Study Protocol Phase II C1-002

08/08/2023

Version 2.1

TABLE OF CONTENTS

DOCUMENT HISTORY

Version	Date	Description
V1.0	25/05/2023	**Submission to EMA**
V2.0	27/06/2023	**Version 2 including comments from EMA**
V2.1	08/08/2023	**EUPAS register number added**

Study Title	DARWIN EU® - Drug utilization study of prescription opioids.
Protocol version identifier	V2.1
Date of last version of protocol	8 August 2023
EU PAS register number	EUPAS105641
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 2012-2022, stratified by age, sex, calendar year and country, as well as characterisation of new users, indications and treatment duration stratified by calendar year and country
Countr-ies of study	Estonia, Germany, Belgium, The Netherlands, France, Spain, Finland
AuthorAuthors	Junqing Xie, Annika Jödicke

LIST OF ABBREVIATIONS

Acronyms/terms	Description
ACI VARHA	Auria Clinical Informatics VARHA
CDM	Common Data Model
CHUBX	Bordeaux University Hospital
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real World Interrogation Network
DUS	Drug Utilization 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
IPCI	Integrated Primary Care Information Project
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. MARKETING AUTHORISATION HOLDER

N/A

3. 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	Organization
Principal Investigator(s)	Annika Jödicke Junqing (Frank) Xie	University of Oxford
Data Scientist(s)	Marti Catala Sabate Yuchen Guo Mike Du	University of Oxford
Clinical Epidemiologist	Daniel Prieto Alhambra	University of Oxford
Statistician	NA	
Data Manager	NA	
Data Partner*	**Names**	**Organization**
Local Study Coordinator/Data Analyst	James Brash	IQVIA
	Talita Duarte Salles	IDIAP JGol
	Raivo Kolde	University of Tartu
	Mees Mosseveld	Erasmus MC
	Tommi Kauko	Varha
	Romain Griffier	CHU Bordeaux

*Data partners' role is only to execute code at their data source. These people do not have an investigator role.

4. ABSTRACT (STAND ALONE SUMMARY OF THE STUDY PROTOCOL)

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 utilization patterns are imperative. A drug utilization 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 calendar year, age, sex and country/database during the study period 2012-2022.

(ii) To determine duration of prescription opioid use, as well as characteristics of new users and indication for opioid prescribing/dispensing, all stratified by calendar year and country/database.

Research Methods

Study design

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

Population

Population-level utilization of opioids: All people registered in the respective databases on 1st of January of each year in the period 2012-2022 (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 <1year will be excluded.

New users of opioids in the period between 1/1/2012 and 31/12/2022 (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 [or 6 months for sensitivity analyses], will be included for incidence rate calculations in Objective 1.

Patient-level drug utilization: New users of opioids in the period between 1/1/2012 and 31/12/2022 (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 12months [6 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 Disease Analyzer Germany (IQVIA DA Germany), Germany
3. IQVIA LBD Belgium, Belgium
4. Integrated Primary Care Information Project (IPCI), The Netherlands
5. The Information System for Research in Primary Care (SIDIAP), Spain
6. Clinical Data Warehouse of Bordeaux University Hospital (CHUBX), France
7. Auria Clinical Informatics VARHA (ACI Varha), Finland

Sample size

No sample size has been calculated.

Data analyses

Population-level drug utilisation will be conducted in all databases, with ACI VARHA not contributing to the prevalence analyses. Patient-level DUS analyses will be conducted in all databases, with ACI VARHA not contributing to the analysis of duration of opioid prescriptions as duration of use is not reliably recorded in their inpatient records.

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: Large-scale patient-level characterization 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.

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
Version 2.1	08/08/2023	Document history	update	EUPAS register number added

6. MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE
Draft Study Protocol	19/05/2023
Final Study Protocol	27/06/2023
Creation of Analytical code	July 2023
Execution of Analytical Code on the data	July 2023
Interim Study Report (if applicable)	NA
Draft Study Report	August 2023
Final Study Report	To be confirmed

7. 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 utilization patterns of opioids among this demographic[6].

A drug utilization 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.

8. 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) and route (oral, transdermal or parenteral)), stratified by calendar year, age, sex and country/database during the study period 2012-2022.
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 2012-2022 (or the latest available, whatever comes foirst), 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 <1year will be excluded. New users of opioids in the period between 1/1/2012 and 31/12/2022 (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 [6 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 , namely1st of January for each calendar year between 2012-2022 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 (e.g. 31st December 2022), whatever comes first.
Setting:	Inpatient and outpatient setting using data from the following 7 data sources: EBB [Estonia], IQVIA DA Germany [Germany], IQVIA LBD

	Belgium [Belgium], SIDIAP [Spain], IPCI [The Netherlands], CHUBX [France], ACI VARHA [Finland]
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, all stratified calendar year and country/database.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	New users of opioids in the period between 1/1/2012 and 31/12/2022 (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[6 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 (31st December 2022), whatever comes first.
Setting:	Inpatient and outpatient setting using data from the following 7 data sources: EBB [Estonia], IQVIA DA Germany [Germany], IQVIA LBD Belgium [Belgium], SIDIAP [Spain], IPCI [The Netherlands], CHUBX [France], ACI VARHA [Finland]
Main measure of effect:	Duration of opioid use (first treatment era) expressed as minimum, p25, median, p75, and maximum days Large-scale characterisation for new opioid users (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 recorded in the month/week before/at the date of treatment start.

9. RESEARCH METHODS

9.1 Study Design

A cohort study will be conducted using routinely-collected health data from 7 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 characterize individual-level opioid utilization in terms of summary patient characteristics, indication and duration of use.

9.2 Study Setting

9.2.1 Study population

The study cohort will comprise all individuals present in the database during the study period (2012-2022) and with at least 365 days of data availability before the day they become eligible for study inclusion. Therefore, children aged <1year 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 31/12/2022 (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 [6 months],

9.2.2 Study period and follow-up

The study period will be from the 1st of January 2012 until the earliest of either 31st December 2022 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 (2012-2022) 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 (2012-2022) and with at least 1 year of valid database history	Multiple	Incident	[-365 to ID, [sensi-tivity: -180 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 2022) 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.

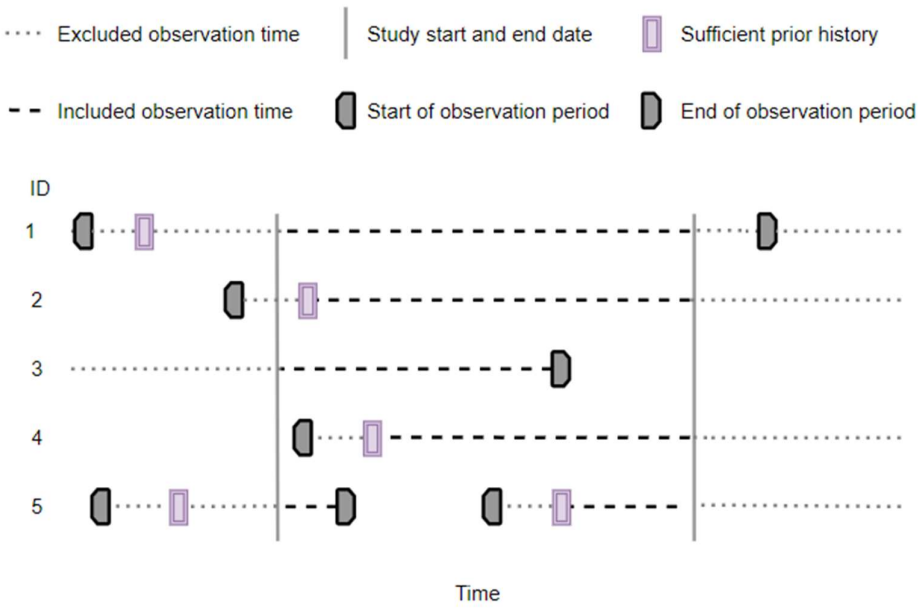


Figure 1: Included observation time for the denominator population

9.2.3 In- and exclusion criteria

9.2.3.1 Population-level Utilisation of opioids

The study cohort will comprise all individuals present in the period 2012-2022 (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 31/12/2022 (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 [6 months],

9.2.3.2 Patient-level Utilisation of opioids

All new users of opioids, after 365days [180days] of no use of the specific opioid /substance /strength/ route, in the period between 01/01/2012 and 31/12/2022 (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 2012-2022 (or the latest available)	All individuals present in the period 2012-2022 (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 3650days [180days] before a "new" prescription	After	180days, 365days	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

9.3 Variables

9.3.1 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		X	phenoperidine		X
dextromethorphan			pholcodine		
dextromoramide			pirinitramide		
dextropropoxyphene		X	propoxyphene		
dihydrocodeine			remifentanil		
ethylmorphine			sufentanil		
fentanyl	potent		tapentadol	potent	
hydrocodone	weak	X	thebacon		
hydromorphone	potent		tilidine		
ketobemidone			tramadol	weak	
meptazinol					
meperidine (pethidine)			naloxone		
methadone	potent				
morphine	potent		buprenorphine/naloxone		
nicomorphine		X	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, , -180 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

9.3.2 Outcomes

N/A

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

9.3.3.1 Covariates for stratification in population-level drug utilization study:

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

9.3.3.2 Covariates for patient-level drug utilization study:

- Large-scale characterisation of baseline characteristics: the operational definition of the covariates is described in the Table 7 below. 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 recorded in the month/week before/at the date of treatment start. The top 10 most frequent co-morbidities from large-scale patient characterization 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 from large-scale patient characterization	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
Large-scale summary characteristics of new users	Large-scale patient-level characterization with regard to baseline co-variates	Counts	Demographics, co-morbidities and co-medication at index date (ID), and within anytime to 366 days before ID, 365 to-181days before ID, and 180 to 1day before ID	Biobank, primary and secondary care	SNOMED, RxNorm	N/A	Persons with new use during the study period	N/A	N/A

9.4 Data sources

This study will be conducted using routinely collected data from 7 databases in 6 European countries (5 EU countries and United Kingdom). All databases were previously mapped to the OMOP CDM.

1. Estonian Biobank (EBB), Estonia
2. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
3. IQVIA LBD Belgium, Belgium
4. Integrated Primary Care Information Project (IPCI), The Netherlands
5. The Information System for Research in Primary Care (SIDIAP), Spain
6. Clinical Data Warehouse of Bordeaux University Hospital (CHUBX), France
7. Auria Clinical Informatics VARHA (ACI VARHA), Finland

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 conducted among 7 out of the 10 databases onboarded for DARWIN EU® in 2022. The selection of databases for this study was performed based on data reliability and relevance for the proposed research question and feasibility counts.

5 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. To avoid capturing the same persons multiple times in different databases, only one database per country/region was included.

EBB, IQVIA DA Germany, IQVIA LBD Belgium, IPCI, SIDIAP and CHUBX fulfil the criteria required for a population-level drug utilisation study and patient-level drug utilisation study. ACI Varha will contribute to the population prevalence analyses and duration of opioid use as duration of use is not reliably recorded in their inpatient records.

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	1.39 million	Please see Appendix	1/12/2022
France	CHUBX	Database covers hospital care setting where opioid may be initiated	Secondary care (in and outpatients)	EHR	2.13 million		1/3/2023
Spain	SIDIAP	Databases covers primary care / outpatient specialist care setting where opioid prescriptions are issued.	Primary care	EHR	5.8 million		1/6/2022
Belgium	IQVIA LBD Belgium		primary care, outpatient specialist care	EHR	0.4 million		1/1/2022
Germany	IQVIA DA Germany		Primary care, outpatient specialist care	EHR	8.5 million		1/9/2022
Finland	ACI VARHA	Database covers hospital care setting where opioid may be initiated	Secondary care (in and outpatients)	EHR	0.7 million		31/12/2021
Estonia	EBB	Database covers primary care setting where opioid prescriptions are issued.	Biobank	Claims data	0.2 million		31/3/2021

IPCI = Integrated Primary Care Information Project; CHUBX= 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. 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 2.8 million patients out of a Dutch population of 17M starting in 1996[7]. The median follow-up is 4.7 years. 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 (CHUBX), 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 10 years. 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.

Disease Analyser (DA) Germany, Germany (IQVIA)

DA Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings[10]. Data coverage includes more than 34M distinct person records out of at total population of 80M (42.5%) in the country and collected from 2,734 providers. Patient visiting more than one provider are not cross identified for data protection reasons and therefore recorded as separate in the system. Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates. Germany has no mandatory GP system and patient have free choice of specialist. As a result, data are collected from visits to 28.8% General, 13.4% Orthopaedic Surgery, 11.8% Otolaryngology, 11.2% Dermatology, 7.7% Obstetrics/Gynaecology, 6.2% various Neurology and Psychiatry 7.0% Paediatric, 4.6% Urology, 3.7% Cardiology, 3.5% Gastroenterology, 1.5% Pulmonary and 0.7% Rheumatology practices.

Drugs are recorded as prescriptions of marketed products. No registration or approval is required for drug utilization studies.

Auria Clinical Informatics at Turku University Hospital, Hospital District of Southwest Finland (ACI VARHA)
The data covers the patient register at the Hospital District of Southwest Finland (ACI VARHA), containing Turku University Hospital, which is one of the five university hospitals in Finland. It covers the public specialist health care and most emergency health care in the area of Southwest Finland (Varsinais-Suomi) for all demographic groups (765K persons). The data is utilized for scientific research from the data lake in the ACI VARHA under the Finnish legislation (The Act on Secondary Use of Health and Social Data). The most relevant data domains are patients, visits, inpatient episodes, diagnoses, laboratory results, procedures, medication, pathology, radiology, radiotherapy and chemotherapy.

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.

9.5 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

9.6 Data Management

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

9.7 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 utilization study, characterization 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 utilization study.

9.7.1 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.

9.7.2 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.

9.7.3 Statistical model specification and assumptions of the analytical approach considered

R-packages

We will use the R package "DrugUtilization" for the patient-level drug utilization analyses including patient-level characterization, and "IncidencePrevalence package"[11] for the population-level estimation of drug utilization.

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.

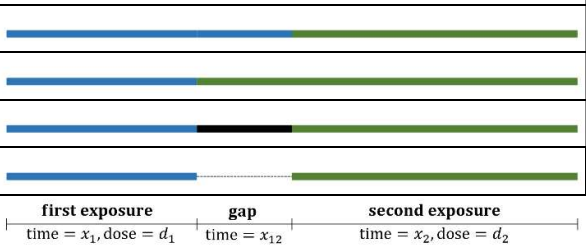
Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"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

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 180 days (365days) prior the current prescription. If the start date of a prescription does not fulfil the exposure washout criteria of 180 days (365days) of no use, the whole exposure is eliminated.

9.7.4 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 birthdayWe 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 recorded at the date of treatment start/ in the week/month before treatment start.

Characterization of patient-level features

Large scale patient characterisation before/on index date (= date of prescription) will be provided for different classifications for opioids [as introduced in section 9.3.1 "Exposures"], 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 -366days [conditions only], -365days to -181days, -180 to -1 day before index date, and at index date.

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

9.7.5.1 Population-level drug utilization 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 and (4) by route (oral, transdermal or parenteral) for overall opioids.

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.

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%.

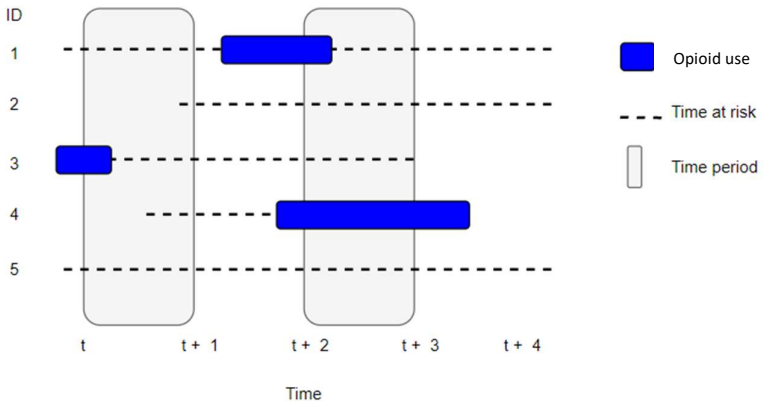


Figure 3: Period prevalence example

Incidence calculations

Annual incidence rates of the opioid of interest will be calculated as the of number of **new users** after 356days (180days) 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.

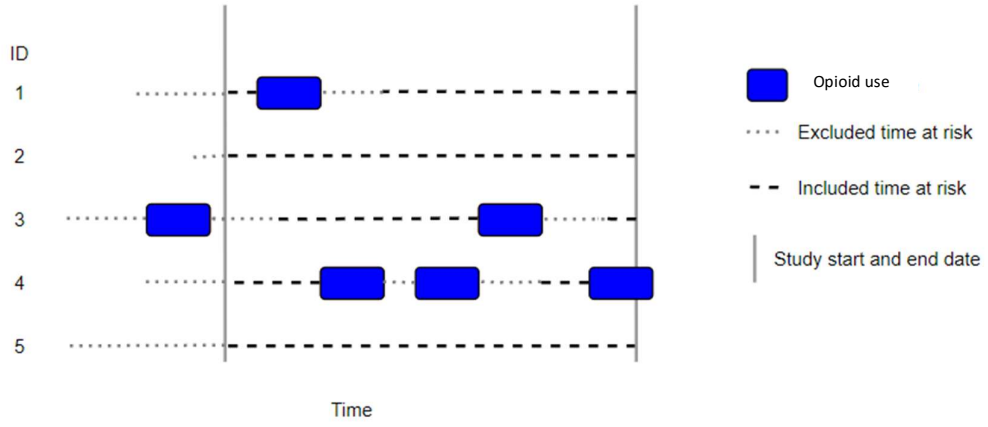


Figure 4: Incidence example

9.7.5.2 Patient-level drug utilization 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 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 summarized 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.

9.7.6 Description of sensitivity analyses.

Table 9 describes the 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
Washout window to define new/incident user	Length of washout window	Washout window of 1 year might be too long as opioids can be used for acute conditions	Number of new users might increase with shorter washout period of 180days	Washout period of 180days might be too short
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

9.8 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) characterize drug utilization 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.

9.9 Limitation 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, e.g. ACI Varha, treatment duration will not be provided.

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

9.10 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.

10. PROTECTION OF HUMAN SUBJECTS

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 in order 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.

11. 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.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 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.

13. REFERENCES

1. Seth P, Scholl L, Rudd RA, Bacon S. Overdose Deaths Involving Opioids, Cocaine, and Psychostimulants - United States, 2015-2016. MMWR Morb Mortal Wkly Rep. 2018;67(12):349-358. doi:10.15585/mmwr.mm6712a1. .
2. Centers for Disease Control and Prevention, National Center for Injury Prevention and Control, Department of Health and Human Services. Annual Surveillance Report Of Drug-related Risks And Outcomes. https://www.cdc.gov/drugoverdose/pdf/pubs/2019-cdc-drug-surveillance-report.pdf. Accessed May 16, 2023. .
3. van Amsterdam J, van den Brink W. The Misuse of Prescription Opioids: A Threat for Europe? Current drug abuse reviews. 2015;8(1):3-14. doi:10.2174/1874473708011506111842l8. .
4. Kennedy J, Wood EG, Wu C-H. Factors associated with frequent or daily use of prescription opioids among adults with chronic pain in the United States. The Journal of international medical research. 2023;51(1):3000605221149289. doi:10.1177/03000605221149289. .
5. Sullivan MD, Edlund MJ, Zhang L, Unützer J, Wells KB. Association between mental health disorders, problem drug use, and regular prescription opioid use. Arch Intern Med. 2006;166(19):2087-2093. doi:10.1001/archinte.166.19.2087. .
6. Dufort A, Samaan Z. Problematic Opioid Use Among Older Adults: Epidemiology, Adverse Outcomes and Treatment Considerations. Drugs & Aging. 2021;38(12):1043-1053. doi:10.1007/s40266-021-00893-z. .
7. Vlug A, van der Lei J, Mosseveld B, van Wijk M, van der Linden P, MC S. Postmarketing surveillance based on electronic patient records: the IPCI project. *Methods of information in medicine*. 1999;38:339-44.
8. Brat GA, Weber GM, Gehlenborg N, et al. International electronic health record-derived COVID-19 clinical course profiles: the 4CE consortium. *NPJ Digit Med*. 2020;3:109. doi:10.1038/s41746-020-00308-0
9. Garcia-Gil Mdel M, Hermosilla E, Prieto-Alhambra D, Fina F, Rosell M, Ramos R. Construction and validation of a scoring system for the selection of high-quality data in a Spanish population primary care database (SIDIAP). *Informatics in primary care*. 2011;19(3):135-45.
10. Rathmann W, Bongaerts B, Carius H, Kruppert S, Kostev K. Basic characteristics and representativeness of the German Disease Analyzer database. *Int J Clin Pharmacol Ther*. 2018;56(10):459-466.
11. Edward Burn etal. IncidencePrevalence: Estimate Incidence and Prevalence using the OMOP Common Data Model.Version: 0.3.0. Published: 2023-05-07 https://cran.r-project.org/web/packages/IncidencePrevalence/index.html.
12. Ger Inberg et al. Diagnostics for OMOP Common Data Model Drug Records: Package 'DrugExposureDiagnostics'. Version 0.4.1. Date/Publication 2023-03-13. https://cran.r-project.org/web//packages//DrugExposureDiagnostics/DrugExposureDiagnostics.pdf.

14. 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	X
dextromethorphan	1119510	
dextromoramide	19021940	
dextropropoxyphene	1153664	X
dihydrocodeine	1189596	
ethylmorphine	19050414	
fentanyl	1154029	
hydrocodone	1174888	X
hydromorphone	1126658	
ketobemidone	40798904	
meptazinol	19003010	
meperidine (pethidine)	1102527	
methadone	1103640	
morphine	1110410	
nicomorphine	37493805	X
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	
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 DA Germany#	IQVIA Belgium#	SIDIAP#	Estonian Biobank*	ACI VARHA*
19059528	alfentanil		1,500					18,900
1133201	buprenorphine	3,400	31,800	93,400	8,100	68,500	600	40,600
1201620	codeine	600	2,334,400	1,159,800	190,100	2,483,600	84,200	216,200
1119510	dextromethorphan	200	15,500	90,100	168,700	892,400	100	500
19021940	dextromoramide		500		15,200			
1189596	dihydrocodeine	200		658,800	87,700	7,600	5,100	
19050414	ethylmorphine	100		100	30,300			13,800
1154029	fentanyl	1,900	88,600	187,400	22,400	202,800	2,300	80,400
1126658	hydromorphone	200	500	71,300	600	5,800		2,900
40798904	ketobemidone						100	
19003010	meptazinol							
1103640	methadone	1,900	6,200	9,200	100	2,700	2,200	1,900
1110410	morphine	137,000	71,400	113,700	2,900	70,600	4,100	16,900
1114122	nalbuphine	11,500	100	100				
19021930	noscapine		113,500	774,700	6,600	16,500	100	
923829	opium	3,100	900	800	100			
1124957	oxycodone	44,900	225,200	202,000	16,500	54,400	12,700	731,000
19129648	papaveretum							
1130585	pentazocine		2,200	200	200		100	
19132884	phenazocine							
19024213	pholcodine	100						
19134009	pirinitramide		100	1,800	300			
1153664	propoxyphene	800	5,300	300				
19016749	remifentanil	100	100					
19078219	sufentanil	1,300						
19026459	tapentadol		2,800	57,500	500	78,100	100	
40799139	thebacon				100			
19002431	tilidine			842,700	19,600			
1103314	tramadol	229,100	855,100	803,700	238,500	2,040,700	157,000	120,900

#Drug era counts, *Descendent record counts

APPENDIX III – ENCEPP CHECKLIST

ENCePP Checklist for Study Protocols (Revision 4)

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

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorization holders when submitting the protocol of a non-interventional post-authorization safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorization safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: DARWIN EU® - Drug utilization study of prescription opioids.
.

EU PAS Register® number:
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				Overview and 6 - milestones
1.1.1 Start of data collection[1]	☒	☐	☐	
1.1.2 End of data collection[2]	☐	☐	☒	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

[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	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	6- Background and 8- 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 generalized)	☒	☐	☐	
	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)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.1 and 9.7.5.1
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?	☒	☐	☐	9.4
4.2	Is the planned study population defined in terms of:				9.2.1
	4.2.1 Study time period	☒	☐	☐	
	4.2.2 Age and sex	☒	☐	☐	

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
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)	☒	☐	☐	9.2.3

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)	☒	☐	☐	9.3.1
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?	☒	☐	☐	9.3.1
5.4 Is intensity of exposure addressed? (e.g., dose, duration)	☒	☐	☐	9.7.3
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)	☐	☐	☒	

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilization, 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)	☒	☐	☐	9.4
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?	☒	☐	☐	9.4 and 9.3.3

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
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)	☒	☐	☐	9.4 and 9.7.3
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)	☒	☐	☐	9.4 and 9.7.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4
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?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7
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?	☒	☐	☐	9.7.6

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)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
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:				9.9
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?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10
13.3 Have data protection requirements been described?	☒	☐	☐	10

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?	☒	☐	☐	5

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)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Dr. Annika Jödicke

Date: 25/05/2023

Signature: A. Jödicke

CLICK OR TAP HERE TO ENTER TEXT.