# Study Protocol

# P4-C2-003

# DARWIN EU® - Antipsychotic prescribing in children in Europe: a descriptive analysis of trends and patient characteristics

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21/05/2025

Version 3.0

Public

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| **Study Title** | DARWIN EU® - Antipsychotic prescribing in children in Europe: a descriptive analysis of trends and patient characteristics |
| **Protocol version** | V3.0 |
| **Date** | 21/05/2025 |
| **EU PAS number**[1] | EUPAS1000000592 |
| **Active substance** | **Drug/s of interest**<br>All antipsychotics under the ATC code N05A (overall, and by typical/atypical grouping); and eleven prespecified drug substances: risperidone, aripiprazole, olanzapine, quetiapine, paliperidone, chlorprothixene, clozapine, methotrimeprazine (levomepromazine), pipamperone, sulpiride and promazine. |
| **Medicinal product** | Not applicable |
| **Research question and objectives** | Study Objectives:<br>1. To characterise children with a first prescription of an antipsychotic in each database in terms of age, sex, comorbidities and indication of use.<br>2. To measure trends in the incidence/prevalence of antipsychotic prescribing in children overall, by typical/atypical grouping and separately for 11 drug substances in each database. Results would be stratified by calendar year, age and sex.<br>3. To characterise first use of antipsychotic initiation in children (overall, by typical/atypical use, and by the 11 prespecified drug substances) in terms of dose and duration in each database. Results will be stratified by age and sex. |
| **Countries of study** | Spain, Denmark, Germany, Netherlands, Croatia, Norway |
| **Authors** | M. Pineda-Moncusí |

[1] *This is a routine repeated study from P3-C1-012, with EUPAS1000000330.*

# DOCUMENT HISTORY

| Version | Date | Description |
|---|---|---|
| **V1.0** | 15/04/2025 | **First Draft** |
| **V2.0** | 30/04/2025 | **Inclusion of changes to address EMA comments** |
| **V2.1** | 16/05/2025 | **Editorial changes to upload it into catalogue** |

# LIST OF ABBREVIATIONS

| Acronyms/terms | Description |
|---|---|
| ADHD | Attention-Deficit/Hyperactivity Disorder |
| ATC | Anatomical Therapeutic Chemical classification |
| BPSD | Behavioural and Psychological Symptoms of Dementia |
| BIFAP | Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público |
| CHI | Catalan Health Institute |
| CDM | Common Data Model |
| DA | Disease Analyzer |
| DARWIN EU | Data Analysis and Real-World Interrogation Network |
| DK-DHR | Danish Data Health Registries |
| DUS | Drug Utilization Study |
| EHR | Electronic Health Records |
| EMA | European Medicines Agency |
| GP | General Practitioner |
| ID | Index Date |
| InGef RDB | Institut für angewandte Gesundheitsforschung |
| IPCI | Integrated Primary Care Information Project |
| IQR | Interquartile Range |
| NA | Not applicable |
| NAJS | Croatian National Public Health Information System |
| NLHR | Norwegian Linked Health Registry data |
| OHDSI | Observational Health Data Sciences and Informatics |
| OMOP | Observational Medical Outcomes Partnership |
| SIDIAP | Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària |

# 1. TITLE

DARWIN EU® - Antipsychotic prescribing in children in Europe: a descriptive analysis of trends and patient characteristics

# 2. RESPONSIBLE PARTIES – STUDY TEAM

| Study team role | Names | Organisation |
|---|---|---|
| Principal Investigator | Marta Pineda Moncusí | University of Oxford |
| Data Scientist | Kim López Güell<br>Edward Burn | University of Oxford |
| Epidemiologist | Annika Jodicke | University of Oxford |
| Clinical Domain Expert | Albert Prats Uribe<br>Abigail Robinson<br>James Bezer | University of Oxford |
| Study Manager | Natasha Yefimenko | Erasmus MC |
| **Data Partner*** | **Names** | **Organisation** |
| Coordinator/Data Analyst | Elisa Martin-Merino<br>Emma Redondo-Álvarez,<br>Cristina Justo Astorgano<br>Miguel Angel Macia Martinez<br>Ana Llorente Garcia | BIFAP (Spain) |
| | Claus Møldrup<br>Elvira Bräuner<br>Susanne Bruun | DK-DHR (Denmark) |
| | Raeleesha Norris<br>Annika Vivirito<br>Alexander Harms<br>Josephine Jacob | InGef RDB (Germany) |
| | Katia Verhamme<br>Mees Mosseveld | IPCI (Netherlands) |
| | Maja Silobrčić Radić<br>Anamaria Jurčević<br>Jakov Vuković<br>Ivan Pristaš<br>Antea Jezidžić<br>Marko Čavlina<br>Karlo Pintarić | NAJS (Croatia) |
| | Saeed Hayati<br>Nhung Trinh<br>Hedvig Nordeng | NLHR (Norway) |
| | Elena Roel Herranz<br>Laura Granés González<br>Agustina Giuliodori Picco<br>Irene López Sánchez | SIDIAP (Spain) |

*Data partners' role is only to execute code at their data source, review and approve their results. They do not have an investigator role. Data analysts/programmers do not have an investigator role and thus declaration of interests (DOI) for them is not needed.

# 3. ABSTRACT

**Title**

DARWIN EU® - Antipsychotic prescribing in children in Europe: a descriptive analysis of trends and patient characteristics

**Rationale and background**

Antipsychotic drugs are indicated for the management of schizophrenia and bipolar disorder. They are also used in adults to manage behavioural and psychological symptoms of dementia (BPSD) with the recommendation to be discontinued after BPSD symptoms resolve. Antipsychotic drugs can be classified into typical and atypical antipsychotics with different recommendations for their use. For example, guidelines recommend the preferential use of atypical antipsychotics when required for the management of BPSD.[1, 2]

Safety concerns in adults have previously led to regulatory warnings and risk communications over their use.[3, 4] Antipsychotic drugs have been associated with several adverse drug reactions, particularly in the elderly. Somnolence, hypotension, extrapyramidal side effects and gait abnormalities are well-recognized side effects that may in turn contribute to the risk of falls and fracture in elderly persons.[1] Similarly, cardiovascular adverse effects, falls and injuries may increase mortality.

Antipsychotics are sometimes used in children and adolescents; however, not all antipsychotics have been approved for use in children and adolescents and if prescribed their use would be considered off-label. A prior study reported an increased use of antipsychotics between 2008 and 2017 in the paediatric populations of Catalonia (35.7%), Norway (45.1%) and Sweeden (57.6%).[5] Likewise, in England, the use of antipsychotics in patients between 3 and 18 years doubled between 2000 and 2019.[6]

This study aims to provide an overview of antipsychotic prescribing in the children in databases from Europe, and to describe the characteristics of children initiating antipsychotics. This will provide a benchmark to understand current clinical practice over their use in children and adolescents and help to understand whether off-label use may occur.

**Research question and objectives**

1. To characterise children with a first prescription of an antipsychotic in each database in terms of age, sex, comorbidities and indication of use.
2. To measure trends in the incidence/prevalence of antipsychotic prescribing in children overall, by typical/atypical grouping and separately for 11 drug substances in each database. Results would be stratified by calendar year, age and sex.
3. To characterise first use of antipsychotic initiation in children (overall, by typical/atypical use, and by the 11 prespecified drug substances) in terms of dose and duration in each database. Results will be stratified by age and sex.

**Methods**

Study design

1. A new user cohort study will be used to describe patient-level characterisation of antipsychotic users.
2. A population-level cohort study will be used to assess incidence rates of antipsychotic use.
3. A new user cohort study will be conducted to describe patient-level antipsychotic utilisation.

Population

The study cohort will comprise all paediatric individuals between 1- and 18-years old present in the database during the study period (i.e., 2013-2023).

Additional eligibility criteria for patient-level antipsychotic characterisation and drug utilisation, and for the calculation of incidence rates will be applied, where a minimum follow-up of 365 days of data availability

will be required to exclude individuals with a prior use of the respective drug of interest (i.e., when overall, no prior use of any of the common antipsychotics will be required; when stratified by specific antipsychotic drug, no prior use of the specific antipsychotic will be required).

Variables

Exposure of interest: all antipsychotics under the ATC code N05A (overall, and by typical/atypical grouping); and eleven prespecified drug substances that cover most antipsychotics prescribed in the paediatric population (selected based upon feasibility in the data sources of interest): risperidone, aripiprazole, olanzapine, quetiapine, paliperidone, chlorprothixene, clozapine, methotrimeprazine (levomepromazine), pipamperone, sulpiride and promazine.

Data sources

- BIFAP (Spain, Primary Care Database)
- DK-DHR (Denmark, National Registry)
- InGef RDB (Germany, Claims Database)
- IPCI (Netherlands, Primary Care Database)
- NAJS (Croatia, National Claims Registry) [Only Objectives 1 and 2]
- NLHR (Norway, National Registry)
- SIDIAP (Spain, Primary Care Database)

Statistical analysis

1. Patient-level characterisation study: characterisation of patient-level features for new users of antipsychotics will be calculated overall, by typical/atypical, and by the 11 pre-specified drug substances for each database, including description of age (mean [SD] and median [IQR]), age groups [N,%] and sex [N,%] at index date (date of first prescription of the antipsychotic of interest),comorbidities [N,%] recorded -7 days, -30 days or any time before (index date), and indications of use [N,%] recorded -30 days or any time before (index date).
2. Population-level drug utilisation study: annual incidence and annual period prevalence estimates will be calculated for antipsychotic treatment overall, by typical/atypical and by the 11 pre-specified drug substances for each database.
3. Patient-level drug utilisation study: patient-level characterisation of new antipsychotic users will be conducted at index date (date of first prescription of the antipsychotic of interest) for overall, by typical/atypical and by the 11 pre-specified drug substances for each database, including median [IQR] prescribed or dispensed initial and cumulative dose of antipsychotics, and median [IQR] treatment duration.

For all analyses a minimum cell counts of 5 will be used when reporting results, with any smaller counts will be noted as <5.

# 4. AMENDMENTS AND UPDATES

| Number | Date | Section of study protocol | Amendment or update | Reason |
|---|---|---|---|---|
| Version 1.0 | 15/04/2025 | N/A | Update from initial study protocol (P3-C1-012 study, EUPAS1000000330) | This is a routinely repeated study |

Comparison with previous protocols

This is a routinely repeated study from the P3-C1-012 study. The P3-C1-012 study was registered in the EMA RWD catalogue (https://catalogues.ema.europa.eu/node/4231/administrative-details) with the EU PAS register number EUPAS1000000330. The study code from P3-C1-012 is available in the GitHub repository: https://github.com/darwin-eu-studies/P3-C1-012-Antipsychotics-general-population

The following updates are the changes included in the routinely repeated analysis P4-C2-003 when compared with P3-C1-012:

| Sections | P3-C1-012 study | P4-C2-003 study |
|---|---|---|
| Data Partners | • SIDIAP<br>• IPCI<br>• DK-DHR<br>• IQVIA DA Germany<br>• IQVIA LPD Belgium<br>• NAJS Croatia | • BIFAP<br>• DK-DHR<br>• InGef RDB<br>• IPCI<br>• NAJS<br>• NLHR<br>• SIDIAP |
| Reference study protocol | NA | P3-C1-012 (EUPAS1000000330) |
| Changes from reference study protocol | • Study population: general population<br>• Objectives 1- 4: patient-level characterisation, population-level DUS, patient-level DUS characterisation, and survival analyses.<br>• Exposure: 20 common antipsychotics (obtained from top 5 substance level antipsychotics in each database)<br>• Age groups: <65, 65-74, 75-84, ≥85 years.<br>• Comorbidities: chronic kidney disease, heart failure, hypertension, myocardial infarction, stroke, type 2 diabetes, obesity<br>• Indications: dementia, schizophrenia, bipolar disorder, depression and insomnia. | • Study population: paediatric population (1-18 years)<br>• Objectives 1-3 (excluding 4, survival analyses)<br>• Exposure: all antipsychotics under the ATC code N05A. For specific ingredient strata, we will analyse a prespecified list of 11 antipsychotics.<br>• Age groups: 1-5, 6-11 and 12-18 years.<br>• Relevant comorbidities for pediatric population: type 2 diabetes, obesity, hypercholesterolemia and hyperlipidaemia.<br>• Indications: schizophrenia, bipolar disorder, autism, ADHD, anxiety, depression, sleep disturbance and any of above. Additionally, the frequency of records of “other” conditions (any condition not included in the specific list above) will be estimated. |

| | | |
|---|---|---|
| | • Objective 1: patient-level characterisation.<br><br>• Objective 2: Incidence of antipsychotics use.<br>• Objective 3: results will be stratified by drug route, age and sex. | • Objective 1: additional study period stratification with two-time windows (2013-2017 and 2018-2023) will be run only in the overall antipsychotics, and typical/atypical cohorts.<br>• Objective 2: Incidence and prevalence of antipsychotics use.<br>• Objective 3: patient-level characterisation for the 11 substances will be stratified by age and sex. |

ADHD = Attention-Deficit/Hyperactivity Disorder, ATC = Anatomical Therapeutic Chemical, DUS = Drug Utilisation Study.

# 5. MILESTONES

| Study deliverables | Timelines |
|---|---|
| Final Study Protocol | April 2024 |
| Creation of Analytical code | May 2024 |
| Execution of Analytical Code on the data | Early June 2025 |
| Draft Study Report | June/July 2025 |
| Final Study Report | July 2025 |

# 6. RATIONALE AND BACKGROUND

Antipsychotic drugs are indicated for the management of schizophrenia and bipolar disorder. They are also used in adults to manage behavioural and psychological symptoms of dementia (BPSD) with the recommendation to be discontinued after BPSD symptoms resolve. Antipsychotic drugs can be classified into typical and atypical antipsychotics with different recommendations for their use. For example, guidelines recommend the preferential use of atypical antipsychotic in adults when required for the management of BPSD.[1, 2]

Safety concerns have previously led to regulatory warnings and risk communications over their use.[3, 4] Antipsychotic drugs have been associated with several adverse drug reactions, particularly in the elderly. Somnolence, hypotension, extrapyramidal side effects and gait abnormalities are well-recognized side effects that may in turn contribute to the risk of falls and fracture in elderly persons.[1] Similarly, cardiovascular adverse effects, falls and injuries may increase mortality.

Antipsychotics are sometimes used in children and adolescents; however, not all antipsychotics have been approved for use in children and adolescents and if prescribed their use would be considered off-label. A prior study reported an increased use of antipsychotics between 2008 and 2017 in the paediatric populations of Catalonia (35.7%), Norway (45.1%) and Sweeden (57.6%).[5] Likewise, in England, the use of antipsychotics in patients between 3 and 18 years doubled between 2000 and 2019.[6]

This study aims to provide an overview of antipsychotic prescribing in children from databases in Europe, and to describe the characteristics of children initiating antipsychotics. This will provide a benchmark to understand current clinical practice over their use in children and adolescents and help to understand whether off-label use may occur.

# 7. RESEARCH QUESTION AND OBJECTIVES

Description of the proposed objectives to be achieved in the study (**Table 1**).

**Table 1.** Research questions and objectives.

**A. Objective 1.**

| | |
|---|---|
| **Objective:** | To characterise children with a first prescription of an antipsychotic in each database in terms of age, sex, comorbidities and indication of use. |
| **Hypothesis:** | Not applicable |
| **Population:** | Paediatric population (1-18 years); new users of antipsychotics in the period between 1/1/2013 and 31/12/2023 with at least 1 year of data availability, and no prior use of the respective antipsychotic drug/s, will be included. |
| **Exposure:** | All antipsychotics under the ATC code N05A (overall, and by typical/atypical grouping);<br>Eleven prespecified drug substances: risperidone, aripiprazole, olanzapine, quetiapine, paliperidone, chlorprothixene, clozapine, methotrimeprazine (levomepromazine), pipamperone, sulpiride and promazine. |
| **Comparator:** | None |
| **Outcome:** | None |

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|---|---|
| **Time:** | Study period: 2013 – 2023 (or, within this period, from the first to last drug record date available in the database)<br><br>Follow-up will start on the date of incident antipsychotic prescription and/or dispensation (index date). End of follow-up will be defined as the earliest of loss to follow-up, end of data availability or death, or end of study period (31st December 2023). |
| **Setting:** | Seven data sources with a population-level coverage (national/regional): BIFAP [Spain], DK-DHR [Denmark], InGef RDB [Germany], IPCI [Netherlands], NAJS [Croatia], NLHR [Norway], SIDIAP [Spain]. |
| **Main measure of effect:** | We will describe demographic characteristics including age, sex, comorbidities recorded in the last month or any time before index date, and indications of use in the week, month or any time before index date. |

**B. Objective 2.**

| | |
|---|---|
| **Objective:** | To measure trends in the incidence/prevalence of antipsychotic prescribing in children overall, by typical/atypical grouping and separately for 11 drug substances in each database. Results would be stratified by calendar year, age and sex. |
| **Hypothesis:** | Not applicable |
| **Population *(mention key inclusion-exclusion criteria):*** | Paediatric patients (1-18 years) using antipsychotics in the period between 1/1/2013 and 31/12/2023.<br><br>Additional eligibility criteria of at least 1 year of data availability and no prior use of the respective antipsychotic drug/s will be included for incidence rate calculations. |
| **Exposure:** | All antipsychotics under the ATC code N05A (overall, and by typical/atypical grouping);<br><br>Eleven prespecified drug substances: risperidone, aripiprazole, olanzapine, quetiapine, paliperidone, chlorprothixene, clozapine, methotrimeprazine (levomepromazine), pipamperone, sulpiride and promazine. |
| **Comparator:** | None |
| **Outcome:** | None |
| **Time *(when follow up begins and ends):*** | Study period: 2013 – 2023 (or, within this period, from the first to last drug record date available in the database).<br><br>Follow-up will start on a pre-specified calendar time point, namely 1st of January for each calendar year between 2013-2023, for the calculation of annual incidence rates and annual period prevalence. End of follow-up will be defined as the earliest of loss |

| | |
|---|---|
| | to follow-up, end of data availability, death, or end of study period (e.g. 31st December 2023). |
| **Setting:** | Seven data sources with a population-level coverage (national/regional): BIFAP [Spain], DK-DHR [Denmark], InGef RDB [Germany], IPCI [Netherlands], NAJS [Croatia], NLHR [Norway], SIDIAP [Spain]. |
| **Main measure of effect:** | Incidence and prevalence of antipsychotic drug use |

**C. Objective 3.**

| | |
|---|---|
| **Objective:** | To characterise first use of antipsychotic initiation in children (overall, by typical/atypical use, and by the 11 prespecified drug substances) in terms of dose and duration in each database. Results will be stratified by age and sex. |
| **Hypothesis:** | Not applicable |
| **Population *(mention key inclusion-exclusion criteria):*** | New users of antipsychotic medications in the paediatric population (1-18 years) between 1/1/2013 and 31/12/2023 with 1 year of prior data availability and no prior use of the respective antipsychotic drug/s. |
| **Exposure:** | All antipsychotics under the ATC code N05A: overall, and by typical/atypical grouping.<br><br>Eleven prespecified drug substances: risperidone, aripiprazole, olanzapine, quetiapine, paliperidone, chlorprothixene, clozapine, methotrimeprazine (levomepromazine), pipamperone, sulpiride and promazine. |
| **Comparator:** | None |
| **Outcome:** | None |
| **Time *(when follow up begins and ends):*** | Study period: 2013 – 2023 (or, within this period, from the first to last drug record date available in the database)<br><br>Follow-up will start on the date of incident antipsychotic prescription and/or dispensation (index date). End of follow-up will be defined as the earliest of loss to follow-up, end of data availability or death, or end of study period (31st December 2023). |
| **Setting:** | Seven data sources with a population-level coverage (national/regional): BIFAP [Spain], DK-DHR [Denmark], InGef RDB [Germany], IPCI [Netherlands], NLHR [Norway], SIDIAP [Spain]. |
| **Main measure of effect:** | Duration of antipsychotic use (first treatment era) expressed as median [IQR]<br><br>Antipsychotics dose (cumulative and initial) expressed as median [IQR] |

# 8. RESEARCH METHODS

## 8.1 Study type and study design

Retrospective cohort studies will be conducted using routinely collected health data from 7 databases. **Table 2** describes the study types and related study designs. The study will comprise of three consecutive parts:

1. A new user cohort study will be used to describe patient-level characterisation of antipsychotic users.

2. A population-level cohort study will be used to assess incidence rates of antipsychotic use.

3. A new user cohort study will be conducted to describe patient-level antipsychotic utilisation.

**Table 2.** Description of potential study types and related study designs.

| Study type | Study design | Study classification |
|---|---|---|
| Patient-level characterisation | Cohort analysis | Off the shelf |
| Population-level DUS | Population Level Cohort | Off the shelf |
| Patient-level DUS | New drug/s user cohort | Off the shelf |

## 8.2 Study setting and data sources

This study will be conducted using routinely collected data from 7 databases from 6 European countries. All databases were previously mapped to the OMOP CDM.

1. BIFAP (Spain, Primary Care Database)
2. DK-DHR (Denmark, National Registry)
3. InGef RDB (Germany, Claims Database)
4. IPCI (Netherlands, Primary Care Database)
5. NAJS (Croatia, National Claims Registry) [Only Objectives 1 and 2]
6. NLHR (Norway, National Registry)
7. SIDIAP (Spain, Primary Care Database

Based on the available data, all data sources will contribute to all objectives except for NAJS. NJAS does not have drug utilisation details such as duration and amount/dose/strength reliably recorded and therefore will not contribute to Objective 3.

We expect *first* prescriptions to be predominantly issued by paediatricians or neurologists in a specialised (inpatient/outpatient) setting, whereas the continuation of treatment is expected to likely happen in primary care. We therefore shortlisted the following databases that have a population-level coverage (national/regional) and cover and outpatient specialist/primary care setting, covering 7 countries across Europe. DK-DHR, NAJS, NLHR and SMPA-GU are national registries that contain records on both, in-patient hospital visits as well as outpatient and primary care visits. InGef RBD contains claims from outpatient and hospital care, whilst IPCI and SIDIAP are primary care databases. Additionally, BIFAP is a primary care database with linkage to hospital records, however, we will not consider the hospital linkage for this study.

Out of the 8 shortlisted databases, 7 accepted the invitation to participate in this study.

Information on data source(s) planned to be used with a justification for their choice in terms of ability to capture the relevant data is described in **Table 3.**

**Table 3.** Description of the selected data sources.

| Country | Name of Database | Justification for Inclusion | Health Care setting | Type of Data | Number of active subjects | Data lock for the last update |
|---|---|---|---|---|---|---|
| Spain | BIFAP | Database covers primary care setting where antipsychotics prescriptions are issued. | Primary Care | EHR | 16.9 million | 12/2023 |
| Denmark | DK-DHR | Database covers primary and hospital in-patient care settings where antipsychotics prescriptions are issued. | Primary Care and Hospital in-patient care | EHR, National registry | 5.98 million | 11/2024 |
| Germany | InGef RDB | Database covers primary and secondary care setting where antipsychotics prescriptions are issued. | Primary and Hospital Care | EHR, Claims data | 7.66 million | 09/2024 |
| Netherlands | IPCI | Database covers primary care setting where antipsychotics prescriptions are issued. | Primary Care | EHR | 2.9 million | 06/2024 |
| Croatia | NAJS | Database covers primary and hospital in-patient care settings where antipsychotics prescriptions are issued. | Primary, Secondary Care and Hospital in-patient care | EHR, National Registry | 3 million | 06/2024 |
| Norway | NLHR | Database covers primary care setting and prescription fills in outpatient specialists where antipsychotics prescriptions are issued. | Primary, Secondary Care and outpatient specialists' diagnosis. All non-hospital medications dispensed. | EHR, National Registry | 6.1 million | 12/2023 |
| Spain | SIDIAP | Database covers primary care setting where antipsychotics prescriptions are issued. | Primary Care | EHR | 5.8 million | 06/2023 |

BIFAP = Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público, DK-DHR = Danish Data Health Registries, InGef RDB = Institut für angewandte Gesundheitsforschung, IPCI = Integrated Primary Care Information, NJAS = Croatian National Public Health Information System, NLHR = Norwegian Linked Health Registry data, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària.

1) Base de Datos para la Investigación Farmacoepidemiológica en el Ámbito Público [BIFAP, Pharmacoepidemiological Research Database for Public Health Systems] (Spain, Primary Care Database)

BIFAP (http://www.bifap.org/index_EN.html) is a longitudinal population-based data source of medical patient records of the Spanish National Health Service (SNS) from 9 participating Regions throughout Spain out of the 17 Spanish Regions. Population currently included represents 36% of the total Spanish population. Spain has a SNS that provides universal access to health services through the Regional Healthcare Services. Primary care physicians (PCPs), both general practitioners and paediatricians, have a central role. They act as gatekeepers of the system and also exchange information with other levels of care to ensure the continuity of care. Most (98.9%) of the population is registered with a PCP and, in addition, most drug prescriptions are written at the primary care level. BIFAP includes a collection of databases linked at individual patient level. The main one is the Primary care Database given the central role of PCPs in the SNS. Linked, there are additional important structural databases like the medicines dispensed at community pharmacies and the patients' hospital diagnosis at discharge. 7 out of the 9 regions have linkage to hospital data. However, hospital data is available for different time periods for each region. From 2014 onwards, linkage to hospital data is available for >68% of patients Linkage to SARS-CoV-2 diagnostics test and COVID-19 vaccination registries are also included. Additional databases are also linked for a subset of patients (hospital pharmacy, cause of death registry). BIFAP program is a non-profit program financed by the Spanish Agency of Medicines and Medical Devices (AEMPS), a government agency belonging to the Ministry of Health in collaboration with the regional health authorities. The main use of BIFAP is for research purposes in order to evaluate the adverse and beneficial effects of drugs and drug utilization patterns in the general population under real conditions of use.

2) Danish Data Health Registries [DK-DHR] (Denmark, National Registry)

Danish health data is collected, stored and managed in national health registers at the Danish Health Data Authority and covers the entire population which makes it possible to study the development of diseases and their treatment over time. There are no gaps in terms of gender, age and geography in Danish health data due to mandatory reporting on all patients from cradle to grave, in all hospitals and medical clinics. Personal identification numbers enable linking of data across registers, so we have data on all Danes throughout their lives, regardless of whether they have moved around the country. High data quality due to standardisation, digitisation and documentation means that Danish health data is not based on interpretation. The Danish Health Data Authority is responsible for the national health registers and for maintaining and developing standards and classifications in the Danish healthcare system. Legislation ensures balance between personal data protection and use.

In the present database, we have access to the following registries for the entire Danish population of 5.9 million persons from 1.1.1995: The central Person Registry, The National Patient Registry, The Register of Pharmaceutical Sales, The National Cancer Register, The Cause of Death registry, The Clinical Laboratory Information Register, COVID-19 test and vaccination Registries, The complete Vaccination registry. All data registered from 1.1.1995 will be included.

3) Institut für angewandte Gesundheitsforschung Research Database [InGef RDB] (Germany, Primary and Secondary Care Database)

The InGef RDB database comprises anonymized longitudinal claims data of about 10 million individuals across more than 70 statutory health insurance providers (SHIs) throughout Germany. Data are longitudinally linked over a period of currently ten years. Patients can be traced across health care sectors. All patient-level and provider-level data in the InGef RDB research database are anonymised to comply with German data protection regulations and German federal law. German SHI claims data available in the InGef RDB database includes information on demographics (year of birth, gender, death date if applicable, region of residence on administrative district level); hospitalizations; outpatient services (diagnoses, treatments; specialities of physicians); dispensing of drugs; dispensing of remedies and aids; and sick leave and sickness

allowance times. In addition, costs or cost estimates from SHI perspective are available for all important cost elements. All diagnoses in Germany are coded using the International Classification of Diseases, version 10 in the German Modification (ICD-10-GM). Outpatient and primary care diagnoses are recorded only by quarter of the year, with no actual diagnosis date being recorded. The persistence (membership over time) is rather high in the InGef RDB database: During a time period of 5 years (2009 to 2013), 70.6% of insurance members survived and remained insured with the same SHI without any gap in their observational time. Persons leaving one of the participating SHIs and entering another participating SHI, can be linked during yearly database consistency updates and are thus not lost over time. The InGef RDB database is dynamic in nature, i.e. claims data are updated in an ongoing process and new SHIs may join or leave the database. By law, only the last 10 years of data are allowed to be used. At every new release this window shifts, dropping older data and adding new data. Additionally, drug data in InGef RDB captures dispensation of medicines, with the records of the specific date of dispensation driven from the claims data based dispensing record. All drugs that are reimbursed by the German statutory health insurance are captured within the data. However, a minority of prescription records from outpatient procedure codes (OPS-code) that represents procedures were a drug was administered, and which have been mapped to the observation table instead of the drug table, do not have a specific date associated and therefore will not be included in this study. Additionally, over-the-counter medication cannot be found in the database.

4) Integrated Primary Care Information [IPCI] (Netherlands, Primary Care Database)

The Integrated Primary Care Information (IPCI) database is a longitudinal observational database containing routinely collected data from computer-based patient records of a selected group of GPs throughout the Netherlands (N=723). IPCI was started in 1992 by the department of Medical Informatics of the Erasmus University Medical Center in Rotterdam with the objective to enable better post marketing surveillance of drugs. The current database includes patient records from 2006 on, when the size of the database started to increase significantly. In 2016, IPCI was certified as Regional Data Center. Since 2019 the data is also standardized to the Observational Medical Outcomes Partnership common data model (OMOP CDM), enabling collaborative research in a large network of databases within the Observational Health Data Sciences and Informatics (OHDSI) community. The primary goal of IPCI is to enable medical research. In addition, reports are generated to inform GPs and their organizations about the provided care. Contributing GPs are encouraged to use this information for their internal quality evaluation. The IPCI database is registered on the European Medicines Agency (EMA) ENCePP resources database (http://www.encepp.eu).

5) Croatian National Public Health Information System [NAJS] (Croatia, National Registry)

The National Public Health Information System (Nacionalni javnozdravstveni informacijski sustav - NAJS) is an organised system of information services by Croatian Institute of Public Health. NAJS enables data collecting, processing, recording, managing and storing of health-related data from health care providers as well as production and management of health information. NAJS contains medical and public health data collected and stored in health registries and other health data collections including cancer registry, mortality, work injuries, occupational diseases, communicable and non-communicable diseases, health events, disabilities, psychosis and suicide, diabetes, drug abuse and others.

6) Norwegian Linked Health Registry data [NLHR] (Norway, National Registry)

Norway has a universal public health care system consisting of primary and specialist health care services covering a population of approximately 5.4 million inhabitants. Many population-based health registries were established in the 1960s with use of unique personal identifiers facilitating linkage between registries. Data in these health registries are used for health analysis, health statistics, improving the quality of healthcare, research, administration and emergency preparedness. NLHR harmonized data from the following registries: the Medical Birth Registry of Norway (MBRN), the Norwegian Prescription Registry (NorPD), the Norwegian Patient Registry (NPR), Norway Control and Payment of Health Reimbursement

(KUHR), the Norwegian Surveillance System for Communicable Diseases (MSIS), the Norwegian Immunisation Registry (SYSVAK), the National Death Registry, and the National Registry (NR). Linkage between the registries was facilitated using project-specific person ID generated from unique personal identification assigned at birth or immigration for all legal residents in Norway.

This study will use linked data from Norwegian health registries to describe antipsychotic prescribing patterns in children. The Norwegian Patient Registry (NPR) provides diagnostic information from specialist and hospital care, while KUHR contains diagnoses and consultation records from primary care, including general practitioners and outpatient specialists. The Norwegian Prescription Database (NorPD) captures all medications dispensed in community pharmacies. Together, these registries enable a comprehensive assessment of antipsychotic initiation and the characteristics of children receiving these medications.

7) Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària [SIDIAP] (Spain, Primary Care Database)

The Information System for Research in Primary Care (SIDIAP) is a clinical database of anonymised patient records in Catalonia, Spain. The Spanish public healthcare system covers more than 98% of the population, and more than two thirds of the Catalan population see their GP at least once a year. The computerisation of the primary care patient records of the Catalan Health Institute (CHI) was complete in 2005. SIDIAP was designed to provide a valid and reliable database of information from clinical records of patients registered in primary care centres for use in biomedical research. SIDIAP contains data of anonymized patients' healthcare records for nearly six million people (approximately 80% of the Catalan population) registered in 287 primary care practices throughout Catalonia since 2005. It includes data collected by health professionals during routine visits in primary care, including anthropometric measurements, clinical diagnoses (International Classification of Diseases 10th revision ICD-10), laboratory tests, prescribed and dispensed drugs, hospital referrals, demographic and lifestyle information. It was previously shown that SIDIAP population is highly representative of the entire Catalan region in terms of geographic, age, and sex distributions. The high quality of these data has been previously documented, and SIDIAP has been successfully applied to epidemiological studies of key exposures and outcomes. Quality checks to identify duplicate patient IDs are performed centrally at each SIDIAP database update. Checks for logical values and data harmonisation are performed. For biochemistry data, consistency for measurements taken in different laboratories is assessed, and unit conversion is undertaken when needed.

## 8.3 Study period

The study period will be from the 1st of January 2013 until the earliest of either 31st December 2023, or, within this period, from the first to last drug record date available in the respective databases. In the NLHR, study period will start in 2018 (see 11. LIMITATIONS section for further details). For the population-level analyses for incidence, individuals will contribute person-time from the date they have reached at least 365 days of data availability.

## 8.4 Follow-up

The operational definition of follow-up is reported in **Age stratification** in incidence and prevalence

**Table 4.**

For patient-level antipsychotic characterisation and drug utilisation, follow up will start with first prescription of the antipsychotic of interest, and patients will be followed until loss to follow up, lack of data availability, death or end of study period, whichever comes first. In the age stratification, patients will start and stop contributing, switching age groups, dynamically. To estimate the incidence and prevalence estimates, we require the appropriate population and their contributed observation time to first be identified:

For incidence rates, follow-up will start from the date they have reached at least 365 days of data availability. Study participants in the denominator population will begin contributing person time on the respective date of the latest of the following: 1) study start date, 2) date at which the observation period starts, 3) date at which the observation period has reached sufficient prior history, 4) date when age criteria is satisfied in the age stratification. Participants will stop contributing person time at the earliest date of the following: 1) date when age criteria is not satisfied in the age stratification, 2) end of available data in each of the data sources or 3) date at which the observation period of the specific person ends.

An example of entry and exit into the denominator population for incidence rates is shown in **Figure 1**. In this example, person ID 1, and 3 are included as denominators after the study start date as all are being observed in the database from a prior date. Person ID 2 and 4 enter the study after the study start date, when they have reached sufficient prior history of 365 days. Person ID 1, 2 and 4 will be followed until the study end date (end of available data in each of the data sources) whilst Person ID 3 leaves when exiting the database (the end of observation period). Lastly, person ID 5 has two observation periods in the database. The first period contributes time from study start until end of observation period, the second starts contributing time again on the date of their second observation period start and exits at study end date.

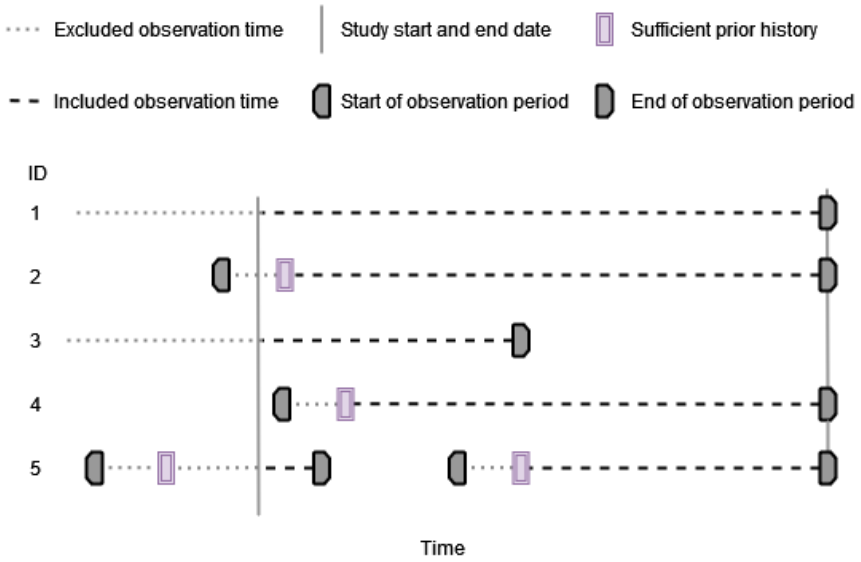



**Figure 1**. Included observation time for denominator population of incidence calculations.

For prevalence estimates, study participants in the denominator population will begin contributing to the denominator on the respective date of the latest of the following: 1) study start date, 2) date at which the observation period starts, 3) date when age criteria is satisfied in the age stratification. Participants will stop contributing person time at the earliest date of the following: 1) date when age criteria is not satisfied in the age stratification, 2) end of available data in each of the data sources or 3) date at which the observation period of the specific person ends.

An example of entry and exit into the denominator population is shown in **Figure 2.** In this example, person ID 1 and 3 are included as denominators at the study start date as both are being observed in the database from a prior date. Person ID 2 enters the study at the date of starting their period of observation, which was later than the study start date. Person ID 1 and 2 will be followed until the study end date (end of available data in each of the data sources) whilst Person ID 3 leaves when exiting the database (the end of observation period). Lastly, person ID 4 has two observation periods in the database. The first period contributes time from study start until end of observation period, the second starts contributing time again on the date of their second observation period start and exits at study end date.

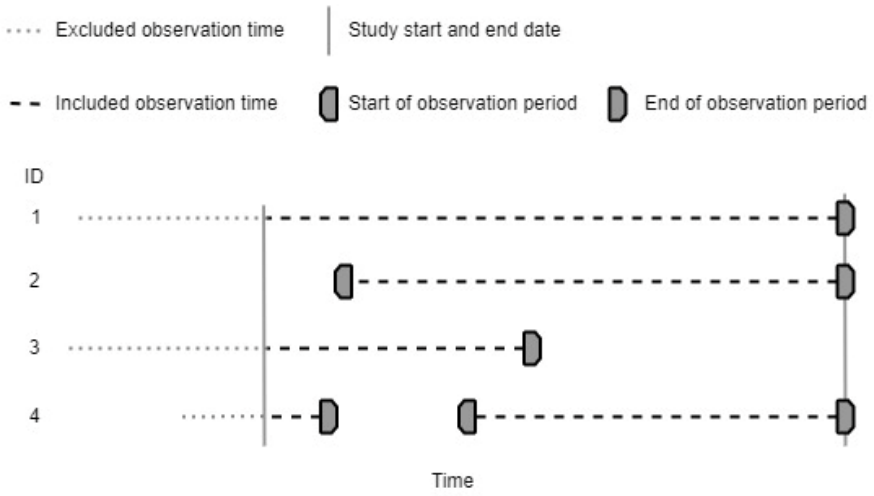



**Figure 2**. Included observation time for the denominator population in prevalence rates.

Age stratification in incidence and prevalence

**Table 4.** Operational definition of time 0 (index date) and other primary time anchors.

| Study population name(s) | Time Anchor Description (e.g. time 0) | Number of entries | Type of entry | Washout window | Care Setting | Code Type | Diagnosis position | Incident with respect to… | Measurement characteristics/ validation | Source of algorithm |
|---|---|---|---|---|---|---|---|---|---|---|
| All paediatric patients with incident use of medicines of interest | Paediatric patient present in the database during the study period (2013-2023) and with at least 365 days of valid database history. | Multiple | Incident | [-Inf, -1] | PC, OP, SC | n/a | n/a | Specific medicine of interest | n/a | n/a |
| All paediatric patients with prevalent use of medicines of interest | Paediatric patient present in the database during the study period (2013-2023) | Multiple | Prevalent | None | PC, OP, SC | n/a | n/a | n/a | n/a | n/a |

OP = outpatient, PC = Primary Care, SC = Secondary Care, n/a = not applicable.

## 8.5 Study population with inclusion and exclusion criteria

**Population included in objectives 1 to 3:**

The study cohort will comprise all paediatric individuals between 1- and 18-years old present in the database during the study period (i.e., 2013-2023).

Additional eligibility criteria for patient-level antipsychotic characterisation and drug utilisation, and for the calculation of incidence rates will be applied, where a minimum follow-up of 365 days of data availability will be required to exclude individuals with a prior use of the respective drug of interest:

- When overall, no prior use of any of the common antipsychotics will be required. In other words, users with prior use of any of the antipsychotics of interest will be excluded from the analysis.
- When stratified by specific antipsychotic drug, no prior use of the specific antipsychotic will be required. In other words, users with prior use of the same antipsychotic will be excluded from the analysis.

The operational definitions of the inclusion criteria are presented in **Table 5**.

**Table 5.** Operational definitions of inclusion criteria.

| Criterion | Details | Order of application | Assessment window | Care Settings[1] | Code Type | Diagnosis position[2] | Applied to study populations: | Measurement characteristics/ validation | Source for algorithm |
|---|---|---|---|---|---|---|---|---|---|
| All paediatric individuals between 1- and 18-years on the 1st of January of each year in the period (i.e., between 2013 and 2023) | See under inclusion criterion | After | N/A | PC, OP, SC | N/A | N/A | All paediatric individuals between 1- and 18-years within selected databases | N/A | N/A |
| Prior database history of 365 days | Study participants will be required to have a year of prior history observed before contributing observation time in incidence calculations, and for characterisation of new users | After | [-365, -1] | PC, OP, SC | N/A | N/A | New users of the drugs of interest | N/A | N/A |
| Washout period | New users will be required to not have used antipsychotics/the specific antipsychotic before | After | [-Inf, -1] | PC, OP, SC | N/A | N/A | New users of the drugs of interest | N/A | N/A |

[1] OP = outpatient, PC = Primary Care, SC = Secondary Care

[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

n/a = not applicable

## 8.6 Variables

### 8.6.1 Exposure/s

The exposure of interest for this study is all antipsychotics under the ATC code N05A (full ingredient list is included in **Appendix I**). For specific ingredient strata, we will analyse a prespecified list of 11 antipsychotics described in **Table 6**. These 11 drug substances were selected based on a feasibility assessment in the databases of the study, and cover the majority of antipsychotic prescriptions in the paediatric population.

Substances will be included at ingredient level including combinations of the respective ingredient.

Details of exposure are described in **Table 7**.

The exposure will be grouped by:

1) Overall use of antipsychotics*
2) Typical/atypical antipsychotics*
3) Prespecified list of 11 antipsychotics

* Lithium is classified and used as an antipsychotic, but it does not pertain to any of the typical/atypical groups. Therefore, it will be added in the overall antipsychotic use but not in the stratification.

The report will focus on reporting overall, typical and atypical use for objectives 1 (summary characterisation of new users) and 3 (drug utilisation studies). For objective 2 (incidence and prevalence estimates), the report will include the plots for the overall, typical and atypical use, and the prespecified list of 11 antipsychotics. All other analyses will be presented in the interactive web application ("Shiny App") which will accompany the report.

**Table 6.** List of 11 antipsychotics included in the study and their categorisation and use in database.

| Substance Name | Typical/Atypical |
|---|---|
| Risperidone | Atypical |
| Aripiprazole | Atypical |
| Olanzapine | Atypical |
| Quetiapine | Atypical |
| Paliperidone | Atypical |
| Chlorprothixene | Typical |
| Clozapine | Atypical |
| Methotrimeprazine (levomepromazine) | Typical |
| Pipamperone | Typical |
| Sulpiride | Atypical |
| Promazine | Typical |

**Table 7.** Operational definitions of exposure.

| Exposure group name(s) | Details | Wash out window | Assessment Window | Care Setting[1] | Code Type | Diagnosis position | Applied to study populations | Incident with respect to… | Measurement characteristics/ validation | Source of algorithm |
|---|---|---|---|---|---|---|---|---|---|---|
| Antipsychotics | Incident use.<br><br>Preliminary code lists provided in **Appendix I** | [-Inf, -1] | Calendar Year | PC, OP, SC | Rx Norm | NA | All paediatric individuals who have had a prescription of the medicine of interest present in the respective databases during the study period (2013-2023) | Previous antipsychotic use | NA | NA |
| Antipsychotics | Prevalent use.<br><br>Preliminary code lists provided in **Appendix I** | NA | Calendar Year | PC, OP, SC | Rx Norm | NA | All paediatric individuals who have had a prescription of the medicine of interest present in the respective databases during the study period (2013-2023) | NA | NA | NA |

[1] OP = outpatient, PC = Primary Care, SC = Secondary Care. N/A = not applicable

### 8.6.2 Outcome/s

None.

### 8.6.3 Other covariates, including confounders, effect modifiers and other variables

The exposure will be reported overall, grouped by typical/atypical use of antipsychotics, and by the prespecified list of 11 antipsychotics. Additionally, each objective will include the following covariates:

#### *8.6.3.1 Objective 1:*

Description of demographic characteristics (among new users, and by typical/atypical antipsychotics) will include:

- Age (numeric and frequency by age groups: 1-5, 6-11, 12-18 years old)
- Sex (male/female)
- Indication of use: proportion of new users with record of schizophrenia, bipolar disorder, autism, attention-deficit/hyperactivity disorder [ADHD], anxiety, depression, sleep disturbance and any of above (summarised as 'indication for antipsychotic use'). Additionally, "other" conditions (any condition not included in the specific indications mentioned before), and an extra category for no indication (i.e., no other condition/indication recorded in the prespecified window) will be reported.
- Comorbidities: type 2 diabetes, obesity, hypercholesterolemia and hyperlipidaemia in the prespecified window.
- Calendar strata: an additional stratification to the overall study period (i.e., 2013-2023) will be run only in the overall antipsychotics, and typical/atypical cohorts. The stratification will use the following time windows: 2013-2017 and 2018-2023.

#### *8.6.3.2 Objective 2:*

Incidence rates and prevalence estimates will be stratified by calendar year. Additionally, they will be stratified by:

- Age groups: 1-5, 6-11, 12-18 years old
- Sex (male/female)

#### *8.6.3.3 Objective 3:*

Drug utilisation analysis from new users of antipsychotics will include:

- Initial and cumulative dose
- Duration of use of first continuous treatment era (gap of ≤30 days between repeated prescriptions)

These will be stratified by:

- Age groups: 1-5, 6-11, 12-18 years old
- Sex (male/female)

## 8.7 Study size

No sample size has been calculated. Incidence and prevalence of use of antipsychotics among the study population will be estimated as part of Objective 2.

## 8.8 Analysis

This section will describe the details of the analysis approach and rationale for the choice of analysis, with reference to the D1.3.8.1 Draft Catalogue of Data Analysis which describes the type of analysis in function of the study type. Description of type of analysis based on study type is provided in **Table 8**.

**Table 8**. Description of study types and types of analysis.

| Study type | Study classification | Type of analysis |
|---|---|---|
| Patient-level characterisation | Off-the-shelf | - Characterisation of patient-level features for new users of antipsychotics (age and sex description)<br>- Frequency and % of comorbidities and indications of use |
| Population Level DUS | Off-the-shelf | - Population-based incidence rates and prevalence estimates |
| Patient Level DUS | Off-the-shelf | - Estimation of median [IQR] prescribed or dispensed initial and cumulative dose of antipsychotics<br>- Estimation of median [IQR] treatment duration for new users of antipsychotics |

### 8.8.1 Federated network analyses

Analyses will be conducted separately for each database. Before study initiation, test runs of the analytics are performed on a subset of the data sources or on a simulated set of patients and quality control checks are performed. Once all the tests are passed, the final package is released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally execute the analytics against the OMOP-CDM in R Studio and review and approve the by default aggregated results before returning them to the Coordination Centre. Sometimes multiple execution iterations are performed, and additional fine tuning of the code base is needed. A service desk will be available during the study execution for support.

The study results of all data sources are checked after which they are made available to the team in the Digital Research Environment and the Dissemination Phase can start. All results are locked and timestamped for reproducibility and transparency.

### 8.8.3 Patient privacy protection

Cell suppression will be applied as required by databases to protect people's privacy. Cell counts <5 will be masked.

### 8.8.4 Statistical model specification and assumptions of the analytical approach considered

R-packages

We will use the R package "CohortCharacteristics" for the patient-level characterisation, "DrugUtilisation" for the patient-level drug utilisation analyses, and "IncidencePrevalence" package for the population-level estimation of drug utilisation.

Drug exposure calculations

Drug eras will be defined as follows: Exposure starts at date of the first prescription, e.g. the index date the person entered the cohort. For each prescription, the estimated duration of use is retrieved from the drug exposure table in the CDM. Subsequent prescriptions will be combined into continuous exposed episodes (drug eras) using the following specifications. Two drug eras will be merged into one continuous drug era if the distance in days between end of the first era and start of the second era is ≤ 30 days. The time between the two joined eras will be considered as exposed by the first era as show in in **Figure 3.**

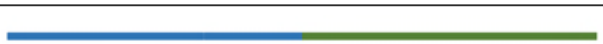
| *Gap era joint mode* | Schematics | Dose in between | Cumulative dose | Cumulative time |
|---|---|---|---|---|
| "first" |  | $d_1$ | $d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$ | $x_1 + x_{12} + x_2$ |
| "second" |  | $d_2$ | $d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$ | $x_1 + x_{12} + x_2$ |
| "zero" |  | 0 | $d_1 \cdot x_1 + d_2 \cdot x_2$ | $x_1 + x_{12} + x_2$ |
| "join" |  | NA | $d_1 \cdot x_1 + d_2 \cdot x_2$ | $x_1 + x_2$ |



**Figure 3.** Gap era joint mode.

If two eras overlap, the overlap time will be considered exposed by the first era (**Figure 4**). No time will be added at the end of the combined drug era to account for the overlap.

| *Overlap mode* | Schematics | Dose overlap |
|---|---|---|
| "first" | | $d_1$ |
| "second" | | $d_2$ |
| "both" | | $d_1 + d_2$ |
| "maximum" | | $\max(d_1, d_2)$ |

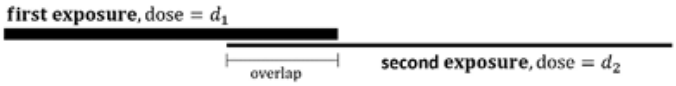



**Figure 4.** Gap era overlap mode.

New user cohorts

New users will be selected based on their first prescription of the respective drug of interest after the start of the study and/or in a pre-defined time window. For each patient, at least 365 days of data visibility will be required prior to that prescription. New users will be required to not have been exposed to the drug of interest any time prior the current prescription. If the index day does not fulfil the exposure washout criteria the whole exposure is eliminated.

### 8.8.5 Methods to derive parameters of interest

Calendar time

Calendar time will be based on the calendar year of the index prescription (e.g., 01/01/2014 – 31/12/2014, 01/01/2015 – 31/12/2015, etc.).

Calendar strata: an additional stratification to the overall study period (i.e., 2013-2023) will be run only in the overall antipsychotics, and typical/atypical cohorts. The stratification will use the following time windows: 2013-2017 and 2018-2023.

Age

Age at index date will be calculated using the full date of birth. Where day, or day and month of birth are missing, 1st of the month or January 1st of the year of birth will be used as proxy for the actual birthday. The following age groups will be used for stratification: 1-5, 6-11, 12-18 years of age.

Sex

Record of male/female sex.

Indications

Indications for antipsychotics will be determined based on recordings of 7 pre-defined conditions, namely schizophrenia, bipolar disorder, autism, attention-deficit/hyperactivity disorder [ADHD], anxiety, depression and sleep disturbance in the prespecified window.

Additionally, we will differentiate indications of use in the following three groups, which will be mutually exclusive:

- Indication for antipsychotic use: the presence of any of the 7 pre-defined conditions in the prespecified window.

- Other conditions: record of any condition not included in the specific indications mentioned before, during the prespecified window.
- None: no other condition recorded in the prespecified window.

The prespecified window for indications will be -7 days, -30 days or any time before the first prescription of the respective drug (index date).

Characterisation of patient-level features (comorbidities)

Patient-level characterisation will be conducted. Covariates will be extracted for the following time intervals: -30 days before index date, and any time prior to index date.

### 8.8.6 Methods planned to obtain point estimates with confidence intervals of measures of occurrence

Patient-level characterisation study

*Age and sex distribution*

Mean [SD] and median [IQR] age at index date, number of persons (N, %) by age groups (1-5, 6-11, 12-18 years) at index date, and number of persons (N, %) by sex (male/female) will be reported overall, by typical/atypical and by the 11 pre-specified drug substances for each database.

*Indications and comorbidities*

The number of persons (N, %) with a record of the respective indication of use and comorbidities will be provided. If a person has a record of more than one of the pre-specified indications/comorbidities, that person will be included in both specific indication groups separately. Conversely, in the indications of use groups (indication for antipsychotic use, other conditions or none) will be mutually exclusive.

Population-level drug utilisation study

Incidence and prevalence estimates will be calculated annually for antipsychotic treatment overall, by typical/atypical and by the 11 pre-specified drug substances for each database:

*Incidence rates calculations*

Annual incidence rates for antipsychotic use will be calculated as the of number of new users per 100,000 person-years of the population at risk of getting exposed during the period for each calendar year. Any study participants with use of the medication of interest prior to the date at which they would have otherwise satisfied the criteria to enter the denominator population (as described above) will be excluded. Those study participants who enter the denominator population will then contribute time at risk up to their first prescription (e.g. antipsychotic use) during the study period. Or if they do not have a drug exposure, they will contribute time at risk, as described above in section 8.4 (study end, end of observation period, or the last day of maximum age). An illustration of the calculation of incidence of antipsychotic use is shown below in **Figure 5**.

Patient ID 1 and 4 contribute time at risk up to the point at which they become incident users of antipsychotics. Patient ID 2 and 5 are not seen to use antipsychotics and so contribute time at risk but no incident outcomes. Meanwhile, patient ID 3 is excluded from the analysis as they are seen to have had the outcome before the study start date.

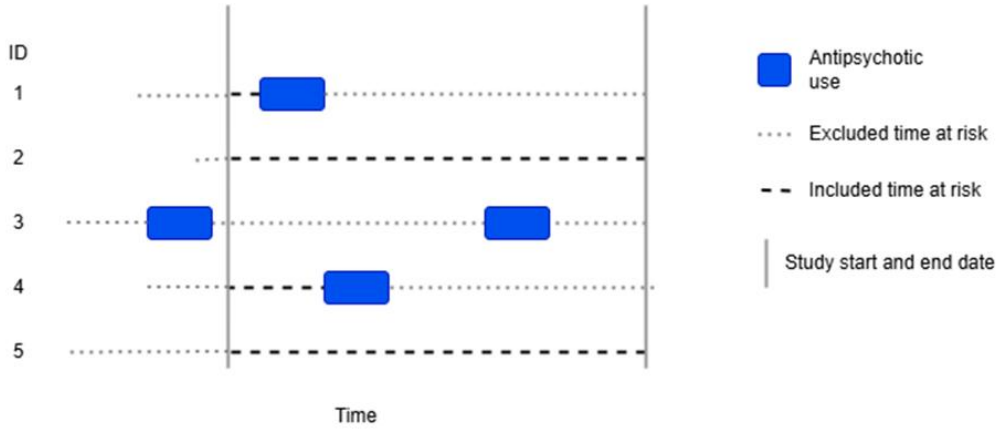



**Figure 5.** Incidence rates calculations example.

*Prevalence estimates calculations*

Annual period prevalence estimates of the medicines of interest will be calculated as the total number of individuals who were prescribed/dispensed the medicine of interest during the calendar year of interest, divided by the population at risk of getting exposed during that same year. Therefore, period prevalence gives the proportion of individuals exposed during of each calendar year.

Period prevalence will be given together with 95% confidence intervals. Binomial 95% confidence intervals will be calculated using the Wilson Score method for binomial distribution.

An illustration of the calculation of period prevalence is shown below in **Figure 6**. Between time t+2 and t+3, two of the five study participants are users of medicines of interest giving a prevalence of 40%. Meanwhile, for the period t to t+1 all five also have some observation time during the time with one of the five study participants being a user of a medicine of interest, giving a prevalence of 20%.

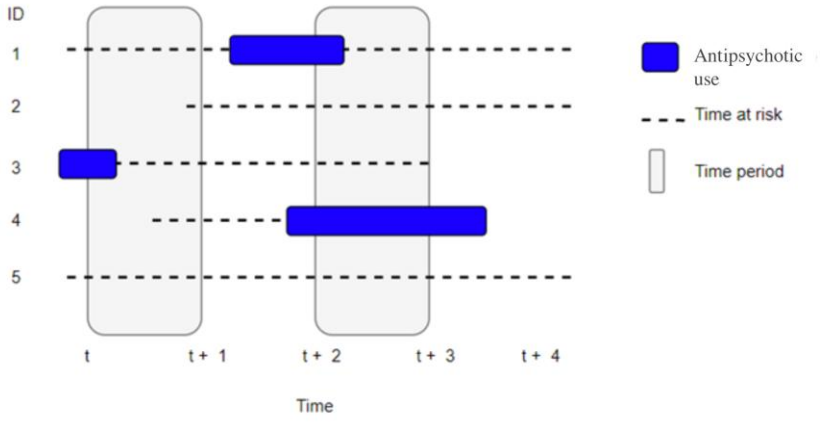



**Figure 6.** Period prevalence calculations example

Patient-level drug utilisation study

*New drug user patient-level characteristics on/before index date*

For each drug concept extracted before/at index date, the number of persons (N, %) with a record of overall, typical/atypical and by the 11 pre-specified drug substances for each database will be provided.

*Initially prescribed or dispensed dose*

For each prescription at index date, the prescribed dose will be retrieved from the drug_exposure tables, where the amount quantity and units are available.

The quality of recording of drug dose might be of varying quality for different databases. Therefore, data quality checks will be conducted to evaluate the quality of the recording of units, dosage (OMOP drug_exposure tables) for antipsychotics in the databases this study will be conducted in.

From this, the initial dose in the cohort will be characterised by median [IQR].

*Treatment duration*

Treatment duration will be calculated as the duration of the first continuous exposure episode, with less than a 30-day gap between prescriptions. Estimations of treatment duration will be summarized providing the median [IQR] treatment duration. For databases, where duration cannot be calculated due to e.g. missing information on quantity or dosing, treatment duration will not be provided.

#### 8.8.7 Methods to control for potential sources of bias

None.

#### 8.8.8 Methods to deal with missing data

None.

### 8.9 Evidence synthesis

Results from analyses described in Section 8.8 will be presented separately for each database and no meta-analysis of results will be conducted.

# 9. DATA MANAGEMENT

## 9.1 Data management

All databases will have been mapped to the OMOP common data model. This enables the use of standardised analytics and tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM is 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

This analytic code for this study will be written in R. Each data partner will execute the study code against their database containing patient-level data and will then return the results set 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.

## 9.2 Data storage and protection

For this study, participants from various EU member states will process personal data from individuals which is collected in national/regional electronic health record databases. 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 databases 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 Remote Research

Environment. These output files do not contain any data that allow identification of subjects included in the study. The RRE 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) 679/20161 in the various member states.

# 10. QUALITY CONTROL

Description of any mechanisms and procedures to ensure data quality and integrity, including accuracy and legibility of collected data and original documents, extent of source data verification and validation of endpoints, storage of records and archiving of the statistical programming performed to generate the results.

# 11. LIMITATIONS OF THE RESEARCH METHODS

The study will be informed by routinely collected health care data and so data quality issues must be considered. In particular, a recording of a prescription or dispensation does not mean that the patient actually took the drug. In addition, assumptions around the duration of drug use will be unavoidable.

The actual reason for prescription of the drug is not recorded in any of the databases. We will assess indication via a proxy based on pre-defined conditions recorded on the date of therapy initiation. Therefore, recording of potential indication may be incomplete. In addition, the completeness of recordings of co-morbidities used for patient characterisation may vary across databases.

We decided to restrict the paediatric population to those aged ≥1 year due to programmatic constraints of the study packages regarding the 1-year clinical history requirement. The R packages that will be used to select the study population allow different restrictions to be applied to separate strata, but they cannot accommodate varying requirements within the same group. In other words, when applying the 1-year clinical history restriction to the 0-5 age group, it will be applied uniformly to all individuals in that group, meaning that children under 1 year old will not meet the 1-year clinical history requirement.

Database-specific limitations:

InGef RDB has the potential of missing prescriptions depending on reimbursement of off-label prescriptions in children. Additionally, outpatient and primary care diagnoses are recorded only by quarter of the year, with no actual diagnosis date being recorded, which will limit the completion of indication and comorbidities recording, especially for the time windows -7 days and -30 days before index date.

Study period in NLHR will start in 2018 as secondary care data is available from 2018 onwards.

Croatia NAJS does not report dose and will not be included in drug utilisation calculations (Objective 3).

In BIFAP, linkage to hospital data is available for different time periods for each region, thus, reported overall, by typical/atypical and by the 11 pre-specified drug substances for each database. Drug records and diagnosis at primary care are not affected, but we will not be able to distinguish conditions diagnosed at hospitals when the linkage is available, which may have an impact in the completeness of conditions and indications in BIFAP.

# 12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions will not be collected or analysed as part of this evaluation. The nature of this non-interventional evaluation, through the use of secondary data, does not fulfil the criteria for reporting adverse events, according to module VI, VI.C.1.2.1.2 of the Good Pharmacovigilance Practices

(https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf).

Only in case of prospective data collection, there is a need to describe the procedures for the collection, management and reporting of individual cases of adverse events/adverse reactions.

# 13. GOVERNANCE BOARD ASPECTS

SIDIAP, BIFAP, InGef, IPCI, DK-DHR, NLHR, and NAJS will undergo their respective ethical approvals.

# 14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Study Report

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.

Publication

We aim to publish the results of this study in a peer-review journal.

# 15. REFERENCES

1. Huhn, M., et al., *Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis.* Lancet, 2019. **394**(10202): p. 939-951.
2. Frederiksen, K.S., et al., *A European Academy of Neurology guideline on medical management issues in dementia.* Eur J Neurol, 2020. **27**(10): p. 1805-1820.
3. Sultana, J., et al., *Antipsychotic use in dementia patients in a general practice setting: a Dutch population-based study.* Epidemiol Psychiatr Sci, 2016. **25**(4): p. 403-6.
4. Guthrie, B., et al., *Differential impact of two risk communications on antipsychotic prescribing to people with dementia in Scotland: segmented regression time series analysis 2001-2011.* PLoS One, 2013. **8**(7): p. e68976.
5. Gomez-Lumbreras, A., et al., *Psychotropic use in children and adolescents in Scandinavia and Catalonia: a 10-year population-based study.* Psychopharmacology (Berl), 2021. **238**(7): p. 1805-1815.
6. Radojčić, M.R., et al., *Trends in antipsychotic prescribing to children and adolescents in England: cohort study using 2000–19 primary care data.* The Lancet Psychiatry, 2023. **10**(2): p. 119-128.

# 16. ANNEXES

**Appendix I**: List of Stand-Alone documents (e.g. lists with concept definitions (conditions & drugs), validation procedures, questionnaires etc.)

**Appendix II**: ENCePP checklist for study protocols

**Appendix I**: Concept List for Antipsychotic substances.

| ATC Code | Substance Name | Typical/Atypical | Concept ID Ingredient | 11 pre-selected ingredients |
|---|---|---|---|---|
| N05AA04 | acepromazine | Typical | 19018226 | - |
| N05AB07 | acetophenazine | Typical | 19029555 | - |
| N05AL05 | amisulpride | Atypical | 19057607 | - |
| N05AX12 | aripiprazole | Atypical | 757688 | YES |
| N05AH05 | asenapine | Atypical | 40164052 | - |
| N05AD07 | benperidol | Typical | 19016440 | - |
| N05AX16 | brexpiprazole | Atypical | 46275300 | - |
| N05AD06 | bromperidol | Typical | 19039227 | - |
| N05AB09 | butaperazine | Typical | 40798666 | - |
| N05AX15 | cariprazine | Atypical | 35603277 | - |
| N05AA07 | chlorproethazine | Typical | 19122262 | - |
| N05AA01 | chlorpromazine | Typical | 794852 | - |
| N05AF03 | chlorprothixene | Typical | 19095002 | YES |
| N05AF02 | clopenthixol | Typical | 19095002 | - |
| N05AH06 | clotiapine | Atypical | 19100363 | - |
| N05AH02 | clozapine | Atypical | 800878 | YES |
| N05AA06 | cyamemazine | Typical | 19051234 | - |
| N05AB01 | dixyrazine | Typical | 40798772 | - |
| N05AD08 | droperidol | Typical | 739323 | - |
| N05AD09 | fluanisone | Typical | 40798823 | - |
| N05AF01 | flupentixol | Typical | 19055982 | - |
| N05AB02 | fluphenazine | Typical | 756018 | - |
| N05AG01 | fluspirilene | Typical | 19056465 | - |
| N05AD01 | haloperidol | Typical | 766529 | - |
| N05AX14 | iloperidone | Atypical | 19017241 | - |
| N05AA02 | levomepromazine | Typical | 19005147 | YES |
| N05AL07 | levosulpiride | Atypical | 43009023 | - |
| N05AN01 | lithium | -* | 19124477 | - |
| N05AH01 | loxapine | Typical | 792263 | - |
| N05AD10 | lumateperone | Atypical | 37498659 | - |
| N05AE05 | lurasidone | Atypical | 40230761 | - |
| N05AD03 | melperone | Atypical | 19072088 | - |
| N05AC03 | mesoridazine | Typical | 703083 | - |
| N05AE02 | molindone | Typical | 709699 | - |
| N05AD04 | moperone | Typical | 40798964 | - |
| N05AX10 | mosapramine | Atypical | 36848724 | - |
| N05AH03 | olanzapine | Atypical | 785788 | YES |

| | | | | |
|---|---|---|---|---|
| N05AE01 | oxypertine | Typical | 19025922 | - |
| N05AX13 | paliperidone | Atypical | 703244 | YES |
| N05AG03 | penfluridol | Typical | 19028044 | - |
| N05AB10 | perazine | Typical | 19131663 | - |
| N05AC01 | periciazine | Typical | 19053565 | - |
| N05AB03 | perphenazine | Typical | 733008 | - |
| N05AX17 | pimavanserin | Atypical | 42628962 | - |
| N05AG02 | pimozide | Typical | 745790 | - |
| N05AD05 | pipamperone | Typical | 19093225 | YES |
| N05AC04 | pipotiazine | Typical | 19133992 | - |
| N05AB04 | prochlorperazine | Typical | 752061 | - |
| N05AA03 | promazine | Typical | 19052903 | YES |
| N05AX07 | prothipendyl | Typical | 19115044 | - |
| N05AH04 | quetiapine | Atypical | 766814 | YES |
| N05AL04 | remoxipride | Atypical | 19035226 | - |
| N05AX08 | risperidone | Atypical | 735979 | YES |
| N05AE03 | sertindole | Atypical | 19050633 | - |
| N05AL01 | sulpiride | Atypical | 19136626 | YES |
| N05AL02 | sultopride | Atypical | 19100431 | - |
| N05AB05 | thiopropazate | Typical | 19041817 | - |
| N05AB08 | thioproperazine | Typical | 19000305 | - |
| N05AC02 | thioridazine | Typical | 700299 | - |
| N05AL03 | tiapride | Atypical | 19008012 | - |
| N05AF04 | tiotixene | Typical | 700465 | - |
| N05AB06 | trifluoperazine | Typical | 704984 | - |
| N05AD02 | trifluperidol | Typical | 19005101 | - |
| N05AA05 | triflupromazine | Typical | 19005104 | - |
| N05AL06 | veralipride | Atypical | 19043327 | - |
| N05AE04 | ziprasidone | Atypical | 712615 | - |
| N05AX11 | zotepine | Atypical | 19102109 | - |
| N05AF05 | zuclopenthixol | Typical | 19010886 | - |

* Lithium is classified and used as an antipsychotic, but it does not pertain to any of the typical/atypical groups. Therefore, it will be added in the overall antipsychotic group but not in the stratification.

**Appendix II**: ENCePP checklist for study protocols.

# ENCePP Checklist for Study Protocols (Revision 1)

Adopted by the ENCePP Steering Group on 15/10/2018

**Study title:**
DARWIN EU® - Antipsychotic prescribing in the children in Europe: a descriptive analysis of trends and patient characteristics

**EU PAS Register® number: EUPAS1000000592**
**Study reference number (if applicable): P4-C2-003**

| **Section 1: Milestones** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 1.1 Does the protocol specify timelines for | | | | |
| 1.1.1 Start of data collection[1] | ☒ | ☐ | ☐ | 5- milestones |
| 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:

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| **Section 2: Research question** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 2.1 Does the formulation of the research question and objectives clearly explain: | ☒ | ☐ | ☐ | 7 – Research questions and objectives |
| 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 *a priori* hypothesis? | ☐ | ☐ | ☒ | |

Comments:

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[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? | ☒ | ☐ | ☐ | 8.2 |
| 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:

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| **Section 4: Source and study populations** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 4.1 | Is the source population described? | ☒ | ☐ | ☐ | 8.2 |
| 4.2 | Is the planned study population defined in terms of: | | | | 8.3, 8.4, 8.5 |
| | 4.2.1 Study time period | ☒ | ☐ | ☐ | and 8.8.5 |
| | 4.2.2 Age and sex | ☒ | ☐ | ☐ | |
| | 4.2.3 Country of origin | ☒ | ☐ | ☐ | |
| | 4.2.4 Disease/indication | ☒ | ☐ | ☐ | |
| | 4.2.5 Duration of follow-up | ☒ | ☐ | ☐ | |
| 4.3 | Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria) | ☒ | ☐ | ☐ | 8.5 |

Comments:

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| **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) | ☐ | ☐ | ☒ | |
| 5.3 | Is exposure categorised according to time windows? | ☒ | ☐ | ☐ | 8.6.1 |

| | | | | | |
|---|---|---|---|---|---|
| 5.4 | Is intensity of exposure addressed? (e.g., dose, duration) | ☐ | ☐ | ☒ | |
| 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:

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| **Section 6: Outcome definition and measurement** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 6.1 | Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated? | ☐ | ☐ | ☒ | |
| 6.2 | Does the protocol describe how the outcomes are defined and measured? | ☐ | ☐ | ☒ | |
| 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:

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| **Section 7: Bias** | | **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:

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| **Section 8: Effect measure modification** | | **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:

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| **Section 9: Data sources** | | **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) | ☒ | ☐ | ☐ | 8.2 |
| | 9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics) | ☐ | ☐ | ☒ | |
| | 9.1.3 Covariates and other characteristics? | ☒ | ☐ | ☐ | 8.6.3 |
| 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) | ☒ | ☐ | ☐ | 8.6.1 |
| | 9.2.2 Outcomes? (e.g. date of occurrence, multiple events, severity measures related to event) | ☐ | ☐ | ☒ | |
| | 9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle) | ☒ | ☐ | ☐ | 8.6.3 |
| 9.3 | Is a coding system described for: | | | | |
| | 9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System) | ☒ | ☐ | ☐ | Appendix I |
| | 9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA)) | ☐ | ☐ | ☒ | |
| | 9.3.3 Covariates and other characteristics? | ☒ | ☐ | ☐ | 8.6.3 |
| 9.4 | Is a linkage method between data sources described? (e.g. based on a unique identifier or other) | ☐ | ☐ | ☒ | |

Comments:

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| **Section 10: Analysis plan** | | **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? | ☐ | ☐ | ☒ | |

| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 10.7 Does the plan describe methods for handling missing data? | ☐ | ☐ | ☒ | |
| 10.8 Are relevant sensitivity analyses described? | ☐ | ☐ | ☒ | |

Comments:

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| **Section 11: Data management and quality control** | **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) | ☒ | ☐ | ☐ | 9 |
| 11.2 Are methods of quality assurance described? | ☒ | ☐ | ☐ | 10 |
| 11.3 Is there a system in place for independent review of study results? | ☐ | ☐ | ☒ | |

Comments:

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| **Section 12: Limitations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 12.1 Does the protocol discuss the impact on the study results of: | | | | 11 |
| 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). | ☐ | ☐ | ☒ | |
| 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) | ☐ | ☒ | ☐ | |

Comments:

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

Comments:

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| **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:

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| **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)? | ☒ | ☐ | ☐ | 14 |
| 15.2 Are plans described for disseminating study results externally, including publication? | ☒ | ☐ | ☐ | 14 |

Comments:

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Name of the main author of the protocol: Marta Pineda-Moncusí

Date: 10/April/2025

Signature: MPM