Study Protocol

P3-C2-002

DARWIN EU® Drug Utilisation Study of prescription opioids

11/02/2025

Version 2.0

Contents

Study Title	DARWIN EU® - Drug utilisation study of prescription opioids
Protocol version	V2.0
Date	11 February 2025
EU PAS number	EUPAS1000000479
Active substances	**Opioids** (substances listed in ATC classes N01AH, N02A and R05DA), namely: acetyldihydrocodeine, alfentanil, anileridine, bezitramide, butorphanol, buprenorphine, codeine, dezocine, dimemorfan, dextromethorphan, dextromoramide, dextropropoxyphene, dihydrocodeine, ethylmorphine, fentanyl, hydrocodone, hydromorphone, ketobemidone, meptazinol, meperidine (pethidine), methadone, morphine, nicomorphine, normethadone, nalbuphine, noscapine, oliceridine, opium, oxycodone, oxymorphone, papaveretum, pentazocine, phenazocine, phenoperidine, pholcodine, pirinitramide, propoxyphene, remifentanil, sufentanil, tapentadol, thebacon, tilidine, tramadol; naloxone; buprenorphine/naloxone, oxycodone/naloxone,pentazocine/naloxone, tilidine/naloxone
Medicinal product	N/A
Research question and objectives	This study aims to assess the incidence and prevalence of prescription opioids for the period 2012-2024, stratified by history of cancer/no history of cancer and age, sex, calendar year and country, as well as characterisation of new users, indications and treatment duration overall and in people with history of cancer/no history of cancer stratified by calendar year and country
Countr-ies of study	Estonia, Belgium, The Netherlands, France, Spain, Denmark, Norway
AuthorAuthors	Amy Lam, Annika Jödicke

[1] This is a routine repeated study from P2-C1-002 (EUPAS105641).

LIST OF ABBREVIATIONS

Acronyms/terms	Description
ACI VARHA	Auria Clinical Informatics VARHA
CDM	Common Data Model
CDWBORDEAUX	Bordeaux University Hospital
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real World Interrogation Network
DK-DHR	Danish Data Health Registries
DUS	Drug Utilisation Study
EBB	Estonian Biobank
EGCUT	Estonian Genome Center at the University of Tartu
EHR	Electronic Health Records
EMA	European Medicines Agency
GP	General Practitioner
ID	Index date
IMASIS	Institut Municipal Assistència Sanitària Information System
IPCI	Integrated Primary Care Information Project
NLHR	Norwegian Linked Health Registry
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
WHO	World Health Organisation

1. TITLE

DARWIN EU® - Drug Utilisation Study of prescription opioids

2. RESPONSIBLE PARTIES – STUDY TEAM

Table 1 shows a description of the Study team by role, name and organization.

Table 1. Description of study team.

Study team Role	Names	Organisation
Principal Investigator(s)	Amy Lam	University of Oxford
Data Scientist(s)	Mike Du Edward Burn	University of Oxford
Clinical Epidemiologist	Annika Jödicke Junqing (Frank) Xie	University of Oxford
Data Partner*	**Names**	**Organisation**
Local Study Coordinator/Data Analyst	Gargi Jadhav Isabella Kaczmarczyk Akram Mendez Dina Vojinovic	IQVIA
	Talita Duarte Salles Irene López Sánchez Agustina Giuliodori Picco Anna Palomar Cros	IDIAP JGol
	Raivo Kolde Marek Oja Ami Sild	University of Tartu
	Katia Verhamme	Erasmus MC
	Romain Griffier Guillaume Verdy	CHU Bordeaux
	Claus Møldrup Elvira Bräuner Susanne Bruun Monika Roberta Korcinska Handest	Danish Medicines Agency
	Juan Manuel Ramírez-Anguita Angela Leis Miguel-Angel Mayer	Consorci Mar Parc de Salut Barcelona
	Saeed Hayati Nhung Trinh Hedvig Nordeng Maren Mackenzie Olson	University of Oslo

*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® - Drug Utilisation Study of prescription opioids.

Rationale and Background

Prescription opioids, while effective for managing severe pain, have led to a public health crisis due to misuse, addiction, and overdose, particularly in the US. Recently, concerns have been growing in Europe due to increasing opioid use and related mortality. Factors such as chronic pain, mental health disorders, and advanced age can exacerbate misuse and the development of dependence. Given the potential for global spread of this issue, enhanced surveillance and in-depth research into opioid utilisation patterns are imperative. A drug utilisation study using a Common Data Model (CDM) is a promising approach to supplement European opioid monitoring systems, providing more granular data to inform evidence-based decisions on this complex topic.

Research question and Objectives

The objectives of this study are

(i) To investigate the annual incidence and annual period prevalence of use of opioids (overall, active drug substance, strength (weak/strong opioids) and route (oral, transdermal or parenteral), stratified by history of cancer/no history of cancer and for calendar year, age, sex and country/database during the study period.

(ii) To determine duration of prescription opioid use, as well as characteristics of new users and indication for opioid prescribing/dispensing overall and in people with history of cancer/no history of cancer, all stratified by calendar year and country/database.

Research Methods

Study design

- Population level cohort study (Objective 1, Population-level drug utilisation study on opioids)
- New drug user cohort study (Objective 2, Patient-level drug utilisation analyses regarding summary characterisation, duration, and indication of opioid use)

Population

Population-level utilisation of opioids: All people registered in the respective databases on 1st of January of each year in the period 2012-2024 (or the latest available, whatever comes first), with at least 1 year of prior data availability, will participate in the population-level analysis (period prevalence calculation in Objective 1). Therefore, children aged <1 year will be excluded.

New users of opioids in the period between 1/1/2012 and 31/12/2024 (or latest date available, whatever comes first), with at least 1 year of data availability, and no use of the respective opioid in the previous 12 months, will be included for incidence rate calculations in Objective 1.

Patient-level drug utilisation: New users of opioids in the period between 1/1/2012 and 31/12/2024 (or latest date available, whatever comes first), with at least 1 year of data availability, and no use of the respective opioid in the previous 12 months, will be included for patient-level drug utilisation analyses.

Variables

Drug of interest: Opioids (substances listed in ATC classes N01AH, N02A and R05DA); naloxone; and fixed naloxone-opioid combinations.

Data sources

1. Estonian Biobank (EBB), Estonia
2. IQVIA LBD Belgium, Belgium
3. Integrated Primary Care Information Project (IPCI), The Netherlands
4. The Information System for Research in Primary Care (SIDIAP), Spain
5. Clinical Data Warehouse for Bordeaux University Hospital (CDWBORDEAUX), France
6. Danish Data Health Registries (DK-DHR), Denmark
7. Institut Municipal Assistència Sanitària Information System (IMASIS), Spain
8. Norwegian Linked Health Registry (NLHR), Norway

Sample size

No sample size has been calculated.

Data analyses

Population-level drug utilisation will be conducted in all databases. Patient-level DUS analyses will be conducted in all databases. No duration will be calculated for EBB.

Population-level opioid use: Annual period prevalence of opioid use and annual incidence rates per 100,000 person years will be estimated.

Patient-level opioid use: Summary patient-level characterisation by list of pre-defined conditions/medications of interest will be conducted at index date, including patient demographics, and history of comorbidities and comedication. Frequency of indication at index date, and in the immediate time before will be calculated. Cumulative treatment duration will be estimated for the first treatment era and the minimum, p25, median, p75, and maximum will be provided.

For all analyses a minimum cell count 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	06/02/2025	N/A	Update from initial study protocol (P2-C1-002, EUPAS105641)	This is a routine-repeated study.

Comparison with Previous Protocols

	P2-C1-002 (EUPAS105641)	P3-C2-002 (Current study protocol)
Study period	2012-2022	2012-2024
Data partner		
EBB [Estonia]	*	*
IQVIA DA Germany [Germany]	*	
IQVIA LBD Belgium [Belgium]	*	*
SIDIAP [Spain]	*	*
IPCI [The Netherlands]	*	*
CDWBORDEAUX [France]	*	*
ACI VARHA [Finland]	*	
DK-DHR [Denmark]		*
IMASIS [Spain]		*
NLHR [Norway]		*
Reference study protocol	N/A	P2-C1-002 (EUPAS105641)
Changes from reference study protocol	N/A	- Exposure: Add opioid use with history of cancer/no history of cancer - Patient-level DUS: change large scale characterisation to pre-defined list of conditions and medications - Indication: consider procedures for possible indication in hospital database - Sensitivity analysis: remove 6-month washout period

5. MILESTONES

Study deliverable	Timeline
Draft Study Protocol	17/01/2025
Final Study Protocol	31/01/2025
Creation of Analytical code	February 2025
Execution of Analytical Code on the data	February 2025
Draft Study Report	March 2025
Final Study Report	To be confirmed

*Planned dates are dependent on obtaining approvals from the internal review boards of the data sources.

6. RATIONALE AND BACKGROUND

Prescription opioids are important medications recommended to treat acute and chronic moderate to severe pain but can lead to complex and interconnecting health and social issues related to misuse, abuse, dependence, addiction, overdose, and drug diversion. Abuse of prescription opioids, in particular, is an ongoing public health crisis in the US. By 2016 of all patients with a fatal overdose, 25% were due to prescription opioids[1]. This alarming trend has manifested through distinct waves of opioid-related challenges over several decades, with the most recent wave starting around 2013. Within this latest wave, synthetic opioids, particularly the illicit production of fentanyl, have emerged as a primary focal point of concern and investigation in the US[2].

While no similar concern was observed in Europe by 2015, recent studies in Europe, suggest an increasing trend in the use of prescription opioids and opioid-use related mortality. Given that drug markets are increasingly global, the insufficient surveillance of these trends could potentially overlook the indicators of burgeoning issues.[3]

Clinical use of prescription opioids may also lead to some of the concerns above. Patients with chronic pain may develop dependence and addiction due to prolonged prescription opioid exposure leading to drug tolerance and a need for increased dose or opioid strength[4]. Similarly, patients with mental health disorders are at increased risk of initiation and prolonged opioid treatments and their consequences. Moreover, older adults are more susceptible to the adverse effects of opioids, yet they typically have more pain management requirements due to accumulating a range of chronic disorders leading to painful conditions[5]. There is an imperative need for further investigation to describe the utilisation patterns of opioids among this demographic[6].

A drug utilisation study of prescription opioids based on a Common Data Model (CDM) will provide useful information on the trends of prescription opioids and the characteristics of prescription opioid users in Europe. By supplementing the conventional European monitoring systems for aggregated opioid consumption, this study will offer detailed data on these drugs incl. their strength and route of administration, thereby enabling well-informed, evidence-based decision-making in addressing this multifaceted topic.

Following the completion of P2-C1-002 (EUPAS105641, https://catalogues.ema.europa.eu/node/3796), EMA requested a routine repeated study to include additional databases and more recent data.

7.   RESEARCH QUESTION AND OBJECTIVES

Table 2. Primary and secondary research questions and objectives.

A.   Primary research question and objective

Objective:	To investigate the annual incidence and annual period prevalence of use of opioids (overall, active drug substance, strength (weak/strong opioids), route (oral, transdermal or parenteral)), stratified by history of cancer and calendar year, age, sex and country/database during the study period.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	All people registered in the respective databases on 1st of January of each year in the period 2012-2024 (or the latest available, whatever comes first), with at least 1 year of prior data availability, will participate in the population-level analysis (period prevalence calculation in Objective 1). Therefore, children aged <1 year will be excluded. New users of opioids in the period between 1/1/2012 and 31/12/2024 (or latest date available, whatever comes first), with at least 1 year of data availability, and no use of the respective opioid in the previous 12 months, will be included for incidence rate calculations in Objective 1.
Exposure:	Opioids (substances listed in ATC classes N01AH, N02A and R05DA), as well as naloxone, and fixed combinations (i.e. buprenorphine and naloxone, oxycodone and naloxone)
Comparator:	None
Outcome:	None
Time *(when follow up begins and ends):*	Follow-up will start on a pre-specified calendar time point, namely 1st of January for each calendar year between 2012-2024 for the calculation of annual incidence/prevalence rates. 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, whatever comes first.
Setting:	Inpatient and outpatient setting using data from the following 8 data sources: EBB [Estonia], IQVIA LBD Belgium [Belgium], SIDIAP [Spain], IPCI [The Netherlands], CDWBORDEAUX [France], DK-DHR [Denmark], IMASIS [Spain], NLHR [Norway]
Main measure of effect:	Incidence and prevalence of opioid use

B.   Secondary research question and objective

Objective:	To determine the duration of the first treatment era of opioid use, as well as characteristics of new users and indication for opioid prescribing/dispensing overall and in people with history of

	cancer/no history of cancer, all stratified calendar year and country/database.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	New users of opioids overall and in people with history of cancer/no history of cancer in the period between 1/1/2012 and 31/12/2024 (or latest date available, whatever comes first), with at least 1 year of prior data availability, and no use of the respective opioid in the previous 12 months, will be included for patient-level drug utilisation analyses.
Exposure:	Opioids (substances listed in ATC classes N01AH, N02A and R05DA), as well as naloxone, and fixed combinations (i.e. buprenorphine and naloxone, oxycodone and naloxone)
Comparator:	None
Outcome:	None
Time *(when follow up begins and ends):*	Follow-up will start on the date of incident opioid 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, whatever comes first.
Setting:	Inpatient and outpatient setting using data from the following 8 data sources: EBB [Estonia], IQVIA LBD Belgium [Belgium], SIDIAP [Spain], IPCI [The Netherlands], CDWBORDEAUX [France], DK-DHR [Denmark], IMASIS [Spain], NLHR [Norway]
Main measure of effect:	Duration of opioid use (first treatment era) expressed as minimum, p25, median, p75, and maximum days
	Summary patient-level characterisation by list of pre-defined conditions/medications of interest for new opioid users overall and in people with history of cancer/no history of cancer (1) overall, (2) for the 10 most frequent opioids in each database, (3) by strength, (4) by route.
	Indications, based on a high-level approach considering the most frequent conditions and procedures recorded in the month/week before/at the date of treatment start.

8. RESEARCH METHODS

8.1 Study design

A cohort study will be conducted using routinely-collected health data from 8 databases. The study will comprise two consecutive parts:

1. A population-based cohort study will be conducted to address objective 1, assessing the prevalence and incidence of the respective opioids of interest.
2. A new drug user cohort will be used to address objective 2; to characterise individual-level opioid utilisation in terms of summary patient characteristics, indication and duration of use.

8.2 Study Setting

8.2.1 Study population

The study cohort will comprise all individuals present in the database during the study period (2012-2024) and with at least 365 days of data availability before the day they become eligible for study inclusion. Therefore, children aged <1 year will be excluded.

Additional eligibility criteria will be applied for the calculation of incidence rates and patient-level drug utilisation analyses: New users will have a first prescription of opioids in the period between 1/1/2012 and 31/12/2024 (or latest date available, whatever comes first), with at least 1 year of prior data availability, and no use of the respective opioid in the previous 12 months.

8.2.2 Study period and follow-up

The study period will be from the 1st of January 2012 until the earliest of either 31st December 2024 or the respective latest date of data availability of the respective databases.

For the population-level analyses for incidence and prevalence, individuals will contribute person-time from the date they have reached at least 365 days of data availability.

Table 3. 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[1]	Code Type[2]	Diagnosis position	Incident with respect to...	Measurement characteristics/ validation	Source of algorithm
All patients from the database eligible for the study – Analysis of Prevalent Use	Patient present in the database during the study period and with at least 1 year of valid database history	Multiple	Prevalent	n/a	IP and OP	n/a	n/a	Overall, substance, strength, route	n/a	n/a
All patients from the database eligible for the study – Analysis of incident use	Patient present in the database during the study period and with at least 1 year of valid database history	Multiple	Incident	[-365 to ID]	IP and OP	n/a	n/a	Overall, substance, strength, route	n/a	n/a

[1] IP = inpatient, OP = outpatient, n/a = not applicable, ID = index date

Both incidence and prevalence require an appropriate denominator population and their contributed observation time to first be identified. 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 (1st January 2012), 2) date at which they have a year of prior history recorded. Participants will stop contributing person time at the earliest date of the following: 1) study end date (31st December 2024) or 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 1**. In this example, person ID 1 has already sufficient prior history before the study start date and observation period ends after the study end date, so will contribute during the complete study period. Person ID 2 and 4 enter the study only when they have sufficient prior history. 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 once sufficient prior history is reached and exits at study end date.
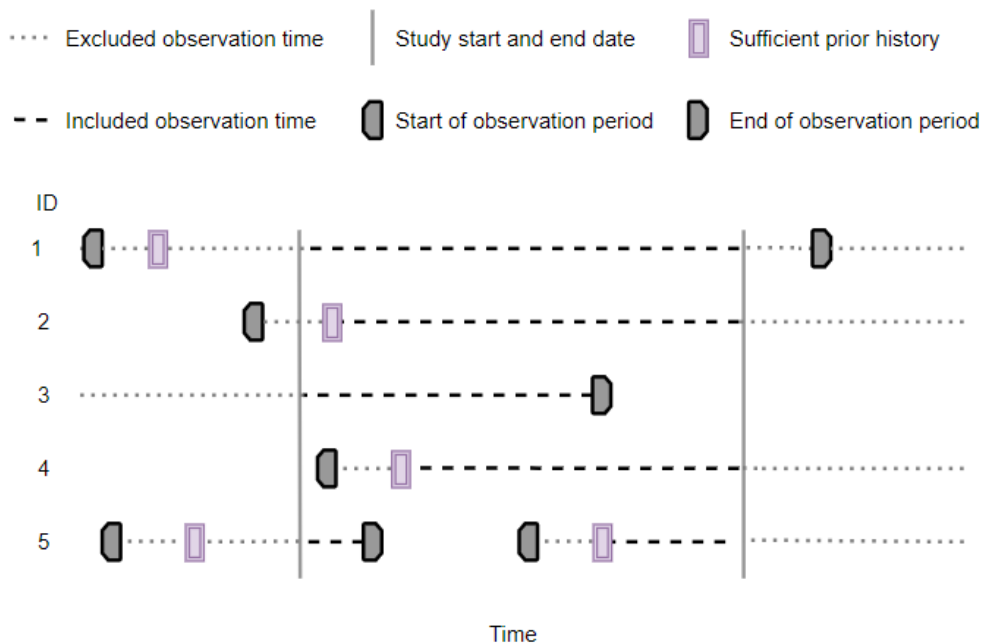

Figure 1. Included observation time for the denominator population.

8.2.3   In- and exclusion criteria

8.2.3.1   *Population-level Utilisation of opioids*

The study cohort will comprise all individuals present in the period 2012-2024 (or the latest available), with at least 365 days of data availability before the day they become eligible for study inclusion.

Additional eligibility criteria will be applied for the calculation of incidence rates: New users will have a first prescription of opioids in the period between 1/1/2012 and 31/12/2024 (or latest date available, whatever comes first), with at least 1 year of prior data availability, and no use of the respective opioid in the previous 12 months.

8.2.3.2 Patient-level Utilisation of opioids

All new users of opioids, after 365 days of no use of the specific opioid /substance /strength/ route, in the period between 1/1/2012 and 31/12/2024 (or latest date available), with at least 365 days of visibility prior to the date of their first opioid prescription.

Table 4. Operational definitions of inclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Observation period in the database during the period 2012-2024 (or the latest available)	All individuals present in the period 2012-2024 (or the latest available)	N/A	N/A	primary care, secondary care (i.e in- and outpatient specialist care)	N/A	N/A	All individuals within the selected databases	N/A	N/A
Prior database history of 1 year	Study participants will be required to have a year of prior history observed before contributing observation time	After	1 year	primary care, secondary care (i.e in- and outpatient specialist care)	N/A	N/A	All individuals within the selected databases	N/A	N/A
Washout period	New users will be required to have not used opioids/ the specific opioid substance /strength/ route 365 days before a "new" prescription	After	365 days	primary care, secondary care (i.e in- and outpatient specialist care)	N/A	N/A	All individuals within the selected databases	N/A	N/A

8.3 Variables

8.3.1 Exposure

For this study, the exposure of interest is use (during study period) of opioids, naloxone and fixed opioid-naloxone combinations.

Opioids will be grouped

(1) Overall
(2) by drug substance (incl. combinations and products for all indications)
(3) by strength (weak/potent opioids) for those opioids where strength is labelled by the WHO
(4) by route (oral, transdermal or parenteral) for overall opioids

This list of opioids is described in Table 5. Details of exposure are described in **Table 6**.

Table 5. Exposure of interest.

Substance Name	Strength*	No record counts in databases expected based on feasibility	Substance Name	Strength*	No record counts in databases expected based on feasibility
acetyldihydrocodeine			noscapine		
alfentanil			oliceridine		X
anileridine		X	opium		
bezitramide		X	oxycodone	potent	
butorphanol		X	oxymorphone	potent	X
buprenorphine	potent		papaveretum		
codeine	weak		pentazocine		
dezocine		X	phenazocine		
dimemorfan			phenoperidine		X
dextromethorphan			pholcodine		
dextromoramide			pirinitramide		
dextropropoxyphene		X	propoxyphene		
dihydrocodeine			remifentanil		
ethylmorphine			sufentanil		
fentanyl	potent		tapentadol	potent	
hydrocodone	weak		thebacon		
hydromorphone	potent		tilidine		
ketobemidone			tramadol	weak	
meptazinol					
meperidine (pethidine)			naloxone		
methadone	potent				
morphine	potent		buprenorphine/naloxone		
nicomorphine			oxycodone/naloxone		
normethadon		X	pentazocine/naloxone		
nalbuphine			tilidine/naloxone		

*Drug strength has been assigned bases on the WHO analgesic ladder (https://www.ncbi.nlm.nih.gov/books/NBK554435/):
weak opioids (hydrocodone, codeine, tramadol),
potent opioids (morphine, methadone, fentanyl, oxycodone, buprenorphine, tapentadol, hydromorphone, oxymorphone)

Table 6. Exposure details.

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting	Code Type	Diagnosis position	Applied to study populations:	Incident with respect to...	Measurement characteristics/ validation	Source of algorithm
Overall opioids, substance, strength, route	Preliminary code lists provided in Table 5.	[-365 to ID]	Calendar year	Biobank, primary and secondary care	RxNorm	N/A	All individuals present in the database during the study period	Previous opioid use	N/A	N/A
Opioid use (overall, strength, route) with history of cancer/no history of cancer	Preliminary code lists provided in Table 5. History of cancer defined as cancer-related observation or condition within 1 year before index date or use of antineoplastic treatment within 1 year before index date.	[-365 to ID]	Calendar year	Biobank, primary and secondary care	RxNorm	N/A	All individuals present in the database during the study period	Previous opioid use	N/A	N/A

8.3.2 Outcomes

None.

8.3.3 Other covariates, including confounders, effect modifiers and other variables (where relevant)

8.3.3.1 Covariates for stratification in population-level drug utilisation study:

- Calendar year

- Age: 10-year age bands will be used: 1-10, 11-20, 21-20 […] , and >80

- Sex: male or female

- History of cancer: yes or no

8.3.3.2 Covariates for patient-level drug utilisation study:

Baseline characteristics given by the list of pre-defined conditions/medications of interest: the operational definition of the included covariates are as follows: anxiety, asthma, autoimmune disease, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease, dementia, depressive disorder, diabetes, gastro-oesophageal reflux disease, heart failure, HIV, hypertension, hypothyroidism, inflammatory bowel disease, malignant neoplastic disease, lung cancer, colorectal cancer, prostate cancer, pancreatic cancer, ovarian cancer, leukemia, multiple myeloma, breast cancer, endometrial cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, myocardial infarction, osteoporosis, pneumonia, rheumatoid arthritis, stroke, venous thromboembolism. Covariates for the baseline medications will be pre-defined as follows: agents acting on the renin-angiotensin system, antibacterials for systemic use, antidepressants, antiepileptics, anti-inflammatory and antirheumatic products, antineoplastic agents, antithrombotic agents, beta blocking agents, calcium channel blockers, diuretics, drugs for acid related disorders, drugs for obstructive airway diseases, drugs used in diabetes, hormonal contraceptives, immunosuppressants, lipid modifying agents, psycholeptics, psychostimulants. Index date is the start of the (first) incident prescription during the study period.

Indication: We will use a high-level approach considering the most frequent conditions (all databases) and procedures (hospital database only) recorded in the month/week before/at the date of treatment start. The top 10 most frequent co-morbidities from large-scale patient characterisation recorded (1) at index date [primary definition] and (2) in the week before index date, (2) in the month before index date [sensitivity analyses] will be provided as proxies for indication.

Table 7. Operational definitions of covariates.

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Indication of Use	Top 10 most frequent co-morbidities and procedures from large-scale patient characterisation	Counts	At index date and as sensitivity analyses in windows around index date (ID): [-7, ID] and [-30, ID]	Biobank, primary and secondary care	SNOMED	N/A	Persons with new use during the study period	N/A	N/A
Summary characteristics of new users by list of pre-defined conditions/medications of interest	Patient-level characterisation with regard to baseline co-variates by pre-defined conditions/medications of interest.	Counts	Demographics, co-morbidities and co-medication at index date (ID), and within anytime to 366 days before ID, 365 to-181 days before ID, and 180 to 1 day before ID	Biobank, primary and secondary care	SNOMED, RxNorm	N/A	Persons with new use during the study period	N/A	N/A

8.4 Data sources

This study will be conducted using routinely collected data from 8 databases from 7 European countries. All databases were previously mapped to the OMOP CDM.

1. Estonian Biobank (EBB), Estonia
2. IQVIA LBD Belgium, Belgium
3. Integrated Primary Care Information Project (IPCI), The Netherlands
4. The Information System for Research in Primary Care (SIDIAP), Spain
5. Clinical Data Warehouse of Bordeaux University Hospital (CDWBordeaux), France
6. Danish Data Health Registries (DK-DHR), Denmark
7. Institut Municipal Assistència Sanitària Information System (IMASIS), Spain
8. Norwegian Linked Health Registry (NLHR), Norway

Information on the data source(s) with a justification for their choice in terms of ability to capture the relevant data is described below and in a **Table 8**.

Fit for purpose: This study will be repeated in 5 out of the 7 databases from the initial study P2-C1-002 and will include 3 additional databases. The selection of databases for this study was performed based on data reliability and relevance for the research question and feasibility counts.

6 databases include records from primary care and outpatient specialist care where opioids are expected to be prescribed. 2 databases are covering in-and outpatient records from hospitals, where opioids are expected to be initiated and prescribed for outpatient use following hospital discharge.

Table 8. Description of data sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Feasibility count of exposure (if relevant)	Data lock for the last update
The Netherlands	IPCI	Database covers primary care where opioid prescriptions are issued.	Primary care	EHR	1.25 million	Please see Appendix	21/10/2024
France	CDWBORDEAUX	Database covers hospital care setting where opioid may be initiated	Secondary care (in and outpatients)	EHR	0.2 million		22/02/2024
Spain	SIDIAP	Databases covers primary care / outpatient specialist care setting where opioid prescriptions are issued.	Primary care	EHR	6.0 million		30/06/2023
Belgium	IQVIA LBD Belgium		Primary care, outpatient specialist care	EHR	0.2 million		30/09/2024
Estonia	EBB	Database covers primary care setting where opioid prescriptions are issued.	Biobank	Claims data	0.2 million		01/06/2023
Denmark	DK-DHR	Database covers secondary care specialist setting where opioid prescriptions are issued.	Community pharmacy, secondary care specialist	EHR	5.96 million		21/5/2024
Norway	NLHR	Database covers primary care and secondar care specialists where opioid	Primary care, secondary care specialist, hospital inpatient care	Registries, EHR	6.95 million		29/10/2024

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Feasibility count of exposure (if relevant)	Data lock for the last update
		prescription are issued.					
Spain	IMASIS	Database covers secondary care specialists where opioid prescription are issued.	Secondary care specialist, hospital inpatient	EHR	0.1 million		13/07/2024

IPCI = Integrated Primary Care Information Project; CDWBORDEAUX= Bordeaux University Hospital, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, DA = Disease Analyzer, EBB = Estonian Biobank, EHR = Electronic Heath record, DK-DHR = Danish Data Health Registries, NLHR = Norwegian Linked Health Registry data, IMASIS = Institut Municipal Assistència Sanitària Information. Exposure is based on prescription data.

Integrated Primary Care Information Project (IPCI), The Netherlands

IPCI is collected from electronic health records (EHR) of patients registered with their general practitioners (GPs) throughout the Netherlands.[7] The selection of 374 GP practices is representative of the entire country. The database contains records from 3.0 million (as of 01-2025) patients out of a Dutch population of 17M starting in 1996[7]. The median follow-up is 4.6 years as of 01/2025. The observation period for a patient is determined by the date of registration at the GP and the date of leave/death. The observation period start date is refined by many quality indicators, e.g. exclusion of peaks of conditions when registering at the GP. All data before the observation period is kept as history data. Drugs are captured as prescription records with product, quantity, dosing directions, strength and indication. Drugs not prescribed in the GP setting might be underreported. Indications are available as diagnoses by the GPs and, indirectly, from secondary care providers but the latter might not be complete. Approval needs to be obtained for each study from the Governance Board[7].

Bordeaux University Hospital (CDWBORDEAUX), France

The clinical data warehouse of the Bordeaux University Hospital comprises electronic health records on more than 2 million patients with data collection starting in 2005. The hospital complex is made up of three main sites and comprises a total of 3,041 beds (2021 figures). The database currently holds information about the person (demographics), visits (inpatient and outpatient), conditions and procedures (billing codes), drugs (outpatient prescriptions and inpatient orders and administrations), measurements (laboratory tests and vital signs) and dates of death (in or out-hospital death).[8]

Information System for Research in Primary Care (SIDIAP), Spain (IDIAP Jordi Gol)

SIDIAP is collected from EHR records of patients receiving primary care delivered through Primary Care Teams (PCT), consisting of GPs, nurses and non-clinical staff[9]. The Catalan Health Institute manages 286 out of 370 such PCT with a coverage of 5.6M patients, out of 7.8M people in the Catalan population (74%). The database started to collect data in 2006. The mean follow-up is 15.5 years as of 01/2025. The observation period for a patient can be the start of the database (2006), or when a person is assigned to a Catalan Health Institute primary care centre. Date of exit can be when a person is transferred-out to a primary care centre that does not pertain to the Catalan Health Institute, or date of death, or date of end of follow-up in the database. Drug information is available from prescriptions and from dispensing records in pharmacies. Drugs not prescribed in the GP setting might be underreported; and disease diagnoses made at specialist care settings are not included. Studies using SIDIAP data require previous approval by both a Scientific and an Ethics Committee.

Longitudinal Patient Database (LPD) Belgium, Belgium (IQVIA)

LPD Belgium is a computerised network of GPs who contribute to a centralised database of anonymised data of patients with ambulatory visits. Currently, around 300 GPs from 234 practices are contributing to the database covering 1.1M patients from a total of 11.5M Belgians (10.0%). The database covers time from 2005 through the present. Observation time is defined by the first and last consultation dates. Drug information is derived from GP prescriptions. Drugs obtained over the counter by the patient outside the prescription system are not reported. No explicit registration or approval is necessary for drug utilisation studies.

Estonian Biobank – University of Tartu (Estonia)

The Estonian Biobank (EBB) is a population-based biobank of the Estonian Genome Center at the University of Tartu (EGCUT). Its cohort size is currently close to 200,000 participants ("gene donors" >= 18 years of age) which closely reflects the age, sex and geographical distribution of the Estonian adult population.

Genomic GWAS analysis have been performed on all gene donors. The database also covers health insurance claims, digital prescriptions, discharge reports, information about incident cancer cases and causes of death from national sources for each donor.

Danish Data Health Registries (DK-DHR), Denmark

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. High data quality due to standardisation, digitisation and documentation means that Danish health data is not based on interpretation. The present database has 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, and the complete vaccination registry. The median follow-up is 21.7 years (as of 01/2025).

Norwegian Linked Health Registry data (NLHR), Norway

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 from registries includes information about the pregnancy, diagnosis in secondary care (e.g., hospital), diagnosis and contact in primary care (e.g, GPs and outpatient specialists), all medications dispensed outside of hospitals, test results of communicable diseases (e.g., Sars-Cov-2), and records on vaccinations. The median follow-up is 16 years (as of 01/2025).

Institut Municipal Assistència Sanitària Information System (IMASIS), Spain

The Institut Municipal Assistència Sanitària Information System (IMASIS) is the Electronic Health Record (EHR) system of Parc de Salut Mar Barcelona (PSMar) which is a complete healthcare services organisation. The information system includes and shares the clinical information of two general hospitals (Hospital del Mar and Hospital de l'Esperança), one mental health care centre (Centre Dr. Emili Mira) and one social-healthcare centre (Centre Fòrum) including emergency room settings, that are offering specific and different services in the Barcelona city area (Spain). At present, IMASIS includes clinical information from around 1 million patients with at least one diagnosis and who have used the services of this healthcare system since 1990 and from different settings such as admissions, outpatients, emergency room and major ambulatory surgery. The average follow-up period per patient is 6.4 years.

8.5 Study size

No sample size has been calculated as this is a descriptive study. Prevalence and Incidence of opioid use among the study population will be estimated as part of Objective 1. Feasibility counts are provided in the Appendix.

8.6 Data analysis

This section describes the details of the analysis approach and rationale for the choice of analysis, with reference to the D1.3.8.3 Complete Catalogue of Data Analysis which describes the type of analysis in function of the study type.

The analysis will include calculation of population-based incidence rates and prevalence, as described in section 9.7.5.1 – Population-level drug utilisation study, characterisation of patient-level baseline covariates for opioid users, percentages of indications, and descriptive statistics of treatment duration of opioid, as described in section 9.7.5.2 – Individual-level drug utilisation study.

8.6.1   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.

8.6.2   Patient privacy protection

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

8.6.3   Statistical model specification and assumptions of the analytical approach considered

R-packages

We will use the R package "DrugUtilization" for the patient-level drug utilisation analyses including patient-level characterisation, and "IncidencePrevalence package"[11] 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, using start and end date of the exposure. 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 ≤ 7 days. The time between the two joined eras will be considered as exposed by the first era as shown in **Figure 2**, first row. Note: dose is not considered for this study.

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	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$

first exposure
time = x_1, dose = d_1

gap
time = x_{12}

second exposure
time = x_2, dose = d_2
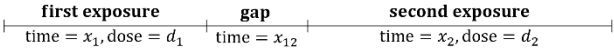
Figure 2. Gap era joint mode.

If two eras start at the same date, the overlapping period will be considered exposed by both. We will not consider repetitive exposure.

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. For each patient, at least 365 days of data availability will be required prior to that prescription. New users will be required to not have been exposed to the drug of interest for at least 365 days prior the current prescription. If the start date of a prescription does not fulfil the exposure washout criteria of 365 days of no use, the whole exposure is eliminated.

8.6.4   Methods to derive parameters of interest

Calendar time

Calendar time will be based on the calendar year of the index prescription.

Age

Age at index date will be calculated using January 1st of the year of birth as proxy for the actual birthday. We will use 10-year age bands for stratification for population-level analyses: 1-10,11-20, 21-20 […] and >80

Sex

Results for population-level analyses will be presented stratified by sex.

Indication

Indications will be assessed based on a high-level approach considering the most frequent conditions (all databases) and procedures (hospital database only) recorded at the date of treatment start/ in the week/month before treatment start.

Characterisation of patient-level features

Patient characterisation by pre-defined conditions/medications of interest before/on index date (= date of prescription) will be provided for different classifications for opioids [as introduced in section 9.3.1 "Exposures"] overall and in patients with history of cancer/no history of cancer, namely for (1) opioids overall, (2) for the 10 most frequent opioids in each database, (3) weak/potent opioids and (4) transdermal/oral/parenteral opioids, stratified for database/country. Co-variates will be extracted for the following time intervals: Concepts in the "condition" and "drug" domain will be assessed for anytime to -366 days [conditions only], -365 days to -181 days, -180 to -1 day before index date, and at index date. List of pre-defined conditions/medications of interest will be given in section 9.3.3.2 "Covariates for patient-level drug utilisation study"

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

8.6.5.1 Population-level drug utilisation study

Prevalence and incidence calculations will be conducted separately for (1) opioids overall, (2) by drug substance (incl. combinations and products for all indications), (3) by strength (weak/potent opioids) for those opioids where strength is labelled by the WHO, (4) by route (oral, transdermal or parenteral) for overall opioids and stratified by history of cancer.

Prevalence calculations

Prevalence will be calculated as annual period prevalence which summarises the total number of individuals who use the drug of interest during a given year divided by the population at risk of getting exposed during that year. Therefore, period prevalence gives the proportion of individuals exposed at any time during a specified interval. Binomial 95% confidence intervals will be calculated.
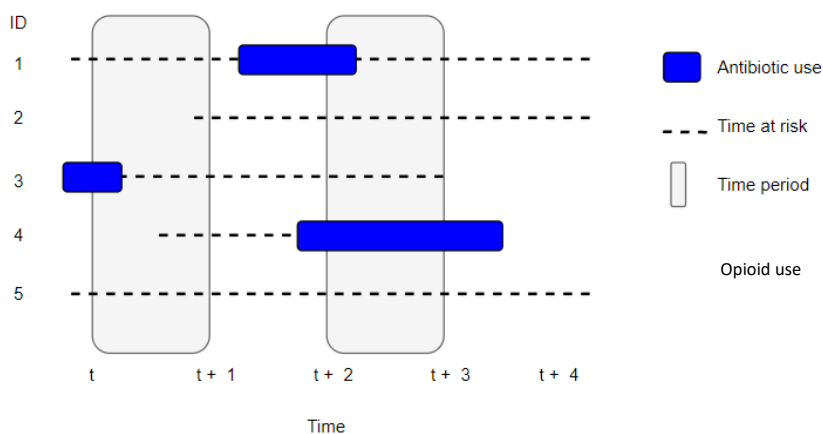

Figure 3. Period prevalence example**.**

An illustration of the calculation of period prevalence is shown below in **Figure 3**. Between time t+2 and t+3, two of the five study participants are opioid users giving 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 an opioid user, giving a prevalence of 20%.

Incidence calculations

Annual incidence rates of the opioid of interest will be calculated as the of number of **new users** after 356 days (180 days) of no use 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 during the study period. Or if they do not have a drug exposure, they will contribute time at risk up as described above in section 9.2.2 (study period and end of follow-up). Incidence rates will be given together with 95% Poisson confidence intervals.

An illustration of the calculation of incidence of opioid use is shown below in **Figure 4**. Patient ID 1 and 4 contribute time at risk up to the point at which they become incident users of opioid. Patient ID 2 and 5 are not seen to use opioid and so contribute time at risk but no incident outcomes. Meanwhile, patient ID 3 first contributes time at risk starting at the day when the washout period of a previous exposure, before study start, has ended before the next exposure of opioid is starting. A second period of time at risk again starts after the washout period. For person ID 4, only the first and third exposures of opioid count as incident use, while the second exposure starts within the washout period of the first exposure. The time between start of the first exposure until the washout period after the second exposure is not considered as time at risk.
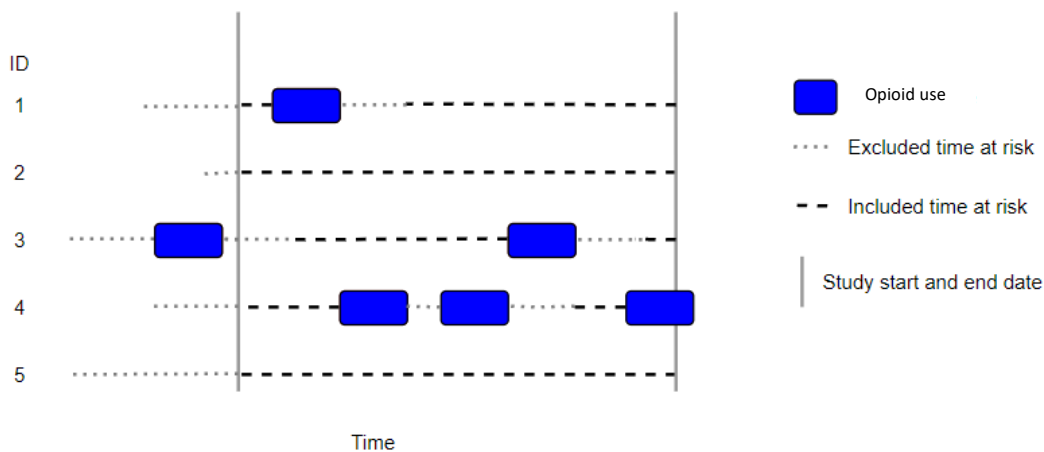

Figure 4. Incidence example.

8.6.5.2   Patient-level drug utilisation study

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

For each concept extracted before/at index date, the number of persons (N, %) with a record within the pre-specified time windows will be provided.

Indication

Indications will be assessed based on a high-level approach considering the 10 most frequent conditions (all databases) and procedures (hospital database only) recorded at the date of treatment

start/ in the week/month before treatment start. The number of persons (N, %) with a record of the respective indication will be provided.

Treatment duration

Treatment duration will be calculated as the duration of the first treatment era of the opioid of interest during the study period. Treatment duration will be summarised providing the minimum, p25, median, p75, and maximum 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.

8.6.6 Description of sensitivity analyses.

Table 9. Sensitivity analyses – rationale, strengths and limitations.

	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
Window to assess indication of use	Indication of use will be explored at index date (ID), and in a period of [-30 to ID] days of the index date and in a period from [-7 to ID] days before index date	Indication of use might not always be recorded on the date of prescription of the opioid of interest	Proportion of patients with an indication of use might increase.	Potential misclassification of indication of use if the disease code registered in the week/month before has nothing to do with prescription of the opioid of interest

8.7 Evidence synthesis

Results from analyses described in Section 9.7 will be presented separately for each database and no pooling of results will be conducted.

9. 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.

10. QUALITY CONTROL

General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, it is expected that data partners will have run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard). This tool provides numerous checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values. Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

When defining cohorts for drugs, a systematic search of possible codes for inclusion will be identified using CodelistGenerator R package (https://github.com/darwin-eu/CodelistGenerator). A pharmacist will review the codes of the opioids of interest. This software allows the user to define a search strategy and using this will then query the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, DrugExposureDiagnostics[12] will be run if needed to assess the use of different codes across the databases contributing to the study.

The study code will be based on two R packages currently being developed to (1) estimate Incidence and Prevalence and (2) characterise drug utilisation using the OMOP common data model. 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.

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. For databases, where duration cannot be calculated due to e.g. missing information on quantity, dosing or end date, treatment duration will not be provided.

In addition, the recording of events used for patient characterisation and identification of the (potential) indication may vary across databases and recording of indication may be incomplete.

12. GOVERNANCE BOARD

EBB, SIDIAP, IMASIS and CDWBordeaux will require to undergo their respective ethical approvals.

13. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

In agreement with the new guideline on good pharmacovigilance practice (EMA/873138/2011), there will be no requirement for expedited reporting of adverse drug reactions as only secondary data will be used in this study.

14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

14.1 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, and made available at EUPAS

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.

15. OTHER ASPECT

None.

16. REFERENCES

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17.   ANNEXES

Appendix I: Lists with preliminary concept definitions for exposure

Appendix II: Feasibility counts

Appendix III: ENCePP checklist for study protocols

APPENDIX I: Lists with preliminary concept definitions for exposure

Prescriptions will be identified based on the relevant ingredient. Non-systemic products will be excluded from the code list.

Substance Name	Concept Id	No record counts in databases expected based on feasibility
acetyldihydrocodeine	21603407	
alfentanil	19059528	
anileridine	19032662	X
bezitramide	37493802	X
butorphanol	1133732	X
buprenorphine	1133201	
codeine	1201620	
dezocine	19088393	X
dimemorfan	36852751	
dextromethorphan	1119510	
dextromoramide	19021940	
dextropropoxyphene	1153664	X
dihydrocodeine	1189596	
ethylmorphine	19050414	
fentanyl	1154029	
hydrocodone	1174888	
hydromorphone	1126658	
ketobemidone	40798904	
meptazinol	19003010	
meperidine (pethidine)	1102527	
methadone	1103640	
morphine	1110410	
nicomorphine	37493805	
normethadon	19015787	X
nalbuphine	1114122	
noscapine	19021930	
oliceridine	37002667	X
opium	923829	
oxycodone	1124957	
oxymorphone	1125765	X
papaveretum	19129648	
pentazocine	1130585	
phenazocine	19132884	
phenoperidine	19132889	X
pholcodine	19024213	
pirinitramide	19134009	
propoxyphene	1153664	
remifentanil	19016749	
sufentanil	19078219	
tapentadol	19026459	
thebacon	40799139	
tilidine	19002431	
tramadol	1103314	

Substance Name	Concept Id	No record counts in databases expected based on feasibility
naloxone	1114220	
buprenorphine/naloxone	45776270, 37498350, 40015149, 1970413	
oxycodone/naloxone	21160441, 41017321, 45774941, 36269469	
pentazocine/naloxone	40063474	
tilidine/naloxone	40063477, 43799912, 41298261, 36272016, 40063476, 36264356	

APPENDIX II: Feasibility counts

Table 1. Feasibility record counts per database.

Concept Id	Name	Bordeaux University Hospital#	IPCI#	IQVIA Belgium#	SIDIAP#	Estonian Biobank#	DK-DHR#	NLHR#	IMASIS#
19059528	alfentanil		100				100		32,800
1133201	buprenorphine	4,000	26,500	7,300	80,200	400	473,000	236,100	1,500
1201620	codeine	16,300	809,900	192,100	2,884,800	100,700	2,883,800	2,589,900	5,900
1119510	dextromethorphan	200	9,200	151,400	962,900		157,900	100	1,400
19021940	dextromoramide		100				300		
35197951	dimemorfan phosphate				656,400*				
1189596	dihydrocodeine	200		93,900	8,600	3,200		200	
19050414	ethylmorphine	100		29,000			22,100	1,773,000	
1154029	fentanyl	2,800	77,800	24,200	283,600	600	264,500	52,600	149,000
1174888	hydrocodone							1,400	
1126658	hydromorphone	200	400	500	8,200		2,200	200	200
40798904	ketobemidone						141,400	50,700	
1102527	meperidine		200		700	100	108,000	3,800	800
19003010	meptazinol								
1103640	methadone	2,600	5,100	100	3,900	500	131,700	8,000	3,500
1110410	morphine	172,000	64,200	3,700	108,500	1,300	1,662,900	67,500	76,300
1114122	nalbuphine	16,200							
37493800	Nicomorphine hydrochloride						201,700*		
19021930	noscapine		47,100	5,300	17,300		32,500	15,500	
923829	opium	29,300	200	100			1,879,900	4,000	
1124957	oxycodone	58,600	240,100	19,700	71,000	6,600	1,061,100	507,600	3,200
19129648	papaveretum								
1130585	pentazocine		100	100			5,200	100	
19132884	phenazocine								

Concept Id	Name	Bordeaux University Hospital[#]	IPCI[#]	IQVIA Belgium[#]	SIDIAP[#]	Estonian Biobank[#]	DK-DHR[#]	NLHR[#]	IMASIS[#]
19024213	pholcodine	100		10,600					
19134009	pirinitramide		200	300					
1153664	propoxyphene	900	200	100			113,600		
19016749	remifentanil	600					100		16,500
19078219	sufentanil	1,300	100				200		16,100
19026459	tapentadol		4,500	900	124,500		19,300	55,800	3,500
40799139	thebacon			100					
19002431	tilidine			13,100					
1103314	tramadol	275,100	562,800	255,000	2,873,700	90,200	5,105,800	1,801,700	113,100

[#]Drug era record counts unless otherwise specified, *Drug exposure record counts.

APPENDIX III: ENCePP checklist

ENCePP Checklist for Study Protocols (Revision 4)

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

Study title: DARWIN EU® - Drug utilisation study of prescription opioids.
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EU PAS Register® number: EUPAS1000000479
Study reference number: P3-C2-002

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]	☒	☐	☐	
1.1.2 End of data collection[2]	☐	☐	☒	
1.1.3 Progress report(s)	☐	☐	☒	Overview and 5
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:	☒	☐	☐	
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)	☒	☐	☐	6, 7
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 generalized)	☒	☐	☐	

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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 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

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)	☒	☐	☐	8.1 and 8.7.5.1
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
4.2 Is the planned study population defined in terms of:				8.2.1
4.2.1 Study time period	☒	☐	☐	
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)	☒	☐	☐	8.2.3

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 categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.3.1
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 categorized according to time windows?	☒	☐	☐	8.3.1
5.4 Is intensity of exposure addressed? (e.g., dose, duration)	☒	☐	☐	8.7.3
5.5 Is exposure categorized 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:

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:

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:

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:

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)	☒	☐	☐	8.4
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?	☒	☐	☐	8.4 and 8.3.3
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)	☒	☐	☐	8.4 and 8.7.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, 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)	☒	☐	☐	8.4 and 8.7.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.4

Section 9: Data sources	Yes	No	N/A	Section Number
9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.7
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	8.7
10.4 Are stratified analyses included?	☒	☐	☐	8.7
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?	☒	☐	☐	8.7.6

Comments:

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)	☒	☐	☐	8.8
11.2 Are methods of quality assurance described?	☒	☐	☐	8.8
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				8.9
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:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	9
13.3 Have data protection requirements been described?	☒	☐	☐	9

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)?	☒	☐	☐	11
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	11

Comments:

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Date: 06/02/2025

Signature: A. Lam