Study Protocol Phase II C1-004

08/08/2023

Version 2.1

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DOCUMENT HISTORY

Version	Date	Description
V1.0	29/05/2023	**Submission to EMA**
V2.0	27/06/2023	**Version to including comments from EMA**
V2.1	08/08/2023	**EUPAS register number added**

Study Title	DARWIN EU® - Use of take-home naloxone for opioid overdose treatment
Protocol version identifier	V2.1
Date of last version of protocol	8 August 2023
EU PAS register number	EUPAS105644
Active substance	Take-home Naloxone
Medicinal product	N/A
Research question and objectives	This study aims to assess the incidence and prevalence of use of take-home naloxone (THN) in the general population and among people with opioid use disorder (OUD) for the period 2017-2022, stratified by age, sex, calendar year and country (database). Summary baseline characteristics of users incl. demographics and history of opioid use, overdose and summary statistics of THN prescriptions (e.g. mean (SD), median, q25 and q75)
Countries of study	Germany, Belgium, UK, Spain
Author	Junqing Xie, Annika Jödicke

LIST OF ABBREVIATIONS

Acronyms/terms	Description
CDM	Common Data Model
CPRD GOLD	Clinical Practice Datalink GOLD
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real World Interrogation Network
DUS	Drug Utilization Study
EHR	Electronic Health Records
EMA	European Medicines Agency
GP	General Practitioner
IP	inpatient
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OUD	Opioid Use Disorder
OP	outpatient
PCT	Primary care teams
RRE	Remote Research Environment
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
THN	Take-home Naloxone

1. TITLE

DARWIN EU® - Use of take-home naloxone for opioid overdose treatment

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)	Junqing (Frank) Xie Annika Jödicke	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
	Antonella Delmestri Hezekiah Omulo	University of Oxford

*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® - Use of take-home naloxone for opioid overdose treatment

Rationale and Background

Opioid overdoses are the primary cause of mortality among problematic drug users globally. Naloxone, an opioid antagonist, can avert such fatalities by rapidly counteracting opioid effects. To address the frequent untreated overdoses due to the lack of recognition, fear of legal consequences, and lack of naloxone access, Take-Home Naloxone (THN) programs have been established, providing naloxone to potential bystanders in 12 European countries. This study will investigate the trend of naloxone use, particularly THN, across Europe, and elucidate user profiles to augment aggregated data from existing THN programs, thereby aiding the monitoring of naloxone use and informing regulatory decisions.

Research question and Objectives

The objectives of this study are

(i) To investigate the incidence and prevalence of THN use in (1) the general population and (2) among people with a recorded history of opioid use disorder during the study period 2017-2022. Analyses will be stratified by age, sex, calendar year and country/database.

(ii) To provide summary baseline characteristics of “new” THN users including demographics, previous medical history, previous medication use and history of opioid use, overdose

(iii) To study the use of THN in ”new” users including summary statistics of number of packages of THN products prescribed at index date for each “new” user (e.g. mean (SD), median, q25 and q75)

Research Methods

Study design

- Population level cohort study (Objective 1, Population-level drug utilization study on THN)
- New drug user cohort study (Objective 2+3, Patient-level drug utilization analyses with regard to number of packages of THN products prescribed at index date and summary patient characteristics incl. history of opioid use, overdose)

Population

Population-level utilization of THN: All individuals present in the database in the period between 01/01/2017 and 31/12/2022 will be included in the analysis after 365 days of database history. Therefore, children aged <1year will be excluded.

Patient-level THN utilization: All “new” users of THN in the period between 01/01/2017 and 31/12/2022, with “new” users being defined as all people with a prescription THN within the study period, with at least 365 days of availability prior to the date of their THN prescription and no prescription of THN in the last 7 days (180 days for sensitivity analysis). Therefore, the same person can be a “new” user multiple times during the study period.

Variables

Drug of interest: Take-Home Naloxone

Data sources

1. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
2. IQVIA LBD Belgium, Belgium
3. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
4. The Information System for Research in Primary Care (SIDIAP), Spain

Sample size

No sample size has been calculated as this is a descriptive study.

Data analyses

Population-level THN use: Annual period prevalence of THN use and annual incidence rates per 100,000 person years in (1) the general population and (2) among people with a recorded history of opioid use disorder (OUD). The statistical analyses will be performed based on OMOP-CDM mapped data using the "IncidencePrevalence" R package. a.

Patient-level THN use: Summary baseline characteristics of "new" users incl. demographics and history of opioid use, overdose will be conducted. Index date will be the date of the respective prescription of THN for each person. Number of THN packages prescribed per "new" user at index date will be summarised and mean (SD), median, p25 and p75 provided. The statistical analyses will be performed based on OMOP-CDM mapped data using the "DrugUtilization" R package.

For all analyses a minimum cell count of 5 will be used when reporting results, with any smaller counts reported 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	28 July 2023
Final Study Report	To be confirmed

7. RATIONALE AND BACKGROUND

Opioid overdoses, largely attributed to opioids often mixed with other substances with central nervous system depressing effects such as benzodiazepines or alcohol, are the leading cause of death among people with problematic drug use worldwide[1, 2]. Naloxone, a potent opioid antagonist, can prevent such fatalities by rapidly reversing opioid effects, primarily respiratory depression, through competitive binding at μ2 opioid receptors[3]. This drug was discovered in the early 1960s and approved by the US Food and Drug Administration in 1971 for intravenous, intramuscular, and subcutaneous injection. The World Health Organization added it to its essential medicines list in 1983.

There is growing support for making naloxone available for layperson use in emergencies. This has been facilitated by the introduction of nasal spray formulations, piloted by France in 2016, and approved by the European Commission in 2017[4]. Since then, these formulations have been adopted in several European countries, expanding the reach of this potentially life-saving intervention[5].

Take-Home Naloxone (THN) programs have been developed and implemented in many countries to mitigate the impact of the high rate of opioid overdoses, which often go untreated due to witnesses' lack of recognition, fear of legal consequences, and lack of naloxone access. These initiatives distribute naloxone, a life-saving medication traditionally administered only by emergency personnel, to potential bystanders, including opioid users themselves. According to the latest records, THN are in operation in 12 countries including Austria, Denmark, Estonia, France, Germany, Ireland, Italy, Lithuania, Norway, Spain (Catalonia), Sweden, and the United Kingdom. In 2018, Finland made preliminary steps towards introducing naloxone[5].

This network study based on a Common Data Model will assess the use of THN in the general and among a recorded history of opioid use disorder across several Europe countries and over time. In addition, we will characterize the user profiles at the individual level to supplement aggregated data from the current implemented THN programs. The results from this study will therefore facilitate timely monitoring of THN use and inform regulatory decision making.

8. RESEARCH QUESTION AND OBJECTIVES

Table 2: Primary and secondary research questions and objective

A. **Primary research question and objective**

Objective:	To estimate the incidence and prevalence of THN use in the general population and among people with a recorded history of opioid use disorder, stratified by calendar year, age, sex and country/database during the study period 2017-2022
Hypothesis:	Not applicable
Population ***(mention key inclusion-exclusion criteria):***	The study cohorts will comprise of 1) all individuals present in the database in the period 2017-2022, with at least 365 days of data availability before the day they become eligible for study inclusion and 2) individuals with a recorded history of opioid use disorder, Additional eligibility criteria will be applied for the calculation of incidence rates where observation time of the respective use of the THN is excluded 180 days afterwards.
Exposure:	Take-Home Naloxone
Comparator:	None
Outcome:	None
Time ***(when follow up begins and ends):***	Follow-up will start on a pre-specified calendar time point e.g., 1st of January for each calendar year between 2017-2022 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 (31st December 2022)
Setting:	Inpatient and outpatient setting using data from the following data sources: IQVIA DA Germany [Germany], IQVIA LBD Belgium [Belgium], CPRD GOLD [UK], SIDIAP [Spain]
Main measure of effect:	Incidence and prevalence of THN use

B. **Secondary research question and objectives**

Objectives:	(1) To summarise baseline characteristics incl. demographics, previous medical history, previous medication use, history of opioid use, and overdose. (2) To summarise numbers of THN packages prescribed at index date for "new" users
Hypothesis:	Not applicable

Population *(mention key inclusion-exclusion criteria):*	The study cohort will comprise all "new users" in the database in the period 2017-2022 (or the latest available, whatever comes first), with at least 365 days of data availability before the day they become eligible for study inclusion and who had received at least one prescription and/or dispensation of THN, without a prescription of the same drug in the previous 7 days (180days for sensitivity analyses).
Exposure:	Take-Home Naloxone
Comparator:	None
Outcome:	None
Time *(when follow up begins and ends):*	Follow-up will start on the date of THN 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)
Setting:	Primary care and outpatient setting using data from the following data sources: IQVIA DA Germany [Germany], IQVIA LBD Belgium [Belgium], CPRD GOLD [UK], SIDIAP [Spain]
Main measure of effect:	Summary baseline characteristics including demographics and history of opioid use and overdose. Number of THN prescriptions/packages at index date for "new" users (expressed as mean[sd], median[q25-q75])

9. RESEARCH METHODS

9.1 Study Design

Retrospective cohort studies will be conducted using routinely-collected health data from 4 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 THN use.
2. A "new" drug user cohort will be used to address objectives 2+3, summarising patient-level characteristics of THN users in terms of demographics, history of opioid use and overdose; and summarise number of THN packages prescribed on index date per "new" user.

9.2 Study Setting

9.2.1 Study population

The study cohort will comprise all individuals present in the database ("general population") during the study period (2017-2022), with at least 365 days of data availability before the day they become eligible for study inclusion. This requirement means children < 1 year will not be studied.

For the calculation of incidence and prevalence among people with an opioid use disorder (OUD), only people with a recorded history of opioid use disorder anytime in their patient history will be included.

Additional eligibility criteria will be applied for the calculation of incidence rates, where new THN users must not have been prescribed TNH in the previous 180 days .

9.2.2 Study period and follow-up

The study period will be from the 1st of January 2017 until the earliest of 31st December 2022 or the respective latest date of data availability of the respective databases. Follow-up will start 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	Wash out 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 (2017-2022) and with at least 1 year of valid database history	Patients can be considered multiple times	Prevalent	None	IP and OP	NA	NA	NA	NA	NA
All patients from the database eligible for the study – Analysis of Incident use.	Patient present in the database during the study period (2017-2022), with at least 1 year of valid database history and no THN prescription in the last 6 months	Patients can be considered multiple times	Incident	[-180, -1]	IP and OP	NA	NA	THN	NA	NA
Patients with opioid use disorder - Analysis of Prevalent Use	Patient present in the database during the study period (2017-2022) and with at least 1 year of valid database history AND a record of "opioid use disorder" anytime in their patient history	Patients can be considered multiple times	Prevalent	None	IP and OP	NA	NA	NA	NA	NA
Patients with opioid use disorder - Analysis of Incident Use	Patient present in the database during the study period (2017-2022) and with at least 1 year of valid database history AND a record of "opioid use disorder" anytime in their patient history and no THN prescription in the last 6 months	Patients can be considered multiple times	Incident	[-180, -1]	IP and OP	NA	NA	THN	NA	NA
"New user cohort"	All people present in the database during the study period (2017-2022) and with at least 1 year of valid database history AND a THN prescription with no THN prescription in the last 7 days	Patients can be considered multiple times	"new" user	Primary analysis [-7, -1] Sensitivity analysis	IP and OP	NA	NA	THN	NA	NA

				[-180, -1]						

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable. THN = take-home naloxone

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 2017), 2) date at which they have a year of prior history. 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 (date of last data extraction) 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.

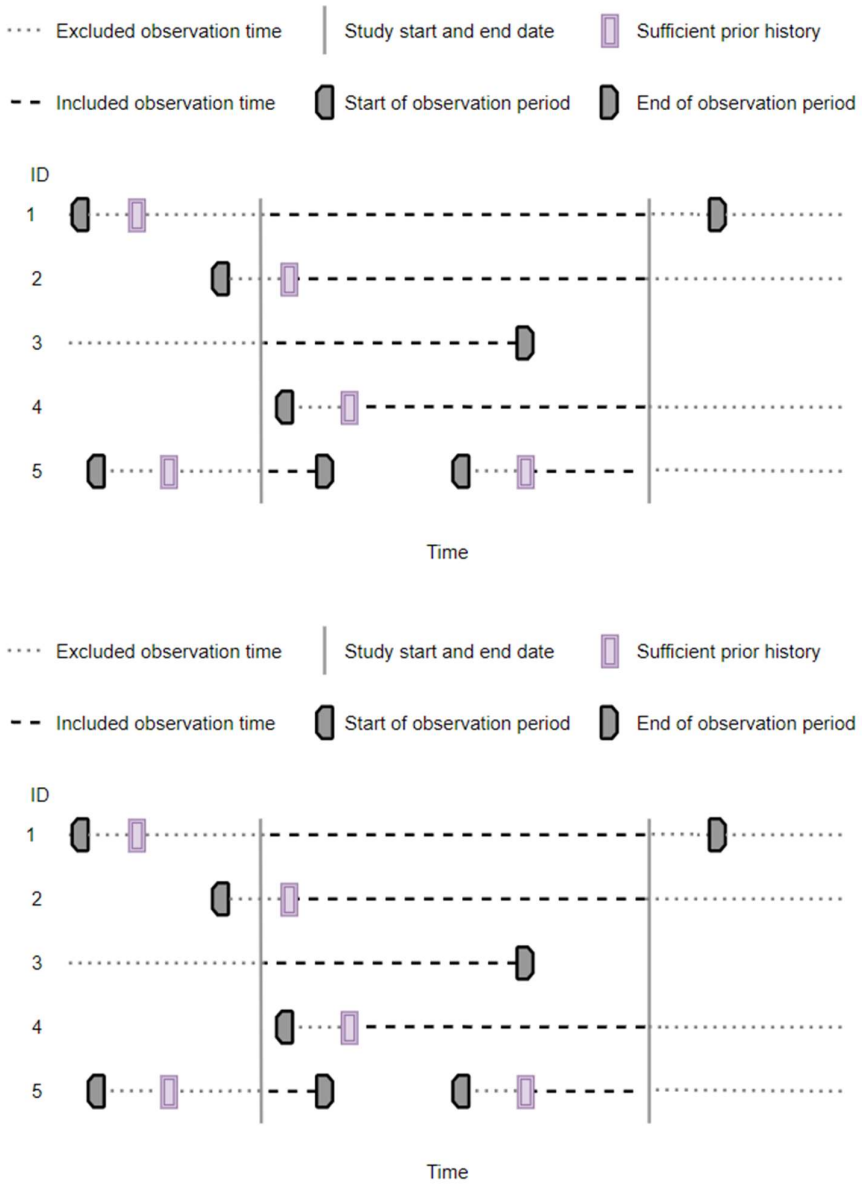

Figure 1: Included observation time for the denominator population

9.2.3 Inclusion and exclusion criteria

9.2.3.1 Population-level Utilisation of THN

The study cohort will comprise all individuals present in the period 2017-2022 (or the latest available, whatever comes first), with at least 365 days of data availability before the day they become eligible for study inclusion.

For the calculation of incidence and prevalence among people with an opioid use disorder (OUD), only people with a recorded history of opioid use disorder anytime in their patient history will be included.

Additional eligibility criteria will be applied for the calculation of incidence rates: The observation time of users of THN is excluded during use and 180 days afterwards.

9.2.3.2 Patient-level Utilisation of THN

All users of THN in the period between 01/01/2017 and 31/12/2022 (or latest date available, whatever comes first), with at least 365 days of availability prior to the date of their THN 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 2017-2022 (or the latest available, whatever comes first)	See under inclusion criterion	After	N/A	Primary care and combination of primary and secondary care for IQVIA Germany	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 and combination of primary and secondary care for IQVIA Germany	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 prescription (during study period) of THN, defined as naloxone products intended for administration including by laypersons in the emergency of opioid overdoses e.g. preparations for injection or nasal sprays.

Table 5: Exposure of interest (list not exhaustive)

Name	Route of administration
naloxone Nasal Spray	nasal
naloxone Prefilled Syringe	injection
naloxone Auto-Injector	injection

Details of exposure are described in Table 6.

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
THN, THN by route --- population-level incidence rates	Preliminary code lists provided in Appendix 1	[-180, -1]	Calendar year	Primary and outpatient secondary care settings	RxNorm	N/A	All individuals present in the database during the study period; people with opioid use disorder	Previous THN use	N/A	N/A
THN, THN by route --- "new user"	Preliminary code lists provided in Appendix 1	[-7, -1]	Calendar year	Primary and outpatient secondary care settings	RxNorm	N/A	All individuals present in the database during the study period; people with opioid use disorder	Previous THN 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: clinical-informed age bands will be used: 1-19, 20-39, 40-59, 60-79, >=80
- Sex: male or female
- Route of administration: injection, nasal

9.3.3.2 Covariates for patient-level drug utilization study:

Covariates for Summary baseline characteristics will include age, sex, route of administration for THN prescription (injection, nasal), comorbidities, incl. history of opioid use, history of overdose and co-medication, e.g. type of opioids in the year before index date.

The operational definition of the covariates is described in the table below.

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
Comorbidities	Asthma, COPD, Chronic Liver disease, Crohn's Disease, Diabetes mellitus, GERD, GI-Bleeding, HIV, Hyperlipidemia, Hypertension, Obesity, Osteoarthritis, Pneumonia, Psoriasis, Renal impairment, Ulcerative Collitis, Urinary Tract infection, Viral Hepatitis, Visual system disorder, Schizophrenia, Dementia, Parkinson, Depressive disorder, Anxiety, Cancer	Counts	In 1 year before index date: [-365, -1]	Primary and secondary care	SNOMED	N/A	Persons with "new" use during the study period	N/A	N/A

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
Comedication	Agents acting on the renin-angiotensin system, Antibacterials for systemic use, Antidepressants, Antiepileptics, Antiinflammatory and antirheumatic products, Antineoplastic agents, Antipsoriatics, Antithrombotic agents, Beta blocking agents, Calcium channel blockers, Diuretics, Drugs for acid related disorders, Drugs for obstructive airway diseases, Drugs used in diabetes, Immunos	Counts	Anytime prior to index date: [-inf, -1]	Primary and secondary care	RxNORM	N/A	Persons with "new" use during the study period	N/A	N/A

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
	uppressants, Lipid modifying agents, Psycholeptics, Psychostimulants, agents used for adhd and nootropics								
History of opioid use	Any opioid use in the year before index date	Counts	In 1 year prior to index date: [-365, -1]	Primary and secondary care	RxNORM	N/A	Persons with "new" use during the study period	N/A	N/A
History of opioid overdose	Diagnosis of opioid overdose in the year before index date	Counts	In 1 year prior to index date: [-365, -1]	Primary and secondary care	SNOMED	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 4 databases in 4 European countries (3 EU countries and United Kingdom). All databases were previously mapped to the OMOP CDM.

1. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
2. IQVIA LBD Belgium, Belgium
3. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
4. The Information System for Research in Primary Care (SIDIAP), Spain

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

Fit for purpose: This study will be conducted among 4 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.

IQVIA DA Germany, IQVIA LBD Belgium, SIDIAP and CPRD include records from primary care and outpatient specialist care where THN is expected to be prescribed. All databases fulfil the criteria required for a population-level drug utilisation study and patient-level drug utilisation study.

2 Hospital databases were considered for inclusion, but will ultimately not contribute to this study as at the present time the requested level of details (i.e. products/route of administration) was not available for outpatients/ discharge prescription.

Table 8: Description of data sources

Country	Name of Database	Justification for Inclusion	Health Care setting (e.g., primary care, specialist care, hospital care)	Type of Data (EHR, claims, registries)	Number of active subjects	Feasibility count of disease (if relevant)	Data lock for the last update
Spain	SIDIAP	Database covers primary care andoutpatient specialist care setting where THN may be prescribed/dispensed	Primary care	EHR	5.8 million	N/A	1/6/2022
Belgium	IQVIA LBD Belgium		Primary care and outpatient specialist care	EHR	0.4 million	N/A	1/1/2022
Germany	IQVIA DA Germany		Primary care and outpatient specialist care	EHR	8.5 million	N/A	1/9/2022
UK	CPRD GOLD	Database covers primary care andoutpatient specialist care setting where THN may be prescribed/dispensed	Primary care	EHR	3 million	N/A	01/07/2022

SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, DA = Disease Analyzer, EHR = Electronic Heath record. Exposure is based on prescription data

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[6]. 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[7]. 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.

Clinical Practice Research Datalink GOLD, United Kingdom (University of Oxford)

The Clinical Practice Research Datalink (CPRD) is a governmental, not-for-profit research service, jointly funded by the National Institute for Health and Care Research and the Medicines and Healthcare products Regulatory Agency, a part of the Department of Health, United Kingdom (UK) (https://cprd.com). CPRD GOLD[8] comprises computerized records of all clinical and referral events in primary care in addition to comprehensive demographic information and medication prescription data in a sample of UK patients (predominantly from Scotland (52% of practices) and Wales (28% of practices). The prescription records include information on the type of product, date of prescription, strength, dosage, quantity, and route of administration. Data from contributing practices are collected and processed into research databases. Quality checks on patient and practice level are applied during the initial processing. Data are available for 20 million patients, including 3.2 million currently registered patients.

Access to CPRD GOLD data requires approval via the Research Data Governance Process.

9.5 Study size

No sample size has been calculated as this is a descriptive study.

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, and 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"[9] package for the population-level estimation of drug utilization.

Drug exposure calculations

Drug eras will be defined as follows: Exposure starts and ends at date of the first prescription, given that THN is to be used as one-off emergency treatment.

New user cohorts

New users will be selected based on their first prescription of THN after the start of the study and/or after a pre-defined time window. For each patient, at least 365 days of data visibility will be required prior to that prescription. New users will be required to not have been prescribed THN for at least 180 days prior the current prescription for incidence calculations, and for at least 7 days (180days for sensitivity analyses) for patient-level characterisation. If the start date of a prescription does not fulfil the exposure washout criteria, 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 birthday. The following age groups will be used for stratification: 1-19, 20-39, 40-59, 60-79, >=80-,

Sex

Results will be presented stratified by sex

Characterization of patient-level features

Summary baseline characteristics will be provided, including demographics, and comorbidities recorded anytime during patient history, including history of opioid use and history of opioid overdose.

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 for THN will be conducted separately the (1) general population and (2) among people with a recorded history of opioid use disorder. Analyses will be stratified by age, sex, calendar year and country/database. Stratification for route (e.g. injection, nasal spray) will be conducted. .

Prevalence calculations

Prevalence will be calculated as annual period prevalence which summarises the total number of individuals who were prescribed THN 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.

Incidence calculations

Annual incidence rates of the THN will be calculated as the of number of **new users** after 180 days of no use per 100,000 person-years of the population at risk of getting exposed during the period for each calendar year. Any study participants with use of the medication of interest prior to the date at which they would have otherwise satisfied the criteria to enter the denominator population (as described above) will be excluded. Those study participants who enter the denominator population will then contribute time at risk up to their first prescription during the study period. Or if they do not have a drug exposure, they will contribute time at risk up as described above in section 9.2.2 (study period and end of follow-up). Incidence rates will be given together with 95% Poisson confidence intervals.

An illustration of the calculation of incidence of THN use is shown below in **Figure 1**. Patient ID 1 and 4 contribute time at risk up to the point at which they become incident users of THN. Patient ID 2 and 5 are not seen to have received THN 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 THN 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 THN 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.

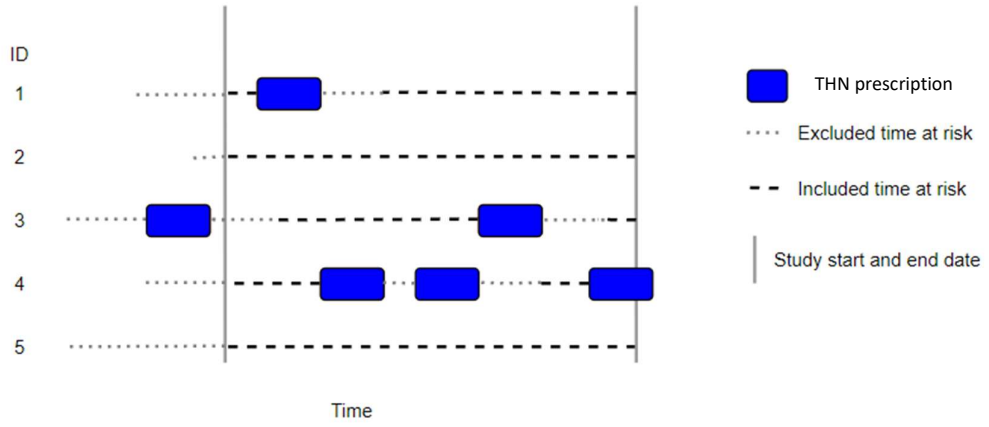

Figure 1: Incidence example

9.7.5.2 Patient-level drug utilization study

Summary baseline characteristics

Summary baseline characteristics will be provided, including demographics, and relevant conditions recorded anytime during patient history, including history of opioid use and history of opioid overdose in the year before index date.

Number of THN prescription per THN user

Summary statistics of number of prescriptions/packages per "new" user (e.g. mean (SD), median, q25 and q75) will be provided.

9.7.6 Description of sensitivity analyses.

No sensitivity analyses will be provided for this study (Table 9 empty).

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 7 days might be too short to define a true new user	It can increase the specificity of defining a new user	It can decrease the sensitivity of defining a new user

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 drug cohorts, non-take home products will be excluded from the list of included codes. A pharmacist will review the code lists.

When defining cohorts for "opioid use disorder" and THN, a systematic search of possible codes for inclusion will be identified using CodelistGenerator R package (https://github.com/darwin-eu/CodelistGenerator). 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, the CohortDiagnostics R package (https://github.com/OHDSI/CohortDiagnostics) will be run if needed to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error.

Likewise, DrugExposureDiagnostics[10] will be run if needed to assess the use of different codes relevant to THN 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 THN prescription/dispensation does not mean that the patient actually took THN or it was administrated, and the index date represents the time of prescription/dispensation and not the time of emergency use. Moreover, in the UK, national legislation has allowed staff at drugs agencies from 2015 onwards to give out THN "without a prescription to individuals who may need it to save a life"[5]. Similar programs are available in other European countries. Relevant underreporting of prescribed THN is therefore to be expected in our databases.

In addition, the recording of covariates used for patient characterization e.g. history of opioid use, history of overdose may vary across databases and recording of "opioid use disorder" 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.

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

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14. ANNEXES

Appendix I: Lists with preliminary concept definitions for exposure

Appendix II: lists with preliminary concept definitions for opioid use disorder

Appendix III: ENCePP checklist for study protocols

APPENDIX I: LISTS WITH PRELIMINARY CONCEPT DEFINITIONS FOR EXPOSURE

CONCEPT ID	Name	Standard Class	Domain	Vocab
35603851	naloxone Nasal Spray	Clinical Drug Form	Drug	RxNorm
40141382	naloxone Prefilled Syringe	Clinical Drug Form	Drug	RxNorm
46275772	naloxone Auto-Injector	Clinical Drug Form	Drug	RxNorm

APPENDIX II: LISTS WITH PRELIMINARY CONCEPT DEFINITIONS FOR OPIOID USE DISORDER

CONCEPT ID	Name	Domain
37016268	Opioid-induced mood disorder due to opioid abuse	Condition
44782731	Intravenous nondependent opioid abuse	Condition
434016	Nondependent opioid abuse, continuous	Condition
435798	Nondependent opioid abuse, episodic	Condition
438130	Opioid abuse	Condition
4099935	Nondependent opioid abuse	Condition
37018689	Opioid-induced mood disorder due to opioid dependence	Condition
37110407	Opioid dependence with current use	Condition
37398751	Opioid analgesic dependence	Condition
42872387	Opioid dependence, on agonist therapy	Condition
438120	Opioid dependence	Condition
440379	Episodic opioid dependence	Condition
440693	Continuous opioid dependence	Condition
4099809	Combined opioid with other drug dependence	Condition
4102817	Combined opioid with other drug dependence, continuous	Condition
4103413	Combined opioid with other drug dependence, episodic	Condition
4138193	Fentanyl dependence	Condition
4332883	Methadone dependence	Condition
4332990	Opium dependence	Condition
4333676	Heroin dependence	Condition
4338027	Morphine dependence	Condition
37207437	Opioid dependence service	Observation
42628327	Opioid addiction treatment program	Observation
2108850	Patient counseled regarding psychosocial and pharmacologic treatment options for opioid addiction (SUD)	Observation
2618195	Opioid addiction treatment program	Observation
44789594	Opiate dependence detoxification	Procedure
40217323	Office-based treatment for opioid use disorder, including care coordination, individual therapy and group therapy and counseling; each additional 30 minutes beyond the first 120 minutes (list separately in addition to code for primary procedure)	Procedure

40217324	Office-based treatment for opioid use disorder, including care coordination, individual therapy and group therapy and counseling; at least 60 minutes in a subsequent calendar month	Procedure
40217325	Office-based treatment for opioid use disorder, including development of the treatment plan, care coordination, individual therapy and group therapy and counseling; at least 70 minutes in the first calendar month	Procedure

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 – Use of take-home naloxone for opioid overdose treatment

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				
1.1.1 Start of data collection[1]	☐	☐	☒	Overview, 6-milestones
1.1.2 End of data collection[2]	☐	☐	☒	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

[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 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7– 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

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.2	Is the planned study population defined in terms of:				9.2.1 and 9.2.2
	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)	☒	☐	☐	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)	☒	☐	☐	
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?	☐	☐	☒	

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
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 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)	☐	☐	☒	

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4 and 9.3.3
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)	☒	☐	☐	9.4
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 9.3.3
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?	☒	☐	☐	9.7.4
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 Jodicke

Date: 25/05/2023

Signature: A. Jodicke