	Antidepressants	N06A	19006186	Yes
duloxetine	duloxetine	Antidepressants	N06A	715259	Yes
isocarboxazid	isocarboxazid	Antidepressants	N06A	781705	Yes
opipramol	opipramol	Antidepressants	N06A	19129635	Yes
desipramine	desipramine	Antidepressants	N06A	716968	Yes
nomifensine	nomifensine	Antidepressants	N06A	19128066	Yes
ALAPROCLATE	ALAPROCLATE	Antidepressants	N06A	36856226	Yes
lofepramine	lofepramine	Antidepressants	N06A	19091830	Yes
mianserin	mianserin	Antidepressants	N06A	19007737	Yes
phenelzine	phenelzine	Antidepressants	N06A	733896	Yes
PIVAGABINE	PIVAGABINE	Antidepressants	N06A	36856232	Yes
viloxazine	viloxazine	Antidepressants	N06A	19008261	Yes
amoxapine	amoxapine	Antidepressants	N06A	713109	Yes
bupropion	bupropion	Antidepressants	N06A	750982	Yes
citalopram	citalopram	Antidepressants	N06A	797617	Yes

Substance Name*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
melitracen	melitracen	Antidepressants	N06A	19110751	Yes
quinupramine	quinupramine	Antidepressants	N06A	19098514	Yes
paroxetine	paroxetine	Antidepressants	N06A	722031	Yes
trimipramine	trimipramine	Antidepressants	N06A	705755	Yes
mirtazapine	mirtazapine	Antidepressants	N06A	725131	Yes
St. John's wort extract	St. John's wort extract	Antidepressants	N06A	1398039	Yes
toloxatone	toloxatone	Antidepressants	N06A	19100775	Yes
Dimetacrine	Dimetacrine	Antidepressants	N06A	40798767	Yes
Hypericum perforatum leaf extract	Hypericum perforatum leaf extract	Antidepressants	N06A	42899140	Yes
maprotiline	maprotiline	Antidepressants	N06A	794147	Yes
nialamide	nialamide	Antidepressants	N06A	19127550	Yes
zuranolone	zuranolone	Antidepressants	N06A	747180	Yes
dibenzepin	dibenzepin	Antidepressants	N06A	19023846	Yes
OXAFLOZANE	OXAFLOZANE	Antidepressants	N06A	36862328	Yes
escitalopram	escitalopram	Antidepressants	N06A	715939	Yes
medifoxamine	medifoxamine	Antidepressants	N06A	19072021	Yes
nortriptyline	nortriptyline	Antidepressants	N06A	721724	Yes
reboxetine	reboxetine	Antidepressants	N06A	19084693	Yes
tranylcypromine	tranylcypromine	Antidepressants	N06A	703470	Yes
bifemelane	bifemelane	Antidepressants	N06A	19058055	Yes
ETOPERIDONE	ETOPERIDONE	Antidepressants	N06A	36858847	Yes
protriptyline	protriptyline	Antidepressants	N06A	754270	Yes
brexanolone	brexanolone	Antidepressants	N06A	1510996	Yes
fluoxetine	fluoxetine	Antidepressants	N06A	755695	Yes
venlafaxine	venlafaxine	Antidepressants	N06A	743670	Yes
vortioxetine	vortioxetine	Antidepressants	N06A	44507700	Yes
cyamemazine	cyamemazine	Antipsychotics	N05A	19051234	Yes
perphenazine	perphenazine	Antipsychotics	N05A	733008	Yes
promazine	promazine	Antipsychotics	N05A	19052903	Yes
molindone	molindone	Antipsychotics	N05A	709699	Yes
prothipendyl	prothipendyl	Antipsychotics	N05A	19115044	Yes
sertindole	sertindole	Antipsychotics	N05A	19050633	Yes
aripiprazole	aripiprazole	Antipsychotics	N05A	757688	Yes

Substance Name*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
mosapramine hydrochloride	mosapramine hydrochloride	Antipsychotics	N05A	35198101	Yes
sultopride	sultopride	Antipsychotics	N05A	19100431	Yes
asenapine	asenapine	Antipsychotics	N05A	40164052	Yes
Moperone	Moperone	Antipsychotics	N05A	40798964	Yes
perazine	perazine	Antipsychotics	N05A	19131663	Yes
thiopropazine	thiopropazine	Antipsychotics	N05A	19000305	Yes
risperidone	risperidone	Antipsychotics	N05A	735979	Yes
paliperidone	paliperidone	Antipsychotics	N05A	703244	Yes
sulpiride	sulpiride	Antipsychotics	N05A	19136626	Yes
Butaperazine	Butaperazine	Antipsychotics	N05A	40798666	Yes
Dixyrazine	Dixyrazine	Antipsychotics	N05A	40798772	Yes
levosulpiride	levosulpiride	Antipsychotics	N05A	43009023	Yes
loxapine	loxapine	Antipsychotics	N05A	792263	Yes
olanzapine	olanzapine	Antipsychotics	N05A	785788	Yes
lurasidone	lurasidone	Antipsychotics	N05A	40230761	Yes
trifluoperazine	trifluoperazine	Antipsychotics	N05A	704984	Yes
chlorproethazine	chlorproethazine	Antipsychotics	N05A	19122262	Yes
acepromazine	acepromazine	Antipsychotics	N05A	19018226	Yes
Fluanisone	Fluanisone	Antipsychotics	N05A	40798823	Yes
lumateperone	lumateperone	Antipsychotics	N05A	37498659	Yes
haloperidol	haloperidol	Antipsychotics	N05A	766529	Yes
mesoridazine	mesoridazine	Antipsychotics	N05A	703083	Yes
veralipride	veralipride	Antipsychotics	N05A	19043327	Yes
ziprasidone	ziprasidone	Antipsychotics	N05A	712615	Yes
benperidol	benperidol	Antipsychotics	N05A	19016440	Yes
flupenthixol	flupenthixol	Antipsychotics	N05A	19055982	Yes
pipothiazine	pipothiazine	Antipsychotics	N05A	19133992	Yes
cariprazine	cariprazine	Antipsychotics	N05A	35603277	Yes
fluphenazine	fluphenazine	Antipsychotics	N05A	756018	Yes
iloperidone	iloperidone	Antipsychotics	N05A	19017241	Yes
lithium	lithium	Antipsychotics	N05A	19124477	Yes
lithium carbonate	lithium carbonate	Antipsychotics	N05A	751246	Yes
pipamperone	pipamperone	Antipsychotics	N05A	19093225	Yes
penfluridol	penfluridol	Antipsychotics	N05A	19028044	Yes
remoxipride	remoxipride	Antipsychotics	N05A	19035226	Yes

Substance Name*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
amisulpride	amisulpride	Antipsychotics	N05A	19057607	Yes
lithium citrate	lithium citrate	Antipsychotics	N05A	767410	Yes
pimozide	pimozide	Antipsychotics	N05A	745790	Yes
trifluoperidol	trifluoperidol	Antipsychotics	N05A	19005101	Yes
zuclopenthixol	zuclopenthixol	Antipsychotics	N05A	19010886	Yes
acetophenazine	acetophenazine	Antipsychotics	N05A	19029555	Yes
clozapine	clozapine	Antipsychotics	N05A	800878	Yes
fluspirilene	fluspirilene	Antipsychotics	N05A	19056465	Yes
chlorprothixene	chlorprothixene	Antipsychotics	N05A	19095002	Yes
methotrimeprazine	methotrimeprazine	Antipsychotics	N05A	19005147	Yes
triflupromazine	triflupromazine	Antipsychotics	N05A	19005104	Yes
bromperidol	bromperidol	Antipsychotics	N05A	19039227	Yes
periciazine	periciazine	Antipsychotics	N05A	19053565	Yes
tiapride	tiapride	Antipsychotics	N05A	19008012	Yes
chlormpromazine	chlormpromazine	Antipsychotics	N05A	794852	Yes
metylperon	metylperon	Antipsychotics	N05A	19072088	Yes
xanomeline	xanomeline	Antipsychotics	N05A	1735454	Yes
brexpiprazole	brexpiprazole	Antipsychotics	N05A	46275300	Yes
clothiapine	clothiapine	Antipsychotics	N05A	19100363	Yes
prochlorperazine	prochlorperazine	Antipsychotics	N05A	752061	Yes
thioridazine	thioridazine	Antipsychotics	N05A	700299	Yes
zotepine	zotepine	Antipsychotics	N05A	19102109	Yes
droperidol	droperidol	Antipsychotics	N05A	739323	Yes
pimavanserin	pimavanserin	Antipsychotics	N05A	42628962	Yes
quetiapine	quetiapine	Antipsychotics	N05A	766814	Yes
thiopropazate	thiopropazate	Antipsychotics	N05A	19041817	Yes
oxypertine	oxypertine	Antipsychotics	N05A	19025922	Yes
thiothixene	thiothixene	Antipsychotics	N05A	700465	Yes
valeric acid	valeric acid	Antiseizure medications	N03A	45775582	Yes
aminobutyrate	aminobutyrate	Antiseizure medications	N03A	19123696	Yes
barbexaclone	barbexaclone	Antiseizure medications	N03A	19112534	Yes
beclamide	beclamide	Antiseizure medications	N03A	19018520	Yes
brivaracetam	brivaracetam	Antiseizure medications	N03A	35604901	Yes
cannabidiol	cannabidiol	Antiseizure medications	N03A	1510417	Yes
carbamazepine	carbamazepine	Antiseizure medications	N03A	740275	Yes
CARISBAMATE	CARISBAMATE	Antiseizure medications	N03A	36860359	Yes

Substance Name*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
cenobamate	cenobamate	Antiseizure medications	N03A	37497998	Yes
clonazepam	clonazepam	Antiseizure medications	N03A	798874	Yes
dipropylacetamide	dipropylacetamide	Antiseizure medications	N03A	19054995	Yes
eslicarbazepine	eslicarbazepine	Antiseizure medications	N03A	44507780	Yes
ethadione	ethadione	Antiseizure medications	N03A	21604408	Yes
ethosuximide	ethosuximide	Antiseizure medications	N03A	750119	Yes
ethotoin	ethotoin	Antiseizure medications	N03A	750146	Yes
ezogabine	ezogabine	Antiseizure medications	N03A	40239995	Yes
felbamate	felbamate	Antiseizure medications	N03A	795661	Yes
fenfluramine	fenfluramine	Antiseizure medications	N03A	753860	Yes
fosphenytoin	fosphenytoin	Antiseizure medications	N03A	713192	Yes
ganaxolone	ganaxolone	Antiseizure medications	N03A	780003	Yes
lacosamide	lacosamide	Antiseizure medications	N03A	19087394	Yes
lamotrigine	lamotrigine	Antiseizure medications	N03A	705103	Yes
levetiracetam	levetiracetam	Antiseizure medications	N03A	711584	Yes
mephenytoin	mephenytoin	Antiseizure medications	N03A	702661	Yes
mephobarbital	mephobarbital	Antiseizure medications	N03A	702685	Yes
metharbital	metharbital	Antiseizure medications	N03A	19004254	Yes
methsuximide	methsuximide	Antiseizure medications	N03A	759401	Yes
oxcarbazepine	oxcarbazepine	Antiseizure medications	N03A	718122	Yes
paramethadione	paramethadione	Antiseizure medications	N03A	19021932	Yes
perampanel	perampanel	Antiseizure medications	N03A	42904177	Yes
phenacemide	phenacemide	Antiseizure medications	N03A	19023286	Yes
PHENETURIDE	PHENETURIDE	Antiseizure medications	N03A	36854302	Yes
phenobarbital	phenobarbital	Antiseizure medications	N03A	734275	Yes
phensuximide	phensuximide	Antiseizure medications	N03A	19023842	Yes
phenytoin	phenytoin	Antiseizure medications	N03A	740910	Yes
primidone	primidone	Antiseizure medications	N03A	751347	Yes
progabide	progabide	Antiseizure medications	N03A	19095776	Yes
rufinamide	rufinamide	Antiseizure medications	N03A	19006586	Yes
stiripentol	stiripentol	Antiseizure medications	N03A	35200286	Yes
sulthiame	sulthiame	Antiseizure medications	N03A	19000921	Yes
tiagabine	tiagabine	Antiseizure medications	N03A	715458	Yes
topiramate	topiramate	Antiseizure medications	N03A	742267	Yes
trimethadione	trimethadione	Antiseizure medications	N03A	19005629	Yes
valproate	valproate	Antiseizure medications	N03A	745466	Yes

Substance Name*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
vigabatrin	vigabatrin	Antiseizure medications	N03A	19020002	Yes
zonisamide	zonisamide	Antiseizure medications	N03A	744798	Yes
carbamazepine	carbamazepine	Mood stabilisers	N03AF01	740275	Yes
valproate	valproate	Mood stabilisers	N03AG01	745466	Yes
lamotrigine	lamotrigine	Mood stabilisers	N03AX09	705103	Yes
lithium	lithium	Mood stabilisers	N05AN01	19124477	Yes
glycofurof	glycofurof	Psychostimulants	N06B	43532437	Yes
Pipradrol Hydrochloride	Pipradrol Hydrochloride	Psychostimulants	N06B	44012716	Yes
citicoline	citicoline	Psychostimulants	N06B	40223464	Yes
Fencamfamin	Fencamfamin	Psychostimulants	N06B	40798833	Yes
FIPEXIDE	FIPEXIDE	Psychostimulants	N06B	36861758	Yes
LINOPIRDINE	LINOPIRDINE	Psychostimulants	N06B	36858200	Yes
PRAMIRACETAM	PRAMIRACETAM	Psychostimulants	N06B	36851392	Yes
nizofenone fumarate	nizofenone fumarate	Psychostimulants	N06B	35198179	Yes
acetylcarnitine	acetylcarnitine	Psychostimulants	N06B	19037596	Yes
adrafenil	adrafenil	Psychostimulants	N06B	19112518	Yes
amphetamine	amphetamine	Psychostimulants	N06B	714785	Yes
aniracetam	aniracetam	Psychostimulants	N06B	19032667	Yes
armodafinil	armodafinil	Psychostimulants	N06B	19090984	Yes
atomoxetine	atomoxetine	Psychostimulants	N06B	742185	Yes
caffeine	caffeine	Psychostimulants	N06B	1134439	Yes
cinnarizine	cinnarizine	Psychostimulants	N06B	19097481	Yes
deanol	deanol	Psychostimulants	N06B	1311826	Yes
dexmethylphenidate	dexmethylphenidate	Psychostimulants	N06B	731533	Yes
dextroamphetamine	dextroamphetamine	Psychostimulants	N06B	719311	Yes
fenethylamine	fenethylamine	Psychostimulants	N06B	19061288	Yes
fenozolone	fenozolone	Psychostimulants	N06B	19061392	Yes
idebenone	idebenone	Psychostimulants	N06B	19067036	Yes
lisdexamfetamine	lisdexamfetamine	Psychostimulants	N06B	709567	Yes
meclofenoxate	meclofenoxate	Psychostimulants	N06B	19052682	Yes
methamphetamine	methamphetamine	Psychostimulants	N06B	704053	Yes
methylphenidate	methylphenidate	Psychostimulants	N06B	705944	Yes
modafinil	modafinil	Psychostimulants	N06B	710650	Yes

Substance Name*	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
oxiracetam	oxiracetam	Psychostimulants	N06B	19082891	Yes
pemoline	pemoline	Psychostimulants	N06B	727835	Yes
piracetam	piracetam	Psychostimulants	N06B	19046654	Yes
prolintane	prolintane	Psychostimulants	N06B	19029018	Yes
propentofylline	propentofylline	Psychostimulants	N06B	19096031	Yes
pyrisuccideanol	pyrisuccideanol	Psychostimulants	N06B	19097999	Yes
pyrithioxin	pyrithioxin	Psychostimulants	N06B	19060358	Yes
solriamfetol	solriamfetol	Psychostimulants	N06B	1510970	Yes
vinpocetine	vinpocetine	Psychostimulants	N06B	19095462	Yes
BLARCAMESINE	BLARCAMESINE	Dementia medications	N06D	36855342	Yes
HYDROMETHYLTHI ONINE	HYDROMETHYLTHI ONINE	Dementia medications	N06D	36858293	Yes
IPIDACRINE	IPIDACRINE	Dementia medications	N06D	36856435	Yes
aducanumab	aducanumab	Dementia medications	N06D	1537087	Yes
benzgalantamine	benzgalantamine	Dementia medications	N06D	1734980	Yes
donanemab	donanemab	Dementia medications	N06D	1734796	Yes
donepezil	donepezil	Dementia medications	N06D	715997	Yes
galantamine	galantamine	Dementia medications	N06D	757627	Yes
Ginkgo biloba extract	Ginkgo biloba extract	Dementia medications	N06D	1391889	Yes
Ginkgo biloba leaf extract	Ginkgo biloba leaf extract	Dementia medications	N06D	19098505	Yes
lecanemab	lecanemab	Dementia medications	N06D	1301377	Yes
memantine	memantine	Dementia medications	N06D	701322	Yes
rivastigmine	rivastigmine	Dementia medications	N06D	733523	Yes
tacrine	tacrine	Dementia medications	N06D	836654	Yes
gabapentin	gabapentin	Gabapentinoids	N02BF	797399	Yes
pregabalin	pregabalin	Gabapentinoids	N02BF	734354	Yes
mirogabalin	mirogabalin	Gabapentinoids	N02BF	36861333	Yes

*WHO ATC codes were used to identify substances. For each substance, the corresponding OMOP ingredient concept and all descendant drug concepts were included in the concept set.

Preliminary list of healthcare provider concepts definitions is provided in the table below:

Table S4. Preliminary list of healthcare provider definitions.

Phenotype	Concept name	Concept ID (including descendants)	Exclude concept ID	Vocabulary
Primary care	General Practice	38004446	no	Medicare Specialty
Psychiatric care	Psychiatry	38004469	no	Medicare Specialty

Inclusion of these concepts depends on the feasibility of the assessment of type of healthcare provider.

ANNEX V. Illustrative examples of follow-up and censoring for incidence and prevalence analyses

An example of entry and exit into the denominator population to estimate incidence rates is shown in **Figure S1**. In this example, person ID 1 already has sufficient prior history before the study start date, and the observation period ends after the study end date, so this individual will contribute during the complete study period. Person IDs 2 and 4 only enter the study when they have sufficient prior history. Person IDs 3 had an exposure to the medication of interest prior to the study period and will contribute person time again following the washout period. Person ID 3 leaves when exiting the data source (the end of the observation period). Lastly, person ID 5 has two observation periods in the data source. The first period contributes time from the study start until the end of the observation period. The second starts contributing time again once sufficient prior history is reached and exits at the study end date.

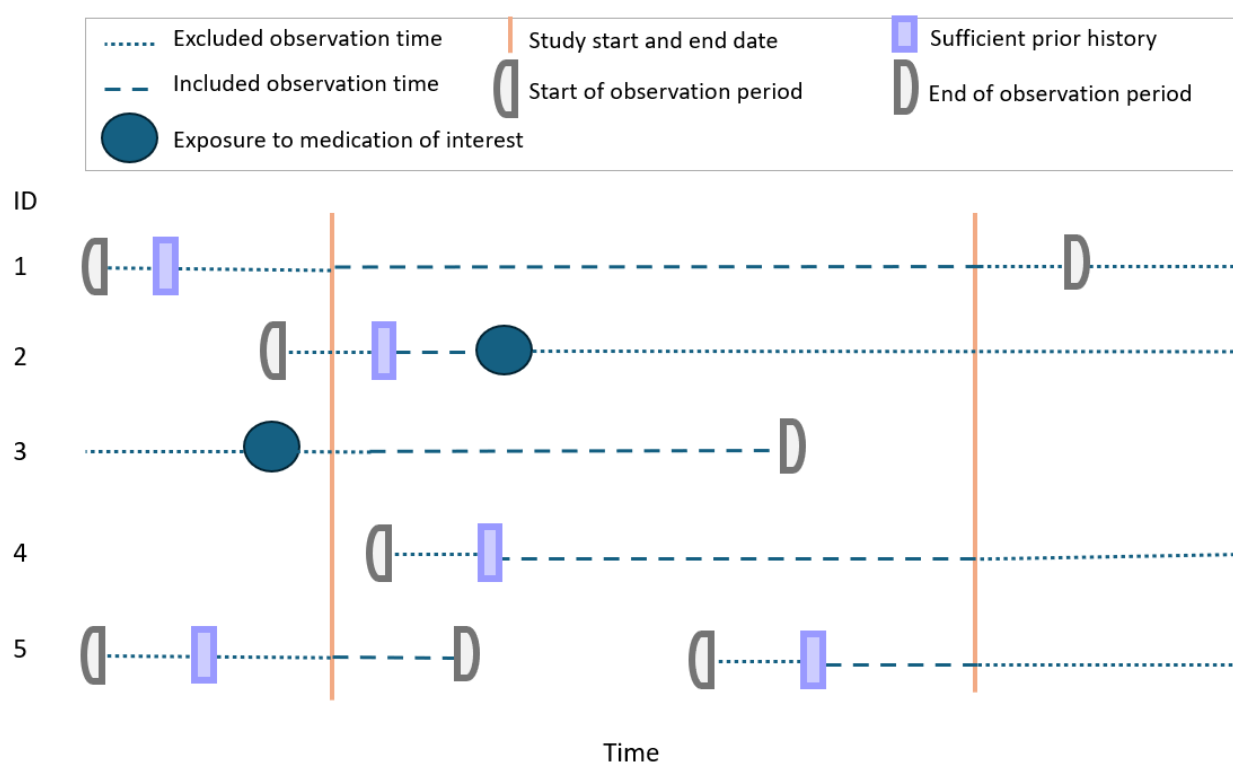


Figure S1. Included observation time for the denominator population for incidence rates.

An illustrative example of entry and exit into the denominator population to estimate prevalence is shown in **Figure S2**. In this example, the observation period of person IDs 1 and 2 starts before the study start date and the observation period ends after the study end date, so these individuals will contribute during the complete study period. Person ID 3 leaves when exiting the data source (the end of the observation period). Person ID 4 enters the study when their observation period starts. Lastly, person ID 5 has two observation periods in the data source. The first period contributes time from the study start until the end of the observation period, the second starts contributing time again once the observation period starts and exits at the study end date.

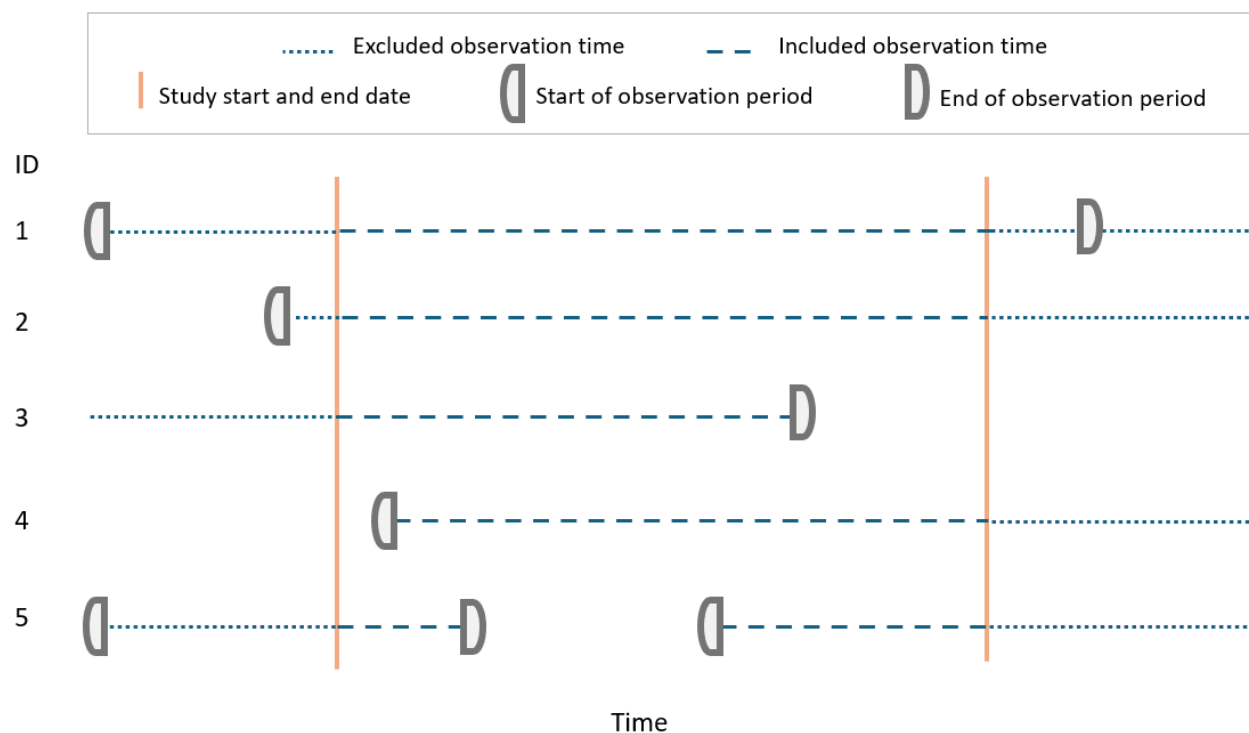


Figure S2. Included observation time for the denominator population for prevalence.

ANNEX VI. ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 4)

Study title: DARWIN EU® - Sex differences in prescribing of benzodiazepines and benzodiazepine-related medicines over time in adolescents and young adults.

EU PAS Register® number: EUPAS1000001096
Study reference number (if applicable): P5-C1-012

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				5
1.1.1 Start of data collection ¹	☒	☐	☐	
1.1.2 End of data collection ²	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no <i>a priori</i> hypothesis?	☒	☐	☐	

Comments:

¹ Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

² Date from which the analytical dataset is completely available.

Section 3: Study design		Yes	No	N/A	Section Number
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.8
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	☒	☐	☐	8
4.2	Is the planned study population defined in terms of:				
4.2.1	Study time period	☒	☐	☐	8.5
4.2.2	Age and sex	☒	☐	☐	8.6
4.2.3	Country of origin	☒	☐	☐	8.4
4.2.4	Disease/indication	☒	☐	☐	8.6
4.2.5	Duration of follow-up	☒	☐	☐	8.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.3

Comments:

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.6.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	

<u>Section 5: Exposure definition and measurement</u>	Yes	No	N/A	Section Number
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	8.8
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

<u>Section 6: Outcome definition and measurement</u>	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.6.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.6.2; 8.8.3.
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

<u>Section 7: Bias</u>	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

<u>Section 8: Effect measure modification</u>	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

<u>Section 9: Data sources</u>	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	ANNEX I; ANNEX II
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	ANNEX I; ANNEX II
9.1.3 Covariates and other characteristics?	☒	☐	☐	ANNEX I; ANNEX II
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	ANNEX I; ANNEX II
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	ANNEX I; ANNEX II
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	ANNEX I; ANNEX II
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	ANNEX I; ANNEX II
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	ANNEX I; ANNEX II
9.3.3 Covariates and other characteristics?	☒	☐	☐	ANNEX I; ANNEX II
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

<u>Section 10: Analysis plan</u>	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.8
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	8.7
10.3 Are descriptive analyses included?	☒	☐	☐	8.8
10.4 Are stratified analyses included?	☒	☐	☐	8.8
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	8.8

Comments:

<u>Section 11: Data management and quality control</u>	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	ANNEX III
11.2 Are methods of quality assurance described?	☒	☐	☐	ANNEX III
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

<u>Section 12: Limitations</u>	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	9

Section 12: Limitations	Yes	No	N/A	Section Number
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	ANNEX II

Comments:

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	ANNEX II
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	ANNEX II
13.3 Have data protection requirements been described?	☒	☐	☐	ANNEX III

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	8.8.4; ANNEX III
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	8.8.4; ANNEX III

Comments:

Name of the main author of the protocol: Ellen Gerritsen

Date: 31/07/2026

Signature:



ANNEX VII. Glossary

Additional definitions are available in the EMA Glossary of terms <https://www.ema.europa.eu/en/about-us/glossaries>.

Aggregated Data

Data collected and combined from multiple sources to generate summary information, typically anonymised.

Benefit-Risk Assessment

Evaluation of the positive therapeutic effects of a medicine compared to its risks (e.g. side effects).

Common Data Model (CDM)

A standardised data structure that enables data from multiple sources to be harmonised, making analysis consistent and reproducible. DARWIN EU® utilises the OMOP CDM maintained by the OHDSI community.

Complex Studies (C3)

Studies requiring the development or customisation of specific study designs, protocols, and Statistical Analysis Plans (SAPs), with extensive collection or extraction of data. Examples include etiological studies measuring the strength and determinants of an association between an exposure and the occurrence of a health outcome in a defined population considering sources of bias, potential confounding factors, and effect modifiers.

Coordination Centre (CC)

The central hub responsible for managing and overseeing the activities within DARWIN EU®. It is based at Erasmus University Medical Center in Rotterdam, the Netherlands.

Data Access

The process of obtaining permission to use specific datasets for regulatory or scientific studies.

Data Quality Framework

A set of standards and procedures to ensure accuracy, completeness, timeliness, and consistency of data used in DARWIN EU®.

Data Source

A data source or repository of structured health-related data, such as electronic health records (EHRs), insurance claims, or registries.

DARWIN EU®

The European Medicines Agency's (EMA) federated network of real-world data sources designed to generate evidence to support regulatory decision-making.

EMA (European Medicines Agency)

The regulatory body responsible for the evaluation and supervision of medicinal products in the EU, overseeing DARWIN EU®.

Evidence Generation

The process of analysing real-world data to produce scientific information that can inform healthcare or regulatory decisions.

Federated Network

A data infrastructure where data remain at their original location but can be analysed in a harmonised way across multiple partners using a common model and tools.

GDPR (General Data Protection Regulation)

The EU regulation governing the protection of personal data and privacy, crucial to how DARWIN EU® handles health data.

Health Technology Assessment (HTA)

A systematic evaluation of properties and impacts of health technology, often using DARWIN EU® data to support assessments.

Metadata

Descriptive information about a data source (e.g. its content, quality, and structure), essential for identifying relevant data sources in DARWIN EU® studies.

Off-the-Shelf Studies (OTS)

Studies for which a standard protocol per study/analysis type and standardised analytics may be developed and applied or adapted, typically relating to a descriptive research question. This includes studies on disease epidemiology, for example, the estimation of the prevalence or incidence of health outcomes in defined time periods and population groups, or drug utilisation studies at the population or patient level.

OHDSI (Observational Health Data Sciences and Informatics)

An open-science collaborative community that develops tools and standards (including the OMOP CDM) to enable large-scale analytics of observational health data. OHDSI provides the technical and scientific foundation for DARWIN EU®'s analytical ecosystem.

Patient-Level Data

Data related to individuals, de-identified, used for longitudinal or detailed analyses.

OMOP (Observational Medical Outcomes Partnership)

A common data model (CDM) that standardises the structure and content of observational healthcare data, enabling systematic analysis across disparate datasets. DARWIN EU® uses the OMOP CDM to ensure interoperability and consistency in real-world evidence generation.

Real-World Data (RWD)

Data relating to individual health status or healthcare delivery that is collected from routine clinical practice rather than from randomised controlled trials.

Real-World Evidence (RWE)

Clinical evidence derived from the analysis of RWD, used to inform decisions by regulators, payers, or clinicians.

Regulatory Decision-Making

The process by which authorities like EMA assess data to authorise, monitor, or modify the use of medicines in the EU.

Routine Repeated Studies (RR)

Studies that are either Off-the-Shelf or Complex studies repeated on a regular basis, following the same protocol and study code, but with updated data and/or different data partners.

Study Protocol

A detailed plan describing how a specific real-world study will be conducted, including objectives, design, data sources, and analyses.

Very Complex Studies (C4)

Studies which cannot rely only on electronic health care data sources, or which would require complex methodological work, for example, due to the occurrence of events that cannot be defined by existing diagnosis codes, including events that do not yet have a diagnosis code, where it may be necessary to combine a diagnosis code with other data such as results of laboratory investigations. These studies might require the collection of data prospectively, or the inclusion of new (not previously onboarded) data sources.