Study Protocol

P4-C2-001

DARWIN EU® Drug Utilisation Study of prescription opioids

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Version 2.0

Public

Contents

Study Title	DARWIN EU® - Drug utilisation study of prescription opioids
Protocol version	V2.0
Date	02 June 2025
EUPAS number	EUPAS1000000615
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	None
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	Croatia, Germany, Hungary, Finland, Italy, Portugal, Sweden
AuthorAuthors	Amy Lam, Annika Jödicke

[1] This is a routine repeated study from P2-C1-002 (EUPAS105641) and P3-C2-002 (EUPAS1000000479).

LIST OF ABBREVIATIONS

Acronyms/terms	Description
ACI	Auria Clinical Informatics
CDM	Common Data Model
CDW Bordeaux	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
EMDB-ULSEDV	Egas Moniz Health Alliance database - Entre o Douro e Vouga
GP	General Practitioner
HI-SPEED	Health Impact - Swedish Population Evidence Enabling Data-linkage
ID	Index date
IMASIS	Institut Municipal Assistència Sanitària Information System
InGef RDB	InGef Research Database
IPCI	Integrated Primary Care Information Project
NAJS	Croatian National Public Health Information System
NLHR	Norwegian Linked Health Registry
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
POLIMI	Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SUCD	Semmelweis University Clinical Data
WHO	World Health Organisation

1. TITLE

DARWIN EU® - Drug Utilisation Study of prescription opioids

2. DESCRIPTION OF THE STUDY TEAM

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

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
Study Manager	Natasha Yefimenko	Erasmus MC
Data Partner*	**Names**	**Organisation**
Local Study Coordinator/Data Analyst	Luís Ruano Firmino Machado	Clinical Academic Center Egas Moniz Health Alliance (EMDB-ULSEDV)
	Tommi Kauko Mikael Högerman Annika Pirnes Otto Ettala Arho Virkki Pia Tajanen-Doumbouya	Hospital District of Southwest Finland (FinOMOP ACI Varha)
	Josephine Jacob Raeleesha Norris Alexander Harms Annika Vivirito	Institut für angewandte Gesundheitsforschung Berlin GmbH (InGef RDB)
	Karlo Pintarić Helena Ivanković Anamaria Jurčević Jakov Vuković Pero Ivanko	Croatian Institute of Public Health (NAJS)
	Gianluigi Galli Mauro Bucalo Vittoria Ramella Gabriele Guazzardi	Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (POLIMI)
	Huiqi Li Fredrik Nyberg Nicklas Pihlström Rickard Ljung	Läkemedelsverket (SMPA-GU)
	Ágota Mészáros Bagyura Zsolt István Kiss Loretta Zsuzsa Héja Tibor	Semmelweis University (SUCD)

*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 (not applicable in hospital databases), 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 (not applicable in hospital databases), 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 (not applicable in hospital databases), 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. Egas Moniz Health Alliance database - Entre o Douro e Vouga (EMDB-ULSEDV), Portugal
2. Auria Clinical Informatics (FinOMOP ACI Varha), Finland
3. Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED), Sweden
4. InGef Research Database (InGef RDB), Germany
5. Croatian National Public Health Information System (NAJS), Croatia
6. Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (POLIMI), Italy
7. Semmelweis University Clinical Data (SUCD), Hungary

Sample size

No sample size has been calculated.

Data analyses

Population-level drug utilisation and *patient-level DUS:* Analyses will be conducted in all databases. No duration will be calculated in databases which cannot provide explicit information on drug exposure end date.

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	06/05/2025	N/A	Update from routine-repeated study protocol (P3-C2-002, EUPAS1000000479)	This is a routine-repeated study.

Comparison with Previous Protocols

	P2-C1-002 (EUPAS105641)	P3-C2-002 (EUPAS1000000479)	P4-C2-001 (EUPAS1000000615)
Study period	2012-2022	2012-2024	2012-2024
Data partner			
CDW Bordeaux [France]	*	*	
DK-DHR [Denmark]		*	
EBB [Estonia]	*	*	
EMDB-ULSEDV [Portugal]			*
FinOMOP ACI Varha [Finland]	Remark 1		*
HI-SPEED [Sweden]			*
IMASIS [Spain]		*	
InGef RDB [Germany]			*
IPCI [The Netherlands]	*	*	
IQVIA DA Germany [Germany]	*		
IQVIA LBD Belgium [Belgium]	*	*	
NLHR [Norway]		*	
NAJS [Croatia]			*
POLIMI [Italy]			*
SIDIAP [Spain]	*	*	
SUCD [Hungary]			*
Reference study protocol	N/A	P2-C1-002 (EUPAS105641)	P3-C2-002 (EUPAS1000000479)
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	Protocol is updated as mentioned in the P3-C2-002 study report *deviation from study protocol* section - Prior data availability: no longer require 1-year prior data availability in hospital database - Assessment window for baseline characteristics:

		indication in hospital database - Sensitivity analysis: remove 6-month washout period	change from [-Inf, -366], [-365, -181], [-180, -1], [ID, ID] to [-Inf, -366], [-365, ID] - Type of cancer for cohort characteristics: update lymphoma with broad definition instead of separate Hodgkin lymphoma and non-Hodgkin lymphoma

Remark:

1. FinOMOP ACI Varha was included in the protocol of initial study P2-C1-002 (EUPAS105641) but did not conduct the study.

5. MILESTONES

Study deliverable	Timeline
Final Study Protocol	02/06/2025
Creation of Analytical code	May 2025
Execution of Analytical Code on the data	June – July 2025
Draft Study Report	31/08/2025
Final Study Report	To be confirmed by EMA

*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) and P3-C2-002 (EUPAS1000000479), 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 (not applicable to hospital databases), will participate in the population-level analysis (period prevalence calculation in Objective 1). 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 7 data sources: EMDB-ULSEDV [Portugal], FinOMOP ACI Varha [Finland], HI-SPEED [Sweden], InGef RDB [Germany], NAJS [Croatia], POLIMI [Italy], SUCD [Hungary]
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 (not applicable to hospital databases), 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 7 data sources: EMDB-ULSEDV [Portugal], FinOMOP ACI Varha [Finland], HI-SPEED [Sweden], InGef RDB [Germany], NAJS [Croatia], POLIMI [Italy], SUCD [Hungary]
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 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 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 (not applicable to hospital databases) before the day they become eligible for study inclusion.

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 (not applicable to hospital databases), 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 (not applicable to hospital databases).

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 (not applicable to hospital databases)	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 (not applicable to hospital databases)	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.

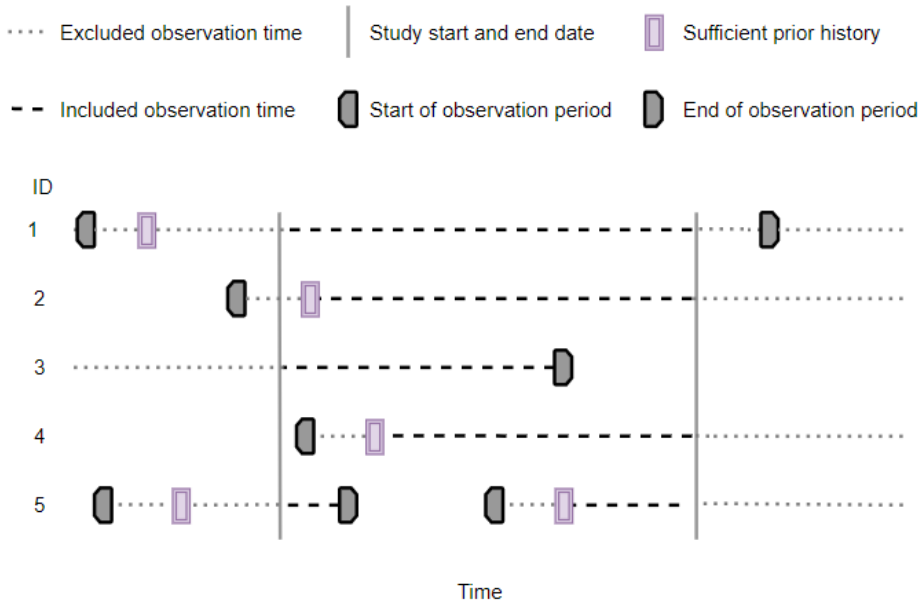


Figure 1. Included observation time for the denominator population.

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 (not applicable to hospital databases) 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 (not applicable to hospital databases), 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 (not applicable to hospital database)	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 (not applicable to hospital 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		X		noscapine		
alfentanil				oliceridine		X
anileridine		X		opium		
bezitramide		X		oxycodone	potent	
butorphanol		X		oxymorphone	potent	X
buprenorphine	potent			papaveretum		X
codeine	weak			pentazocine		
dezocine		X		phenazocine		X
dimemorfan phosphate		X		phenoperidine		X
dextromethorphan				pholcodine		
dextromoramide		X		pirinitramide		
dextropropoxyphene		X		propoxyphene		
dihydrocodeine				remifentanil		X
ethylmorphine				sufentanil		
fentanyl	potent			tapentadol	potent	
hydrocodone	weak	X		thebacon		X
hydromorphone	potent			tilidine		
ketobemidone				tramadol	weak	
meptazinol		X				
meperidine (pethidine)				naloxone		
methadone	potent					
morphine	potent			buprenorphine/naloxone		
nicomorphine hydrochloride		X		oxycodone/naloxone		
normethadon		X		pentazocine/naloxone		X
nalbuphine		X		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	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	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 (for outcome stratification: this covariate will be used to define opioid prescriptions/dispensations in people with/without history of cancer (numerator) in the overall population (denominator))

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, 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]	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 before ID to ID	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 7 databases from 7 European countries. All databases were previously mapped to the OMOP CDM.

1. Egas Moniz Health Alliance database - Entre o Douro e Vouga (EMDB-ULSEDV), Portugal
2. Auria Clinical Informatics (FinOMOP ACI Varha), Finland
3. Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED), Sweden
4. InGef Research Database (InGef RDB), Germany
5. Croatian National Public Health Information System (NAJS), Croatia
6. Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (POLIMI), Italy
7. Semmelweis University Clinical Data (SUCD), Hungary

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: The selection of databases for this study was performed based on data reliability and relevance for the research question and feasibility counts.

3 databases (HI-SPEED, InGef RDB, NAJS) include records from primary care and outpatient specialist care, as well as hospital data, where opioids are expected to be prescribed. 4 databases (EMDB-ULSEDV, FinOMOP ACI Varha, POLIMI, SUCD) 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
Portugal	EMDB-ULSEDV	Database covers both inpatient and outpatient records from secondary care where opioid prescriptions are used	Secondary care specialist, hospital inpatient care	EHR	95 thousand	Please see appendix.	31/08/2023
Finland	FinOMOP ACI Varha	Database covers secondary care specialist and hospital inpatient care where opioid prescriptions are issued.	secondary care specialist, hospital inpatient care	EHR	181 thousand		20/12/2024
Sweden	HI-SPEED	Database contains records from primary care GP, secondary care specialist and hospital inpatient care where opioid prescriptions are issued.	Primary care GPs, secondary care specialists, hospital inpatient care	Registry	10.6 million		10/09/2024
Germany	InGef RDB	Database contains claims data from primary care (GP and specialist), secondary care specialist and hospital inpatient care where opioid prescriptions are issued.	Primary care (GP, specialist), secondary care specialist, hospital inpatient care	Claims data	7.66 million		01/11/2024
Croatia	NAJS	Database contains records from primary care GP, secondary	Primary care GP, secondary	Registry	4.22 million		17/11/2023

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
		specialist and hospital inpatient care where opioid prescriptions are issued.	care specialist, hospital inpatient care				
Italy	POLIMI	Database contains records from secondary care specialist and hospital inpatient care where opioid prescriptions are issued.	Secondary care specialists, hospital inpatient care	EHR	89 thousand		14/02/2022
Hungary	SUCD	Database contains records from secondary care specialist and hospital inpatient care where opioid prescriptions are issued.	Secondary care specialist, hospital inpatient care	EHR	212 thousand		30/11/2024

EHR = Electronic Heath record, EMDB-ULSEDV = Egas Moniz Health Alliance database - Entre o Douro e Vouga; ACI = Auria Clinical Informatics; HI-SPEED = Health Impact - Swedish Population Evidence Enabling Data-linkage; InGef RDB = InGef Research Database; NAJS = Croatian National Public Health Information System; POLIMI = Research Repository @Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico; SUCD = Semmelweis University Clinical Data. Exposure is based on prescription or dispensation data according to the data type available in the dataset.

EMDB-ULSEDV (Portugal)

Unidade Local de Saúde de Entre Douro e Vouga (ULSEDV) is an integrated public medical care centre comprising both primary, secondary and tertiary healthcare. It fully serves approximately 274.000 patients of the municipalities of Santa Maria da Feira, Arouca, São João da Madeira, Oliveira de Azeméis, Vale de Cambra, Ovar and Castelo de Paiva. The ULSEDV includes 32 primary care centres assisted by three hospitals (Hospital de São Sebastião, Hospital São João da Madeira, and Hospital São Miguel), however the current database contains only hospital data. The median observation period is 9.5 years.

FinOMOP ACI Varha (Finland)

The data covers the patient register at the Hospital District of Southwest Finland (HDSF), 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. The data is utilized for scientific research from the data lake in the HDSF 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, chemotherapy, obstetrics and narrative patient reports, however there are also other data domains available. The median observation period is 8.4 years.

HI-SPEED (Sweden)

The Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED) study is a nationwide linked multi-register, regularly updated, observational study for timely response over time to scientific questions around effectiveness and safety of approved drugs that can arise suddenly, requiring rapid evidence for timely regulatory action - to protect patients' health and lives. The study data covers the whole Swedish population (about 10 million), with data on specialist care (National Patient Register), drug use (Prescribed Drug Register), cause of death (Cause-of-Death Register), sociodemographic data, and selected clinical data. Most data start from 2015; prescription drug data is available from 2018. The study population and all data are updated quarter-yearly. HI-SPEED builds on the predecessor project SCIFI-PEARL (Swedish COVID-19 Investigation for Future Insights - a Population Epidemiology Approach using Register Linkage) that was initiated in 2020 to conduct research on Covid-19 and pandemic-relations (https://www.gu.se/en/research/scifi-pearl). The median observation period is 9.7 years.

InGef RDB (Germany)

The InGef database comprises anonymized longitudinal claims data of about 10 million individuals across more than 70 statutory health insurance providers (SHIs) throughout Germany. Data are longitudinally linked over a period of currently ten years. Patients can be traced across health care sectors. All patient-level and provider-level data in the InGef research database are anonymised to comply with German data protection regulations and German federal law. German SHI claims data available in the InGef database includes information on demographics (year of birth, gender, death date if applicable, region of residence on administrative district level); hospitalizations; outpatient services (diagnoses, treatments; specialities of physicians); dispensing of drugs; dispensings of remedies and aids; and sick leave and sickness allowance times. In addition, costs or cost estimates from SHI perspective are available for all important cost elements. All diagnoses in Germany are coded using the International Classification of Diseases, version 10 in the German Modification (ICD-10-GM). The persistence (membership over time) is rather high in the InGef database: During a time period of 5 years (2009 to 2013), 70.6% of insurance members survived and remained insured with the same SHI without any gap in their observational time. Persons leaving one of the participating SHIs and entering another participating SHI, can be linked during yearly database consistency updates and are thus not lost over time. The InGef database is dynamic in nature, i.e. claims data are updated in an ongoing process and new SHIs may join or leave the database. By law, only the last 10 years of data are allowed to be used. At every new release this window shifts, dropping older data and adding new data. All ambulatory diagnosis records are recorded by calendar quarter, with diagnosis date set to the first date of calendar quarter.

NAJS (Croatia)

The National Public Health Information System (Nacionalni javnozdravstveni informacijski sustav - NAJS) is an organised system of information services by Croatian Institute of Public Health (CIPH). NAJS enables data collecting, processing, recording, managing and storing of health related data from health care providers as well as production and management of health information. NAJS contains medical and public health data collected and stored in health registries and other health data collections including cancer registry, mortality, work injuries, occupational diseases, communicable and non-communicable diseases, health events, disabilities, psychosis and suicide, diabetes, drug abuse and others. The median observation period is 9.3 years.

POLIMI (Italy)

Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, known simply as Policlinico of Milan, is a general hospital that can count on important excellence in different areas of care with a strong interdisciplinary focus. Given its nature as IRCCS – Institute for Research, Hospitalization and Health Care - in addition to care, it carries out biomedical and health research activities of a clinical and translational nature, involving the rapid transfer of therapies from the laboratories to the bedside of the sick person. The research activity is conducted in the different fields of medicine, from neurology to cardiology, from transplantation to hematology, to excellence of care in gynecology, neonatology, geriatrics and rare diseases. Our DWH was born a few years ago with the aim of helping researchers in identifying patient cohorts and in obtaining large amounts of data for their studies more easily. A few years later, thanks to the EHDEN Project, we were also able to introduce the CDM OMOP. Currently the DWH contains data from Hospitalization, Outpatients visits, Laboratory test, Therapies, Radiology, Anatomic Pathology and a REDCap instance for non-profit studies. The median observation period is 121 days.

SUCD (Hungary)

Semmelweis University is the largest provider of health care services in Hungary. Most of the departments cater for the most serious cases and patients requiring complex treatment, thus making the university a national health care provider. The overwhelming majority of patient data originates from Hungary, mainly from central region of the country: Budapest and Pest County. The database contains approximately 2 million individual patients across all care settings of the University since 2011. The hospital information system (MedSolution) is an integrated IT system provides functional support for inpatient and outpatient care processes and serves as an integrated platform for different diagnostic areas, and in some specific area it supports the registration of medications. It supports all kinds of hospital work processes from admission to discharge. The outpatient module serves as a platform for the registration of activities related to care episode within the outpatient specialist care. During the care provision data related to health state of the patient, the diagnosis, the documentation of requested examinations and medical consultations, prescribed medication, final reports and performed interventions are recorded. The functions of the inpatient module assist the care provision within the inpatient settings. It documents the health state of the patient at admission and during the hospital stay, along with the anamnesis, diagnosis, the performed examinations and interventions, hospital final reports and provided medication in some are of care provision such as chemotherapy. Among other modules the diagnostic module registers the requested laboratory and imaging examinations and records the laboratory results. The median observation period is 266 days.

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.

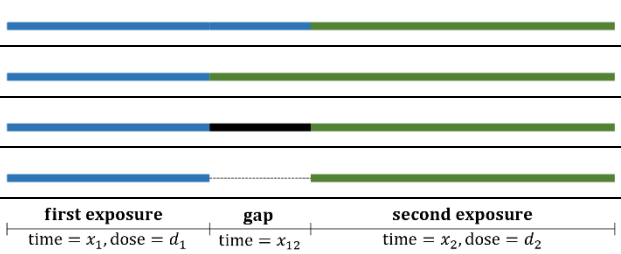
Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"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

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 except in hospital databases, 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] and from -365 days to 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.

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%.

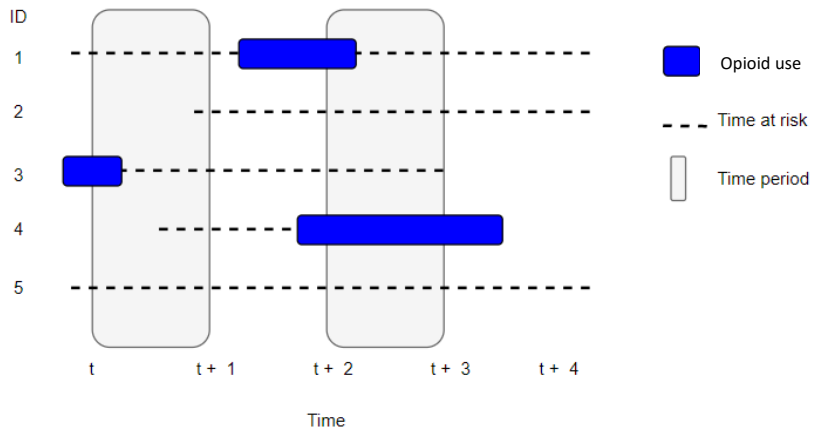


Figure 3. Period prevalence example**.**

Incidence calculations

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

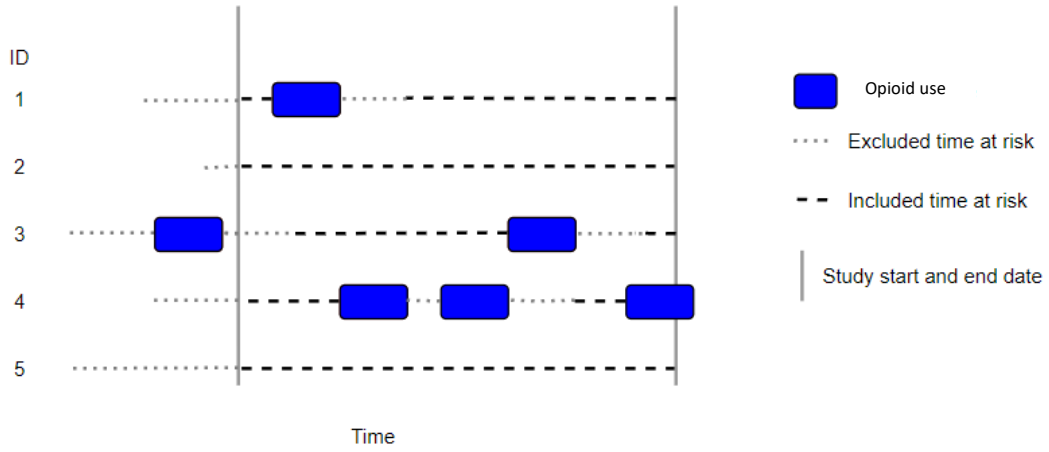


Figure 4. Incidence example.

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

EMDB-ULSEDV, FinOMOP ACI Varha, HI-SPEED and SUCD will require to undergo their respective ethical approvals. Internal approval will be required for POLIMII from Policlinico of Milan.

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. REFERENCES

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16. 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	X
alfentanil	19059528	
anileridine	19032662	X
bezitramide	37493802	X
butorphanol	1133732	X
buprenorphine	1133201	
codeine	1201620	
dezocine	19088393	X
dimemorfan phosphate	35197951	X
dextromethorphan	1119510	
dextromoramide	19021940	X
dextropropoxyphene	1153664	X
dihydrocodeine	1189596	
ethylmorphine	19050414	
fentanyl	1154029	
hydrocodone	1174888	X
hydromorphone	1126658	
ketobemidone	40798904	
meptazinol	19003010	X
meperidine (pethidine)	1102527	
methadone	1103640	
morphine	1110410	
nicomorphine hydrochloride	37493800	X
normethadon	19015787	X
nalbuphine	1114122	X
noscapine	19021930	
oliceridine	37002667	X
opium	923829	
oxycodone	1124957	
oxymorphone	1125765	X
papaveretum	19129648	X
pentazocine	1130585	
phenazocine	19132884	X
phenoperidine	19132889	X
pholcodine	19024213	
pirinitramide	19134009	
propoxyphene	1153664	
remifentanil	19016749	X
sufentanil	19078219	
tapentadol	19026459	
thebacon	40799139	X
tilidine	19002431	
tramadol	1103314	

Substance Name	Concept Id	No record counts in databases expected based on feasibility
naloxone	1114220	
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Substance Name	Concept Id	No record counts in databases expected based on feasibility
	41279474, 41391298, 41155295, 41399436, 44188336, 43674391, 41377229, 43656267, 41381042, 41021905, 36779044, 40874145, 40987712, 41147470, 782864, 41147465, 41178513, 41380200, 41394745, 42712465, 41416309, 44176192, 44196308, 41397737, 43669888, 41296350, 41366103, 41364620, 41186368, 41416310, 44193543, 41373239, 42726206, 41186362, 42720481, 40884598, 42717812, 41061042, 44188338, 44183680, 41175234, 43674394, 41144276, 43818022, 41379078, 43620060, 44179950, 41206786, 41378691, 41134436, 40998837, 41376985, 40998836, 43674387, 40063476, 41368354, 40936329, 41123815, 42721354, 41310802, 43656264, 41061046, 41078048, 36883095, 43584002, 40959708, 40874143, 40842925, 43818020, 41381190, 44198471, 40936328, 42731076, 43584001, 40905083, 41422377, 40936337, 41258959, 41417352, 41178516, 36275525, 41134440, 41279481, 41398030, 42729780, 41021903, 41381417, 36279799, 41155299, 43799914, 41061039, 41279485, 41155296, 44177081, 589066, 43585836, 41310795, 41421138, 36788382, 41379578, 782863, 41418951, 41217691, 41248692, 42731075, 41279483, 44176190, 44163494, 41248700, 36780282, 40884599, 41217690, 40874140, 36788391, 590515, 36880268, 41302875, 40859651, 41240923, 36279484, 41279472, 44158979, 41310800, 42710657, 44174755, 40936343, 43799912, 41366895, 41389363, 44173317, 41175232, 43854159, 41155300, 42721823, 40821004, 42715965, 41422378, 43819919, 41175233, 40874139, 42723990, 41092605, 40936339, 41377582, 44176194, 36779720, 40842918, 40990936, 19107321, 43703648, 41197071, 40977883, 43783947, 41424539, 41426584, 41061029, 43745971, 44188335, 41363896, 41414646, 41109495, 41248706, 43631603, 42722234, 41040330, 41092602, 587726, 41362723, 44195601, 43592014, 41061031, 41310806, 41378442, 36269294, 41186363, 41391297, 40915540, 40063477, 41426585, 41147466, 41321350, 41209925, 43640033, 43763923, 41279467, 40936346, 41109494, 41155303, 40866210, 40967495, 44188332, 43799918, 40967497, 40967493, 36780281, 44184492, 41061033, 40905079, 43728066, 41279482, 41401222, 41371410, 44193786, 41248694, 40967483, 41425088, 41123817, 41392775, 41310803, 42725304, 41398031, 40998831, 44198232, 41400831, 41400830, 41029846, 41416797, 19103711, 40874141, 44188333, 40936342, 42715041, 41379077, 36788393, 41378690, 43745970, 41366893, 43782035, 41155289, 42715458, 41228141, 44198126, 43818024, 41084717, 36788395, 41240921, 41061040, 41029845, 36788385, 41381040, 40998856, 41009235, 41415967, 40967499, 44198328, 41321351, 41265245, 40842924, 41217682, 43620061, 41197068, 41053162, 41147468, 41424538, 42714575, 44192636, 40921960, 44176191, 40842927, 40897379, 41393337, 41361358, 43664307, 40874137, 36274366, 44176193, 41370374, 40874154, 36779724, 44186002, 41203447, 36280797, 587728, 36272016, 40921959, 41398146, 40967482, 40863033, 782868, 44197861, 44198007, 41217692, 40998862, 42714579, 43728065, 36261097, 36886966, 40874138, 41029864, 41078051, 40967485, 36880269, 41321349, 41279476, 41103027, 43584004, 41392388, 40998848, 41368352, 41378444,	

Substance Name	Concept Id	No record counts in databases expected based on feasibility
	782861, 40859650, 43799921, 41123821, 41365339, 40977887, 40998859, 41377945, 782865, 40828375, 41029844, 41394467, 41424537, 41061034, 41414647, 41092604, 41379958, 41217695, 40936327, 41418066, 40953118, 41394466, 41380198, 40915539, 41378693, 41424541, 41395777, 589742, 41379823, 41376983, 44187415, 42717316, 41376984, 42718653, 44187417, 41186366, 41415094, 41155293, 41248704, 41061048, 41380627, 41401486, 44169561, 41018708, 587264, 44177082, 40874152, 41415965, 41165705, 40998840, 40835064, 41123818, 41381044, 44198125, 41378302, 40866209, 41092599, 40905078, 42721355, 41363162, 41381416, 44165796, 41092598, 41061035, 42723525, 41378856, 41399437, 41396422, 42620384, 43631602, 40946910, 41393054, 44198066, 41046679, 42722640, 41399851, 41399546, 41377583, 44192570, 41369153, 40921961, 44195654, 40824407, 586943, 40967490, 44195953, 43603914, 41417171, 41380356, 43799924, 40967501, 44180771, 41391692, 40936324, 40998861, 43818021, 44194351, 41299685, 41217686, 41279489, 41310797, 41071629, 43831659, 40897378, 40828374, 41400523, 43584003, 43602062, 43710051, 41046680, 42727159, 44167274, 41381803, 40842919, 40915545, 41362432, 41217689, 40874136, 44169560, 41387396, 36280270, 41029860, 41414797, 44198429, 44164891, 36267298, 41217696, 40967481, 44158902, 41377231, 41279470, 43763929, 41381964, 41092601, 41378443, 40936347, 587414, 40905080, 41416798, 37592451, 41381189, 41084722, 41084718, 41363895, 41123826, 41391027, 40905071, 43745968, 41279480, 41391416, 41155284, 41397069, 41268676, 44180775, 40936325, 41415093, 41279466, 41415485, 41279468, 43638156, 41217687, 41302871, 41279486	

APPENDIX II: Feasibility counts

Table 1. Feasibility person counts per database.

Concept Id	Name	EMDB - ULSEDV	FinOMOP - ACI Varha	HI-SPEED	InGef RDB	NAJS	POLIMI	SUCD
19059528	alfentanil		16700	100	100	200		
1133201	buprenorphine	2100	14900	158600	7100	14600		100
1201620	codeine	18900	116000	43500	423300	282900	5600	500
1119510	dextromethorphan	100	800	200	100	8500		100
1189596	dihydrocodeine				132600		1500	700
19050414	ethylmorphine		10300			1500		
1154029	fentanyl	3100	40000	64300	17400	23000	1100	2400
1126658	hydromorphone	1200	900	1100	49700		100	300
40798904	ketobemidone			33300				
1102527	meperidine		3600	100	500	26700	100	
1103640	methadone		500	11000	300	2600	300	
1110410	morphine	1700	12100	292300	19600	8800	8100	300
1114122	nalbuphine				100			
19021930	noscapine			9500	133100	100		
923829	opium			1277700	1000			
1124957	oxycodone	1100	244900	1554700	22100	9700	1800	700
1130585	pentazocine			100		100		
19024213	pholcodine					460400		
19134009	pirinitramide				600			
1153664	propoxyphene					800		
19078219	sufentanil				100	9100	100	
19026459	tapentadol	22200		23700	10000	20100	800	
19002431	tilidine				8400			
1103314	tramadol	85000	63700	176500	52000	420900	10900	15400

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. .
EU PAS Register® number: EUPAS1000000615 **Study reference number: P4-C2-001**

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

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	6, 7
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

[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.

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

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
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
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:

Name of the main author of the protocol: Amy Lam

Date: 06/05/2025

Signature: A. Lam