Study Report Phase II C1-004

10/01/2024

Version 2.1

Contents

DOCUMENT HISTORY

Version	Date	Description
V1.0	10/09/2023	**Final Version for EMA review**
V2.0	26/10/2023	**Revised version addressing EMA comments**
V2.1	10/01/2024	**Revised version addressing post-approval EMA comments**

Study Title	DARWIN EU® – Use of take-home naloxone for opioid overdose treatment
Study Report Version identifier	V2.1
Dates Study Report updates	10/01/2024
EU PAS register number	EUPAS105644
Active substance	Take-home Naloxone
Medicinal product	NA
Research question and objectives	This study aims to (1) 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). (2) To provide summary baseline characteristics of "new" THN users including demographics, previous medical history, previous medication use, and history of opioid use, overdose. (3) 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).
Countries of study	Germany, Belgium, UK, Spain
Authors	Dr. Junqing Xie Dr. Annika Jödicke

1. DESCRIPTION OF STUDY TEAM

Study team Role	Names	Organisation
Principal Investigators	Junqing Xie Annika Jödicke	University of Oxford
Data Scientists	Martí Català Sabaté Yuchen Guo Mike Du	University of Oxford
Epidemiologists	Daniel Prieto Alhambra	University of Oxford Erasmus MC
Statistician	NA	
Data Partner*	**Names**	**Organisation**
Data Partner(s)	Talita Duarte Salles	IDIAPJGol
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*Data partners' role is only to execute code at their data source, and they don't have an investigator role.

2. DATA SOURCES

This study was 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 Longitudinal Patient Database Belgium (IQVIA LPD Belgium), Belgium
2. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
3. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
4. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain

Detailed information on data sources is described in Table 1 below.

Table 1: Description of data sources

Country	Name of Database	Health Care setting	Type of Data (EHR, claims, registries)	Number of active subjects	Calendar period covered by each data source.	Contributing to Population-level DUS and/or patient-level DUS?
ES	SIDIAP	Primary care	EHR	5.8 million	01/01/2017 to 01/06/2022	Both
BE	IQVIA LPD Belgium	Primary care and outpatient specialist care	EHR	435,200	01/01/2017 to 01/01/2022	Both
DE	IQVIA DA Germany		EHR	8.5 million	01/01/2017 to 01/09/2022	Both
UK	CPRD GOLD	Primary care	EHR	3 million	01/01/2017 to 01/07/2022	Both

ES = Spain, BE = Belgium, DE = Germany, UK = United Kingdom, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, CPRD GOLD = Clinical Practice Research Datalink GOLD, EHR = Electronic Heath record. Exposure is based on prescription data.

3. ABSTRACT

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 has investigated 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 were

1. 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.
2. To provide summary baseline characteristics of “new” THN users including demographics, previous medical history, previous medication use and history of opioid use, overdose
3. 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 (Objectives 2 and 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 up to 01/09/2022 were included in the analysis.

Patient-level THN utilization: All “new” users of THN in the period between 01/01/2017 and up to 01/09/2022, with “new” users being defined as all people with a prescription THN within the study period, and no prescription of THN in the previous 7 days (180 days for sensitivity analysis) before the identified prescription. 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 LPD Belgium, Belgium
3. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
4. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain

Sample size

No formal sample size calculation has been conducted as this is a descriptive study, and all relevant prescriptions during the study period were included.

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 was performed based on OMOP-CDM mapped data using the "IncidencePrevalence" R package.

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

For all analyses a minimum cell count of 5 were used when reporting results, with any smaller counts and the corresponding frequency suppressed.

Results

Population level DUS

No THN prescriptions was identified in IQVIA LPD Belgium and SIDIAP databases. Within IQVIA DA Germany, there were no recorded THN prescriptions in 2017 and 2018. In 2019 and later, only few THN prescriptions were recorded, with incidence being very low ranging from 0.06 to 0.24 per 100,000 person-years. 7 new THN prescriptions were identified in CPRD GOLD database in 2022, equal to an incidence rate of 0.53 per 100,000 person-years. Only the nasal form was recorded in both databases.

For the opioid use disorder population, 7 new THN users were recorded in IQVIA DA Germany in 2019, resulting in an incidence rate of 197 per 100,000 person-years. However, no THN users within this sub-population was identified in CPRD GOLD database. Again, solely prescriptions of the THN nasal spray was reported in IQVIA DA Germany during the study period.

The prevalence of THN prescription was similar in terms of magnitude, pattern and trend compared to the incidence.

Patient-level DUS

In the study, 53 new THN prescription records were identified in IQVIA DA Germany database from 48 individuals and 8 in CPRD GOLD database from 8 individuals. The median age of THN users from both databases was between 40 and 45 years respectively. IQVIA DA Germany cohort had a higher proportion of men than women (66%), whereas the CPRD GOLD cohort consisted entirely of men (100%). Depressive disorder was the most common comorbidity in both cohorts, recorded in 62% of THN users in IQVIA DA

Germany cohort and 62.5% in CPRD GOLD cohort. No previous records of opioid overdose were recorded in new THN users in both databases, and history of prescribed opioid use was rare.

Discussion

Limited prescriptions of THN (all nasal spray formulation) were recorded in the selected databases covering primary care or specialized outpatient care practices to quantify and characterise THN users. This suggests that THN preparations are mainly dispensed through specialised support services and that data from community-based facilities that take part in the regional or national THN programs are not routinely captured in our currently available data sources.

Our study provides important information for future studies on take-home naloxone, which should consider the very specific distribution pathways, i.e. through specialised support services and facilities, for take-home naloxone in the context of public health programs to prevent opioid overdoses.

4. LIST OF ABBREVIATIONS

Acronyms/terms	Description
CDM	Common Data Model
CPRD GOLD	Clinical Practice Research Datalink GOLD
DARWIN EU	Data Analysis and Real World Interrogation Network
DA Germany	Disease Analyzer Germany
DUS	Drug Utilization Study
EHR	Electronic Health Records
EMA	European Medicines Agency
GP	General Practitioner
LPD Belgium	Longitudinal Patient Database
OMOP	Observational Medical Outcomes Partnership
OUD	Opioid use disorder
PCT	Primary Care Teams
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
THN	Take home naloxone

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
NA				

6. MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE (planned)	TIMELINES (actual)
Final Study Protocol	27/06/2023	27/06/2023
Creation of Analytical Code	07/2023	07/2023
Execution of Analytical Code on the data	08/2023	08/2023
Interim Study Report (if applicable)	NA	NA
Study Report submitted to EMA	10/09/2023	10/09/2023
Revised Study Report	26/10/2023	26/10/2023
Final Study Report	20/12/2023	20/12/2023

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 how well currently available data sources in DARWIN EU can assess the use of THN in the general and among a recorded history of opioid use disorder across several Europe countries and over time.

8. RESEARCH QUESTION AND OBJECTIVES

Table 8.1: Primary research question and objective

Objectives:	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 age, sex, calendar year and country/database during the study period 2017-2022.
Hypothesis:	NA
Population *(mention key inclusion-exclusion criteria):*	The study cohorts will comprise of 1) all individuals present in the database in the period 2017-2022, 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 7 (180 in sensitivity analysis) days afterwards.
Exposure:	Take-home naloxone (THN)
Comparator:	NA
Outcome:	NA
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 LPD Belgium [Belgium], SIDIAP [Spain], CPRD GOLD [UK]
Main measure of effect:	Incidence and Prevalence, Patient-level drug utilisation

Table 8.2 Secondary research question and objectives

Objectives:	To summarise baseline characteristics incl. demographics, previous medical history, previous medication use, history of opioid use, and overdose. To summarise numbers of THN packages prescribed at index date for "new" users.
Hypothesis:	NA
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), 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 (THN)
Comparator:	NA
Outcome:	NA
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, 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 LPD Belgium [Belgium], SIDIAP [Spain], CPRD GOLD [UK]
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 Type and Study Design

Retrospective cohort studies were conducted. The study consisted of two consecutive parts:

1. A population-based cohort study was conducted to address objective 1, assessing the prevalence and incidence of THN use.
2. A "new" drug user cohort was used to address objectives 2+3, summarising patient-level characteristics of THN users in terms of demographics, history of opioid use and overdose; and summarising number of THN packages prescribed on index date per "new" user.

9.2 Study Setting and Data Sources

This study was conducted using routinely-collected health data from 4 databases (3 EU countries and United Kingdom). All databases were previously mapped to the OMOP CDM.

1. IQVIA Longitudinal Patient Database Belgium (IQVIA LPD Belgium), Belgium
2. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
3. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
4. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom

The selection of databases for this study was performed based on data reliability and relevance for the proposed research question, as exposure to naloxone in general appeared well captured in these databases based on feasibility counts for naloxone at the ingredient level. IQVIA DA Germany, IQVIA LPD Belgium, SIDIAP and CPRD include records from primary care and outpatient specialist care, with THN being allowed to be prescribed and dispensed in these settings. 2 additional hospital databases were initially proposed for inclusion, but did ultimately not contribute to this study as it was later identified that at the present time the requested level of details (i.e. products/route of administration) was not available for outpatients/ discharge prescription. No similar THN studies have been found in the literature that utilize these databases.

Detailed information on data sources is described in **Table 9.1**.

Table 9.1. Description of the selected 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	Data lock for the last update
BE	IQVIA LPD Belgium	Database covers primary care setting /outpatient specialist care setting where naloxone prescriptions might be issued.	outpatient specialist care	EHR	435,200	01/06/2022
DE	IQVIA DA Germany		outpatient specialist care	EHR	8.5 million	01/01/2022
ES	SIDIAP		Primary care	EHR	5.8 million	01/09/2022
UK	CPRD GOLD		Primary care	EHR	3 million	01/07/2022

ES = Spain, UK = United Kingdom, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, LPD = Longitudinal Patient Database, DA = Disease Analyzer, CPRD GOLD = Clinical Practice Research datalink GOLD, EHR = Electronic Heath record. Exposure is based on prescription data

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[6]. 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 utilisation studies.

Information System for Research in Primary Care (SIDIAP), Spain (IDIAPJGol)

SIDIAP Icollected from EHR records of patients receiving primary care delivered through Primary Care Teams (PCT), consisting of GPs, nurses and non-clinical staff[7]. 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. Approval for this study was granted by both SIDIAP's Scientific and Ethics Committee.

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. Approval for this study was granted via the Research Data Governance Process.

9.3 Study Period

The study period was 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.

9.4 Follow-up

9.4.1 Population-level Utilization of THN

Both incidence and prevalence require an appropriate denominator population and their contributed observation time to first be identified. Study participants in the denominator population began contributing person time on the respective study start date (1st January 2017). Participants stopped 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 9.4.1**. 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.

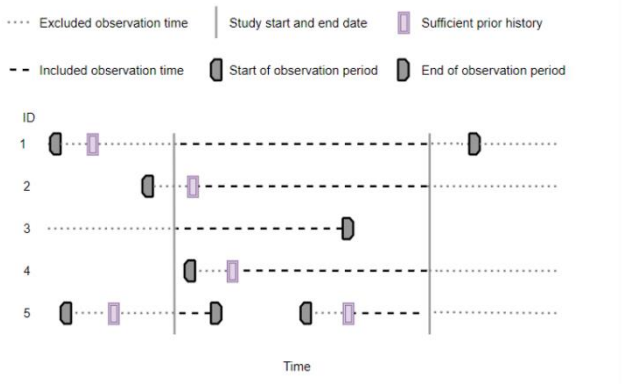


Figure 9.4.1. Included observation time for the denominator population

9.4.2 Patient-level Utilisation of THN

Participants were followed up from the day of therapy initiation, i.e. the date of the first prescription of THN (index date), until the earliest of loss to follow-up, end of data availability, death, or end of continuous exposure.

9.5 Study Population with in and exclusion criteria

9.5.1 Population-level Utilisation of THN

The study cohort comprised all individuals present in the period 2017-2022 (or the latest available, whatever comes first).

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 were included.

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

Operational definition is detailed in **Table 9.2.**

Table 9.2: Operational Definition of Time 0 (index date) and other primary time anchors

Study population name(s)	Time Anchor Description (e.g., time 0)	Number of entries	Type of entry	Washout window	Care Setting	Code Type	Diagnosis position	Incident with respect to…	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)	Patients can be considered multiple times	Prevalent	None	IP and OP	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 no THN prescription in the last 6 months		Incident	[-180, -1]	IP and OP	NA	NA	THN	NA
Patients with–opioid use disorder - Analysis of Prevalent Use	Patient present in the database during the study period (2017-2022) AND with a record of “opioid use disorder” anytime in their patient history		Prevalent	None	IP and OP	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 a record of “opioid use disorder” anytime in their patient history and no THN prescription in the last 6 months		Incident	[-180, -1]	IP and OP	NA	NA	THN	NA

9.5.2 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), were included to the study. Operational definition is detailed in **Table 9.3.**

Table 9.3: Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study popul21haracterizatiement 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	IP and OP	N/A	N/A	All individuals within the selected databases	N/A	N/A

9.6 Variables

9.6.1. Exposure/s

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 in **Table 9.4**.

Table 9.4: Exposure of interest

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

Details of exposure are described in **Table 9.5**

Table 9.5: 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…	Source of algorithm
THN, THN by route --- population-level incidence rates	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
THN, THN by route --- “new user”	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

9.6.2. Outcome/s

N/A

9.6.3. Other covariates, including confounders, effect modifiers and other variables

9.6.3.1 Covariates for stratification in population-level drug utilisation 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

9.6.3.2 Covariates for patient-level drug utilisation study:

Covariates for summary baseline characteristics included age, sex, route of administration for THN prescription (injection, nasal), comorbidities, including history of opioid use, history of overdose and co-medication.

The operational definition of the covariates is described in the **Table 9.6** below.

Table 9.6: Operational Definitions of Covariates

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study population	Source for algorithm
Comorbidities	Asthma, COPD, Chronic Liver disease, Crohn's Disease, Diabetes mellitus, GERD, GI-Bleeding, HIV, Hyperlipidaemia, Hypertension, Obesity, Osteoarthritis, Pneumonia, Psoriasis, Renal impairment, Ulcerative Colitis, Urinary Tract infection, Viral Hepatitis, Visual system disorder, Schizophrenia, Dementia, Parkinson, Depressive disorder, Anxiety, Cancer	Counts	Anytime prior to index date: [-inf, -1]	Primary and outpatient specialist care	SNOMED	N/A	Persons with "new" use during the study period	N/A
Comedication	RAAS-Inhibitors, Antibacterials for systemic use, Antidepressants, Antiepileptics, Anti-inflammatory and antirheumatic products, Antineoplastic agents, Antipsoriatic agent, Antithrombotic	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

	agents, Beta blocking agents, Calcium channel blockers, Diuretics, Drugs for acid related disorders, Drugs for obstructive airway diseases, Drugs used in diabetes, Immunosuppressants, 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
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

9.7 Sample size

No formal sample size calculation has been conducted as this is a descriptive study, and all relevant prescriptions during the study period were included.

9.8 Data transformation

Analyses were conducted separately for each database. Before study execution across all databases, test runs of the study code were performed in the the CPRD database, and quality control checks on the code were performed. After all the tests were passed (see section 11 Quality Control), the final package was released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally executed the analytics against the OMOP-CDM in R Studio and reviewed and approved the by default aggregated results.

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

9.9 Statistical Methods

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

Table 9.7. Description of Study Types and Type of analysis

STUDY TYPE	TYPE OF ANALYSIS
Population Level DUS	- Population-based incidence rates - Population-based prevalence
Patient Level DUS	- Characterisation of patient-level features for new naloxone users - Frequency and % of indication/s - Estimation of minimum, 25th percentile (p25), median, 75th percentile (p75), and maximum initially prescribed or dispensed package of THN

9.9.1 Patient privacy protection

Cell suppression was applied as required by databases to protect people's privacy. Cell counts < 5 were suppressed.

9.9.2 Statistical model specification and assumptions of the analytical approach considered

R-packages

We used the R package "DrugUtilisation"[9] for the patient-level drug utilisation analyses including patient-level characterisation, and "IncidencePrevalence" package[10] for the population-level estimation of drug utilisation.

Drug exposure calculations

Drug eras were 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 were selected based on their first prescription of THN after the start of the study and/or after a pre-defined time window.

New users were required to not have been prescribed THN for at least 180 days prior to 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 did not fulfil the exposure washout criteria, the whole exposure is eliminated.

9.9.3 Methods to derive parameters of interest

Calendar time

Calendar time was based on the calendar year of the index prescription.

Age

Age at index date was calculated using January 1st of the year of birth as proxy for the actual birthday. The following age groups were used for stratification: 1-19, 20-39, 40-59, 60-79, >=80.

Sex

Results are presented stratified by sex.

Indication

THN was assumed to be solely prescribed for the treatment of opioid overdose in this study.

Characterisation of patient-level features

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

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

Population-level drug utilisation study

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

Prevalence calculations

Prevalence was 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 were calculated.

Incidence calculations

Annual incidence rates of the THN was calculated as the ratio of the number of **new users** after 180 days of no use to the total follow-up time of the population at risk of getting exposed during the period for each calendar year, and it was expressed as number of new users per 100,000 person-years. 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) are excluded. Those study participants who entered the denominator population then contributed time at risk up to their first prescription during the study period. Or if they did not have a drug exposure, they contributed time at risk up as described above in section 9.2.2 (study period and end of follow-up). Incidence rates are given together with 95% Poisson confidence intervals.

An illustration of the calculation of incidence of THN use is shown below in **Figure 9.9.2** 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.

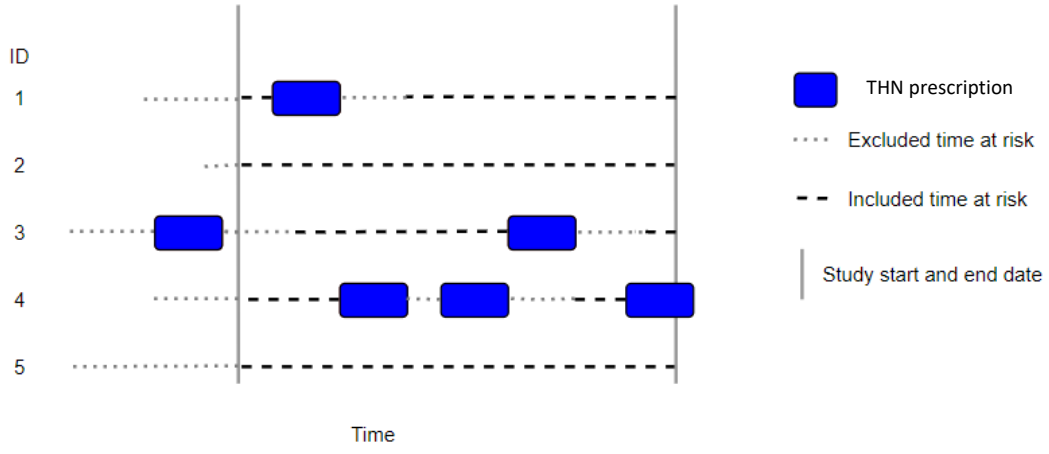


Figure 9.9.2: Incidence example

Patient-level drug utilisation study

Summary baseline characteristics

Summary baseline characteristics are 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) were provided.

9.9.5 Methods to control for potential sources of bias

All databases have been mapped into a standard format using the same OMOP common model to minimise potential bias from various source coding systems. Also, the new user design has been used with different washout periods in primary or sensitivity analysis to control for the bias from duplicate records.

9.9.6 Methods to deal with missing data

Absence of records

For the drug utilisation studies we assumed that the absence of a prescription record meant that the person did not receive the respective drug. For indications, we assumed that the missingness of a record of the respective condition meant that the condition was not present for the individual. Subjects with missing data for stratification factors (i.e., age, sex) were not included in the study.

Censoring

Follow-up time for individuals was censored if people left a GP practice that was contributing to the database (ie deregistered), if a practice stopped contributing data [CPRD only], the date of data extraction, or upon death.

9.9.7 Description of sensitivity analyses

One sensitivity analysis was conducted for this study (**Table 9.8**).

Table 1.8: Sensitivity analysis – 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 was reduced to 7 days	Washout window of 180 days might be too long to define a true new user	It can increase the sensitivity of defining a new user	It can decrease the specificity of defining a new user

9.9.8 Evidence synthesis

Results from analyses described are presented separately for each database and no meta-analysis of results was conducted.

9.10 Deviations from the protocol

Inclusion criteria:

Due to the scarcity of THN prescriptions in the included databases, we abstained from imposing the initial inclusion criteria requiring participants to have a minimum of one year of data availability prior to inclusion in both population-level and patient-level analyses in order to maximize the identification of all THN records.

10. DATA MANAGEMENT

10.1. Data management

All databases have previously mapped their data to the OMOP common data model. This enabled 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 was 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 was written in R. Each data partner executed the study code against their database containing patient-level data and then returned the results set which only contained aggregated data. The results from each of the contributing data sites were then be combined in tables and figures for this study report.

10.2. Data storage and protection

For this study, participants from various EU member states and from the UK processed personal data from individuals which was 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 were 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 were run, which generated non-identifiable aggregate summary results. All and any results with n<5 participants were suppressed using cell suppression to minimise risk of reidentification.

The output files were stored in the DARWIN EU Data transfer zone. These output files did not contain any data that allow identification of subjects included in the study. The DTZ implemented 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. 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 were excluded from the list of included naloxone codes. A pharmacist reviewed and refined the lists of relevant take-home naloxone products.

When defining cohorts for "opioid use disorder" and THN, a systematic search of possible codes for inclusion was conducted 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.

DrugExposureDiagnostic[11] was run in all databases to assess the use of different codes relevant to THN across the databases contributing to the study.

The study code is be based on two R packages developed for DARWIN EU to (1) estimate Incidence and Prevalence[10] and (2) characterize drug utilization[9] using the OMOP common data model.

12. RESULTS

12.1. Population-level DUS

12.1.1 Participants

THN prescriptions were only recorded in 2 (IQVIA DA Germany and CPRD GOLD) of the 4 data sources IQVIA DA Germany, and numbers of THN prescriptions during the study period were very small.

Tables 12.1- 12.4 describe the number of people included and excluded by each criterion in the 4 databases.

The whole background population amounted to 41,974,403 in IQVIA DA Germany and 17,054,819 people in CPRD GOLD. Of those, a small proportion (0.1%) of people were excluded due to the missing value or ineligibility in sex and age. 16,945,132 in IQVIA DA Germany and 11,246,731 in CPRD GOLD were further excluded due to not being observed during the study period.

Table 12.1 Number of participants in IQVIA DA Germany database during the study period overall

Step	number_records	number_subjects	reason	excluded_records	excluded_subjects
1	41,974,403	41,974,403	Starting population	NA	NA
2	41,974,403	41,974,403	Missing year of birth	0	0
3	41,945,861	41,945,861	Missing sex	28,542	28,542
4	41,868,485	41,868,485	Cannot satisfy age criteria during the study period based on year of birth	77,376	77,376
5	24,923,353	24,923,353	No observation time available during study period	16,945,132	16,945,132
6	24,923’353	24,923,353	Doesn't satisfy age criteria during the study period	0	0
7	24,923,353	24,923,353	Prior history requirement not fulfilled during study period	0	0
10	24,802,479	24,802,479	No observation time available after applying age, prior history and strata criteria	120,874	120,874
11	24,802,532	24,802,479	Starting analysis population	NA	NA
12	24,802,518	24,802,479	Excluded due to prior event (do not pass outcome washout during study period)	14	0
14	24,802,518	24,802,479	Not observed during the complete database interval	0	0

Table 12.2 Number of participants in IQVIA LPD Belgium database during the study period overall

Step	number_records	number_subjects	reason	excluded_records	excluded_subjects
1	1,128,345	1,128,345	Starting population	NA	NA
2	1,128,345	1,128,345	Missing year of birth	0	0
3	1,128,345	1,128,345	Missing sex	0	0
4	1,126,035	1,126,035	Cannot satisfy age criteria during the study period based on year of birth	2,310	2,310
5	865,636	865,636	No observation time available during study period	260,399	260,399
6	’65,636	865,636	Doesn't satisfy age criteria during the study period	0	0
7	865,636	865,636	Prior history requirement not fulfilled during study period	0	0
10	863,795	863,795	No observation time available after applying age, prior history and strata criteria	1,841	1,841
11	863,795	863,795	Starting analysis population	NA	NA
12	863,795	863,795	Excluded due to prior event (do not pass outcome washout during study period)	0	0
14	863,795	863,795	Not observed during the complete database interval	0	0

Table 12.3 Number of participants in SIDIAP database during the study period overall

Step	number_records	number_subjects	reason	excluded_records	excluded_subjects
1	8,265,343	8,265,343	Starting population	NA	NA
2	8,265,343	8,265,343	Missing year of birth	0	0
3	8,265,343	8,265,343	Missing sex	0	0
4	8,249,094	8,249,094	Cannot satisfy age criteria during the study period based on year of birth	16,249	16,249
5	6,723,923	6,723,923	No observation time available during study period	1,525,171	1,525,171
6	6,72’,923	6,723,923	Doesn't satisfy age criteria during the study period	0	0
7	6,723,923	6,723,923	Prior history requirement not fulfilled during study period	0	0
10	6,699,649	6,699,649	No observation time available after applying age, prior history and strata criteria	24,274	24,274
11	6,699,649	6,699,649	Starting analysis population	NA	NA
12	6,699,649	6,699,649	Excluded due to prior event (do not pass outcome washout during study period)	0	0
14	6,699,649	6,699,649	Not observed during the complete database interval	0	0

Table 12.4 Number of participants in CPRD GOLD database during the study period overall

Step	number_records	number_subjects	reason	excluded_records	excluded_subjects
1	17,054,819	17,054,819	Starting population	NA	NA
2	17,054,819	17,054,819	Missing year of birth	0	0
3	17,054,819	17,054,819	Missing sex	0	0
4	17,045,991	17,045,991	Cannot satisfy age criteria during the study period based on year of birth	8,828	8,828
5	5,799,260	5,799,260	No observation time available during study period	11,246,731	11,246,731
6	5,79’,260	5,799,260	Doesn't satisfy age criteria during the study period	0	0
7	5,799,260	5,799,260	Prior history requirement not fulfilled during study period	0	0
10	5,757,601	5,757,601	No observation time available after applying age, prior history and, strata criteria	41,659	41,659
11	5,757,625	5,757,601	Starting analysis population	NA	NA
12	5,757,602	5,757,601	Excluded due to prior event (do not pass outcome washout during study period)	23	0
14	5,757,602	5,757,601	Not observed during the complete database interval	0	0

12.1.2 Descriptive Data

Descriptive data on participants is provided in the patient level analyses section 12.2.

12.1.3 Main Results

Table 12.5 shows new prescriptions of THN from 2017 to 2022 in the general population for each database.

In the IQVIA DA Germany, no prescriptions of THN were recorded in 2017 and 2018, and only a very small number of prescriptions were recorded in the year after (21 prescriptions in 2019, 5 prescriptions in 2020, 13 prescriptions in 2021, and 11 prescriptions in 2022). The incidence rate of THN prescriptions in the studied years where exposure was recorded ranged between 0.06 (95% CI: 0.02 to 0.14) and 0.24 (95% CI: 0.15 to 0.36) per 100,000 person-years. Similarly, in CPRD GOLD a small number of THN prescriptions was recorded, with 7 incident THN users only in 2022, corresponding to an incidence rate of 0.53 (95% CI: 0.21 to 1.08) per 100,000 person-years. For the form of THN prescribed, only the nasal sprays were recorded in both databases during the study period with no records of injectable THN.

Table 12.6 shows new prescriptions of THN from 2017 to 2022 among a subgroup of people with "opioid user disorder" for IQVIA DA Germany, SIDIAP and CPRD GOLD. No people with a recorded "opioid use disorder" were identified from IQVIA LPD Belgium.

In IQVIA DA Germany, there were 7 incident THN users in 2019 among patients with opioid use disorder. The incidence rate was 197 (95% 79 to 406) per 100,000 person-years. No THN users were identified within the opioid use disorder population in CPRD GOLD or SIDIAP.

For the form of THN prescribed, only the nasal sprays were recorded in IQVIA DA Germany and CPRD GOLD during the study period with no records of injectable THN.

Table 12.5 Incidence rates of THN use over time in general population

THN drug form	Data Partner	Year	N	Person-Days	Events	Incidence per 100,000 pys (95%CI)
Overall	IQVIA DA Germany	2017	11,309,310	3,248,342,213	0	0 (0 to 0.04)
		2018	11,360,453	3,262,186,556	0	0 (0 to 0.04)
		2019	11,625,537	3,221,166,699	21	0.24 (0.15 to 0.36)
		2020	11,375,015	3,118,093,765	5	0.06 (0.02 to 0.14)
		2021	11,294,129	2,837,867,946	13	0.17 (0.09 to 0.29)
		2022	9,501,222	2,095,690,170	11	0.19 (0.10 to 0.34)
	IQVIA LPD Belgium	2017	496,179	153,191,126	0	0 (0 to 0.9)
		2018	503,514	154,867,641	0	0 (0 to 0.9)
		2019	504,388	155,515,132	0	0 (0 to 0.9)
		2020	482,943	154,283,253	0	0 (0 to 0.9)
		2021	526,830	153,763,798	0	0 (0 to 0.9)
		2022	416,702	109,461,316	0	0 (0 to 1.2)
	SIDIAP	2017	5,932,692	2,112,325,867	0	0 (0 to 0.06)
		2018	5,973,619	2,122,588,609	0	0 (0 to 0.06)
		2019	6,016,044	2,137,185,751	0	0 (0 to 0.06)
		2020	6,016,067	2,152,557,891	0	0 (0 to 0.06)

		2021	6,020,953	2,139,718,808	0	0 (0 to 0.06)
		2022	5,946,177	1,060,000,632	0	0 (0 to 0.12)
	CPRD GOLD	2017	4,632,119	1,530,029,893	0	0 (0 to 0.08)
		2018	4,328,398	1,449,802,120	0	0 (0 to 0.09)
		2019	4,183,296	1,395,564,350	0	0 (0 to 0.09)
		2020	3,904,171	1,294,246,485	NA	NA
		2021	3,574,236	1,158,513,224	0	0 (0 to 0.12)
		2022	3,160,110	485,861,136	7	0.53 (0.21 to 1.08)
Nasal	IQVIA DA Germany	2017	11,309,310	3,248,342,213	0	0 (0 to 0.04)
		2018	11,360,453	3,262,186,556	0	0 (0 to 0.04)
		2019	11,625,537	3,221,166,699	21	0.24 (0.15 to 0.36)
		2020	11,375,015	3,118,093,765	5	0.06 (0.02 to 0.14)
		2021	11,294,129	2,837,867,946	13	0.17 (0.09 to 0.29)
		2022	9,501,222	2,095,690,170	11	0.19 (0.10 to 0.34)
	IQVIA LPD Belgium	2017	496,179	153,191,126	0	0 (0 to 0.9)
		2018	503,514	154,867,641	0	0 (0 to 0.9)
		2019	504,388	155,515,132	0	0 (0 to 0.9)
		2020	482,943	154,283,253	0	0 (0 to 0.9)
		2021	526,830	153,763,798	0	0 (0 to 0.9)
		2022	416,702	109,461,316	0	0 (0 to 1.2)
	SIDIAP	2017	5,932,692	2,112,325,867	0	0 (0 to 0.06)
		2018	5,973,619	2,122,588,609	0	0 (0 to 0.06)
		2019	6,016,044	2,137,185,751	0	0 (0 to 0.06)
		2020	6,016,067	2,152,557,891	0	0 (0 to 0.06)
		2021	6,020,953	2,139,718,808	0	0 (0 to 0.06)
		2022	5,946,177	1,060,000,632	0	0 (0 to 0.12)
	CPRD GOLD	2017	4,632,119	1,530,029,893	0	0 (0 to 0.08)
		2018	4,328,398	1,449,802,120	0	0 (0 to 0.09)
		2019	4,183,296	1,395,564,350	0	0 (0 to 0.09)
		2020	3,904,171	1,294,246,485	NA	NA
		2021	3,574,236	1,158,513,224	0	0 (0 to 0.12)
		2022	3,160,110	485,861,136	7	0.53 (0.21 to 1.08)
Injection	IQVIA DA Germany	2017	11,309,310	3,248,341,848	0	0 (0 to 0.04)
		2018	11,360,453	3,262,186,191	0	0 (0 to 0.04)
		2019	11,625,537	3,221,169,430	0	0 (0 to 0.04)
		2020	11,375,016	3,118,095,351	0	0 (0 to 0.04)
		2021	11,294,129	2,837,869,723	0	0 (0 to 0.04)
		2022	9,501,222	2,095,691,598	0	0 (0 to 0.06)
	IQVIA LPD Belgium	2017	496,179	153,191,126	0	0 (0 to 0.9)
		2018	503,514	154,867,641	0	0 (0 to 0.9)
		2019	504,388	155,515,132	0	0 (0 to 0.9)
		2020	482,943	154,283,253	0	0 (0 to 0.9)
		2021	526,830	153,763,798	0	0 (0 to 0.9)
		2022	416,702	109,461,316	0	0 (0 to 1.2)
	SIDIAP	2017	5,932,692	2,112,325,867	0	0 (0 to 0.06)
		2018	5,973,619	2,122,588,609	0	0 (0 to 0.06)
		2019	6,016,044	2,137,185,751	0	0 (0 to 0.06)
		2020	6,016,067	2,152,557,891	0	0 (0 to 0.06)
		2021	6,020,953	2,139,718,808	0	0 (0 to 0.06)
		2022	5,946,177	1,060,000,632	0	0 (0 to 0.12)
	CPRD GOLD	2017	4,632,119	1,530,029,893	0	0 (0 to 0.08)

		2018	4,328,398	1,449,802,120	0	0 (0 to 0.09)
		2019	4,183,296	1,395,564,350	0	0 (0 to 0.09)
		2020	3,904,171	1,294,246,554	0	0 (0 to 0.10)
		2021	3,574,236	1,158,513,335	0	0 (0 to 0.12)
		2022	3,160,110	485,861,359	0	0 (0 to 0.27)

NA: not available due to number of users less than 5

Table 12.6 Incidence rates of THN use over time among the opioid user disorder population

THN drug form	Data Partner	Year	N	Person-Days	Events	Incidence per 100,000 pys (95%CI)
Overall	IQVIA DA Germany	2017	2,741	357,508	0	0 (0 to 376)
		2018	4,317	887,921	0	0 (0 to 151)
		2019	5,712	1,295,857	7	197 (79 to 406)
		2020	6,627	1,597,117	NA	NA
		2021	6,730	1,695,864	NA	NA
		2022	7,174	1,640,497	NA	NA
	IQVIA LPD Belgium	2017-2022	NA	NA	NA	NA
	SIDIAP	2017	359	61,526	0	0 (0 to 2189)
		2018	736	206,003	0	0 (0 to 654)
		2019	1,113	331,945	0	0 (0 to 405)
		2020	1,698	488,904	0	0 (0 to 275)
		2021	2,475	758,688	0	0 (0 to 177)
		2022	2,676	449,532	0	0 (0 to 299)
	CPRD GOLD	2017	601	101,328	0	0 (0 to 1329)
		2018	1,048	261,188	0	0 (0 to 515)
		2019	1,418	391,297	0	0 (0 to 344)
		2020	1,613	474,940	0	0 (0 to 283)
		2021	1,729	514,278	0	0 (0 to 261)
		2022	1,612	240,509	NA	NA
Nasal	IQVIA DA Germany	2017	2,741	357,508	0	0 (0 to 376)
		2018	4,317	887,921	0	0 (0 to 151)
		2019	5,712	1,295,857	7	197 (79 to 406)
		2020	6,627	1,597,117	NA	NA
		2021	6,730	1,695,864	NA	NA
		2022	7,174	1,640,497	NA	NA
	IQVIA LPD Belgium	2017-2022	NA	NA	NA	NA
	SIDIAP	2017	359	61,526	0	0 (0 to 2189)
		2018	736	206,003	0	0 (0 to 654)
		2019	1,113	331,945	0	0 (0 to 405)
		2020	1,698	488,904	0	0 (0 to 275)
		2021	2,475	758,688	0	0 (0 to 177)
		2022	2,676	449,532	0	0 (0 to 299)
	CPRD GOLD	2017	601	101,328	0	0 (0 to 1329)
		2018	1,048	261,188	0	0 (0 to 515)
		2019	1,418	391,297	0	0 (0 to 344)
		2020	1,613	474,940	0	0 (0 to 283)
		2021	1,729	514,278	0	0 (0 to 261)
		2022	1,612	240,509	NA	NA
Injection	IQVIA DA Germany	2017	2,741	357,508	0	0 (0 to 376)
		2018	4,317	887,921	0	0 (0 to 151)

		2019	5,712	1,296,954	0	0 (0 to 103)
		2020	6,627	1,597,898	0	0 (0 to 84)
		2021	6,730	1,696,493	0	0 (0 to 79)
		2022	7,174	1,641,019	0	0 (0 to 82)
	IQVIA LPD Belgium	2017-2022	NA	NA	NA	NA
	SIDIAP	2017	359	61,526	0	0 (0 to 2189)
		2018	736	206,003	0	0 (0 to 654)
		2019	1,113	331,945	0	0 (0 to 405)
		2020	1,698	488,904	0	0 (0 to 275)
		2021	2,475	758,688	0	0 (0 to 177)
		2022	2,676	449,532	0	0 (0 to 299)
	CPRD GOLD	2017	601	101,328	0	0 (0 to 1329)
		2018	1,048	261,188	0	0 (0 to 515)
		2019	1,418	391,297	0	0 (0 to 344)
		2020	1,613	474,940	0	0 (0 to 283)
		2021	1,729	514,278	0	0 (0 to 261)
		2022	1,612	240,571	0	0 (0 to 560)

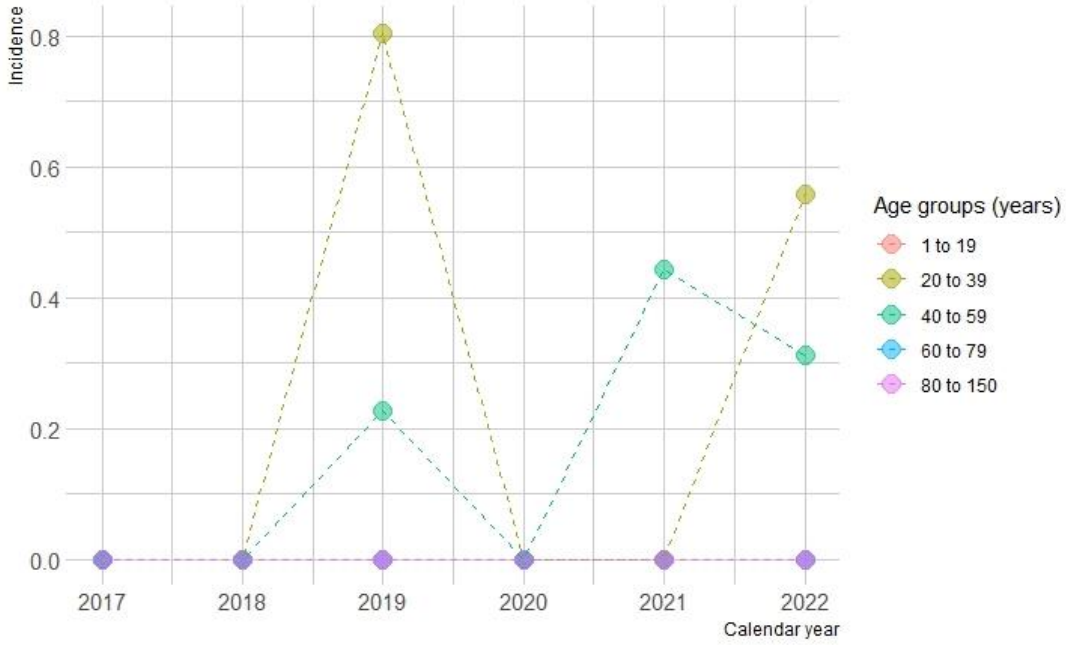
Note: Denominator counts for this cohort are small, hence the upper 95%CI is very large. This upper 95%CI should be interpreted with great caution.

Figure 12.1 shows the incidence of THN prescriptions from 2017 to 2022 within the general population, stratified by age group. The results indicate that in IQVIA DA Germany, only individuals aged between 20 and 59 were prescribed THN, whereas in CPRD GOLD, this age range was narrower, including only individuals between 40 and 59 years old.

Figure 12.2 shows the incidence of THN prescriptions from 2017 to 2022 within the general population, stratified by sex. In general, males consistently had a higher incidence of THN use than females over the years in both IQVIA DA Germany and CPRD GOLD databases.

Figure 12.1 Incidence rates of THN use over time, stratified by age

IQVIA DA Germany



CPRD GOLD

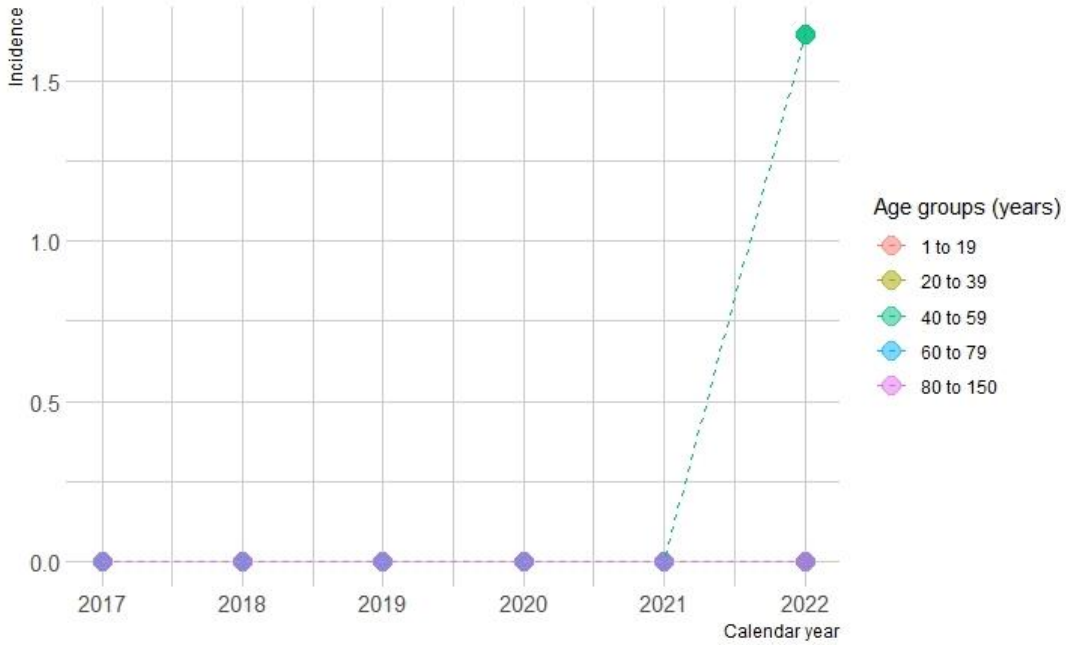
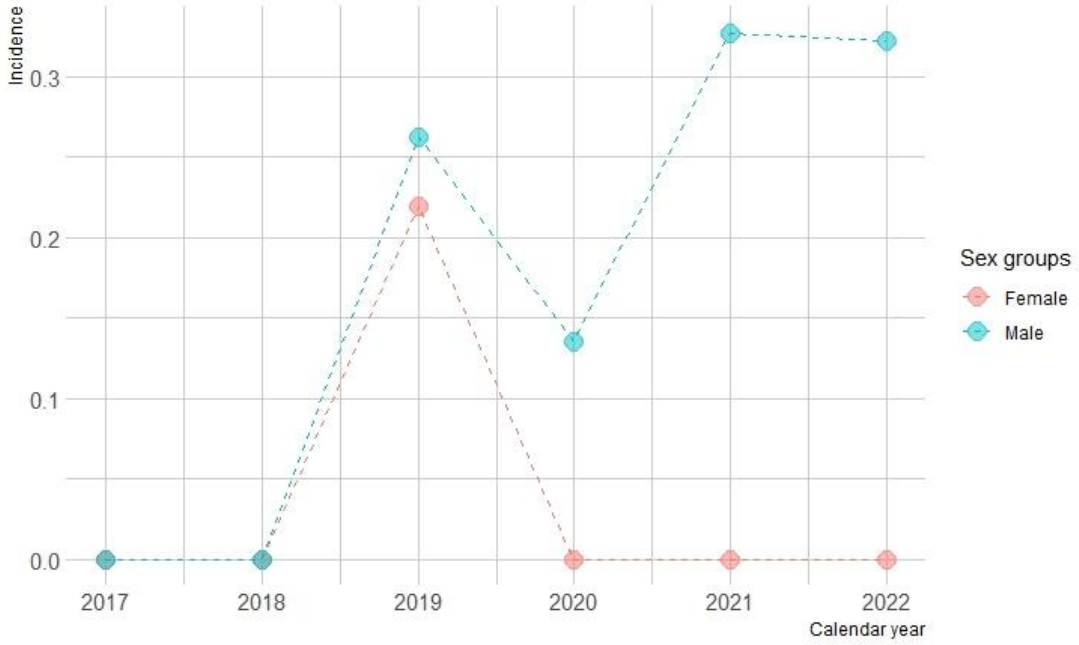


Figure 12.2 Incidence rates of THN use over time, stratified by sex

IQVIA DA Germany



CPRD GOLD

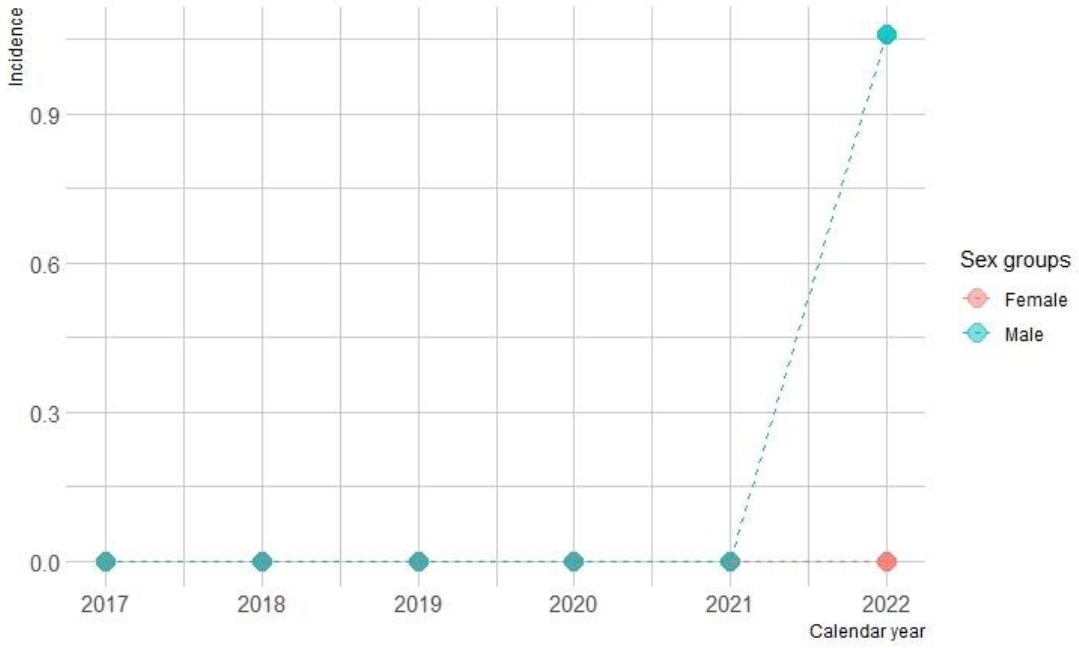


Table 12.5 shows the prevalence of THN from 2017 to 2022 in the general population for each database.

In IQVIA DA Germany, no THN use was recorded in 2017 and 2018, followed by a very small number of THN prescriptions thereafter. The prevalence of THN prescriptions ranged between 0.11 (95% CI: 0.06 to 0.20) and 0.18 (95% CI: 0.11 to 0.27) per 10,000 persons. Similarly, the CPRD GOLD recorded a small number of THN users (7) in 2022, corresponding to a prevalence of 0.22 (95% CI:0.10 to 0.45) per 10,000 persons. No THN records were seen in SIDIAP or IQVIA LPD Belgium. For the drug form of THN prescribed, only the nasal sprays were observed in both databases with no records of injectable THN.

Table 12.6 shows new prescriptions of THN from 2017 to 2022 among the subpopulation of people with opioid user disorder for each database.

In the IQVIA DA Germany, there were 7 THN users in 2019 amongst people with opioid use disorder. The prevalence was 120 (60 to 250) per 10,000 persons. No THN prescriptions were identified among the opioid use disorder population in CPRD GOLD or SIDIAP. For the drug form of THN prescribed, only the nasal sprays were recorded in CPRD GOLD and IQVIA DA Germany. No individuals with a recorded “opioid use disorder” were identified from IQVIA LPD Belgium during the study period.

Table 12.5 Prevalence of THN use over time in general population

THN drug form	Data Partner	Year	N	Events	Prevalence per 10,000 (95% CI)
Overall	IQVIA DA Germany	2017	11,309,310	0	0 (0 to 0.03)
		2018	11,360,453	0	0 (0 to 0.03)
		2019	11,625,537	21	0.18 (0.11 to 0.27)
		2020	11,375,016	NA	NA
		2021	11,294,129	14	0.12 (0.07 to 0.20)
		2022	9,501,222	11	0.11 (0.06 to 0.20)
	IQVIA LPD Belgium	2017	496,179	0	0 (0 to 0.7)
		2018	503,514	0	0 (0 to 0.7)
		2019	504,388	0	0 (0 to 0.7)
		2020	482,943	0	0 (0 to 0.7)
		2021	526,830	0	0 (0 to 0.7)
		2022	416,702	0	0 (0 to 0.9)
	SIDIAP	2017	5,932,692	0	0 (0 to 0.06)
		2018	5,973,619	0	0 (0 to 0.06)
		2019	6,016,044	0	0 (0 to 0.06)
		2020	6,016,067	0	0 (0 to 0.06)
		2021	6,020,953	0	0 (0 to 0.06)
		2022	5,946,177	0	0 (0 to 0.06)
	CPRD GOLD	2017	4,632,119	0	0 (0 to 0.08)
		2018	4,328,398	0	0 (0 to 0.08)
		2019	4,183,296	0	0 (0 to 0.09)
		2020	3,904,171	NA	NA
		2021	3,574,236	0	0 (0 to 0.10)
		2022	3,160,110	7	0.22 (0.10 to 0.45)
Nasal	IQVIA DA Germany	2017	11,309,310	0	0 (0 to 0.03)
		2018	11,360,453	0	0 (0 to 0.03)
		2019	11,625,537	21	0.18 (0.11 to 0.27)
		2020	11,375,016	NA	NA

		2021	11,294,129	14	0.12 (0.07 to 0.20)
		2022	9,501,222	11	0.11 (0.06 to 0.20)
	IQVIA LPD Belgium	2017	496,179	0	0 (0 to 0.7)
		2018	503,514	0	0 (0 to 0.7)
		2019	504,388	0	0 (0 to 0.7)
		2020	482,943	0	0 (0 to 0.7)
		2021	526,830	0	0 (0 to 0.7)
		2022	416,702	0	0 (0 to 0.9)
	SIDIAP	2017	5,932,692	0	0 (0 to 0.06)
		2018	5,973,619	0	0 (0 to 0.06)
		2019	6,016,044	0	0 (0 to 0.06)
		2020	6,016,067	0	0 (0 to 0.06)
		2021	6,020,953	0	0 (0 to 0.06)
		2022	5,946,177	0	0 (0 to 0.06)
	CPRD GOLD	2017	4,632,119	0	0 (0 to 0.08)
		2018	4,328,398	0	0 (0 to 0.08)
		2019	4,183,296	0	0 (0 to 0.09)
		2020	3,904,171	NA	NA
		2021	3,574,236	0	0 (0 to 0.10)
		2022	3,160,110	7	0.22 (0.10 to 0.45)
Injection	IQVIA DA Germany	2017	11,309,310	0	0 (0 to 0.03)
		2018	11,360,453	0	0 (0 to 0.03)
		2019	11,625,537	0	0 (0 to 0.03)
		2020	11,375,016	0	0 (0 to 0.03)
		2021	11,294,129	0	0 (0 to 0.03)
		2022	9,501,222	0	0 (0 to 0.04)
	IQVIA LPD Belgium	2017	496,179	0	0 (0 to 0.7)
		2018	503,514	0	0 (0 to 0.7)
		2019	504,388	0	0 (0 to 0.7)
		2020	482,943	0	0 (0 to 0.7)
		2021	526,830	0	0 (0 to 0.7)
		2022	416,702	0	0 (0 to 0.9)
	SIDIAP	2017	5,932,692	0	0 (0 to 0.06)
		2018	5,973,619	0	0 (0 to 0.06)
		2019	6,016,044	0	0 (0 to 0.06)
		2020	6,016,067	0	0 (0 to 0.06)
		2021	6,020,953	0	0 (0 to 0.06)
		2022	5,946,177	0	0 (0 to 0.06)
	CPRD GOLD	2017	4,632,119	0	0 (0 to 0.08)
		2018	4,328,398	0	0 (0 to 0.08)
		2019	4,183,296	0	0 (0 to 0.09)
		2020	3,904,171	0	0 (0 to 0.09)
		2021	3,574,236	0	0 (0 to 0.10)
		2022	3,160,110	0	0 (0 to 0.12)

NA: not available due to number of users less than 5

Table 12.6 Prevalence of THN use over time among the opioid user disorder population

THN drug form	Data Partner	Year	N	Events	Prevalence per 10,000 (95% CI)
Overall	IQVIA DA Germany	2017	2,741	0	0 (0 to 139)
		2018	4,317	0	0 (0 to 88)
		2019	5,712	7	120 (60 to 250)
		2020	6,627	NA	NA
		2021	6,730	NA	NA
		2022	7,174	NA	NA
	IQVIA LPD Belgium	2017-2022	NA	NA	NA
	SIDIAP	2017	359	0	0 (0 to 1058)
		2018	736	0	0 (0 to 519)
		2019	1,113	0	0 (0 to 343)
		2020	1,698	0	0 (0 to 225)
		2021	2,475	0	0 (0 to 154)
		2022	2,676	0	0 (0 to 143)
	CPRD GOLD	2017	601	0	0 (0 to 635)
		2018	1,048	0	0 (0 to 365)
		2019	1,418	0	0 (0 to 270)
		2020	1,613	0	0 (0 to 237)
		2021	1,729	0	0 (0 to 221)
		2022	1,612	NA	NA
Nasal	IQVIA DA Germany	2017	2,741	0	0 (0 to 139)
		2018	4,317	0	0 (0 to 88)
		2019	5,712	7	120 (60 to 250)
		2020	6,627	NA	NA
		2021	6,730	NA	NA
		2022	7,174	NA	NA
	IQVIA LPD Belgium	2017-2022	NA	NA	NA
	SIDIAP	2017	359	0	0 (0 to 1058)
		2018	736	0	0 (0 to 519)
		2019	1,113	0	0 (0 to 343)
		2020	1,698	0	0 (0 to 225)
		2021	2,475	0	0 (0 to 154)
		2022	2,676	0	0 (0 to 143)
	CPRD GOLD	2017	601	0	0 (0 to 635)
		2018	1,048	0	0 (0 to 365)
		2019	1,418	0	0 (0 to 270)
		2020	1,613	0	0 (0 to 237)
		2021	1,729	0	0 (0 to 221)
		2022	1,612	NA	NA
Injection	IQVIA DA Germany	2017	2,741	0	0 (0 to 139)
		2018	4,317	0	0 (0 to 88)
		2019	5,712	0	0 (0 to 67)
		2020	6,627	0	0 (0 to 57)
		2021	6,730	0	0 (0 to 57)
		2022	7,174	0	0 (0 to 53)
	IQVIA LPD Belgium	2017-2022	NA	NA	NA
	SIDIAP	2017	359	0	0 (0 to 1058)
		2018	736	0	0 (0 to 519)
		2019	1,113	0	0 (0 to 343)

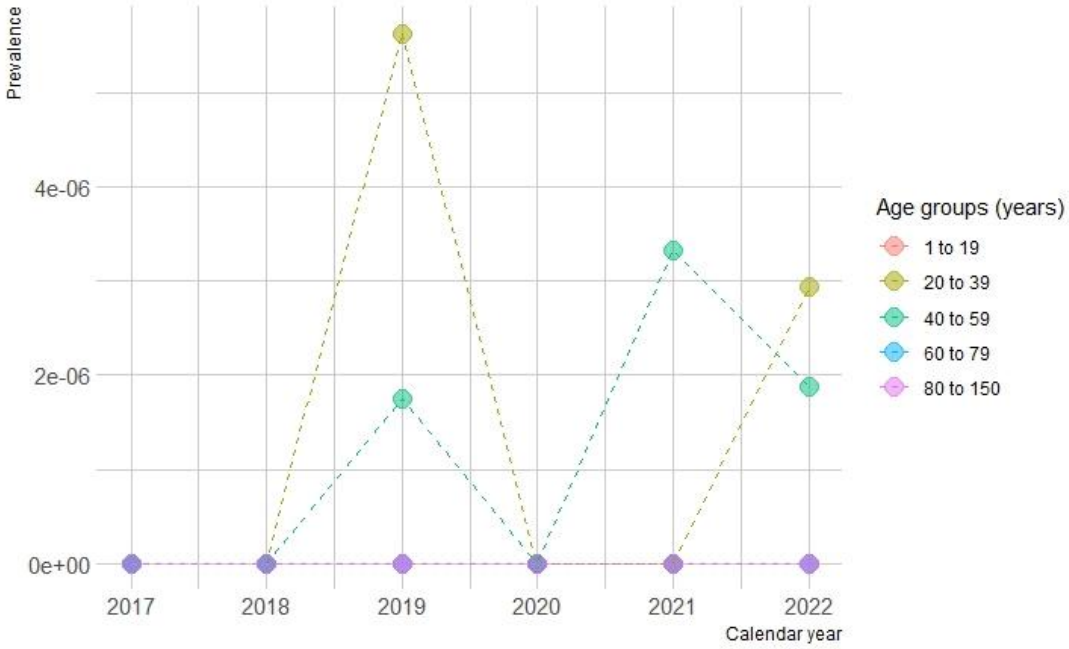
		2020	1,698	0	0 (0 to 225)
		2021	2,475	0	0 (0 to 154)
		2022	2,676	0	0 (0 to 143)
	CPRD GOLD	2017	601	0	0 (0 to 635)
		2018	1,048	0	0 (0 to 365)
		2019	1,418	0	0 (0 to 270)
		2020	1,613	0	0 (0 to 237)
		2021	1,729	0	0 (0 to 221)
		2022	1,612	0	0 (0 to 237)

Figure 12.3 shows the prevalence of THN prescriptions from 2017 to 2022 within the general population, stratified by age group. The results show recorded THN exposure only in individuals aged between 20 and 59 in IQVIA DA Germany, whereas in CPRD GOLD, this age range was narrower, including only individuals between 40 and 59 years old.

Figure 12.4 shows the prevalence of THN prescriptions from 2017 to 2022 within the general population, stratified by sex. In general, male consistently had a higher prevalence of THN use than female over the years in both IQVIA DA Germany and CPRD GOLD databases.

Figure 12.3 Prevalence of THN use over time, stratified by age

IQVIA DA Germany



CPRD GOLD

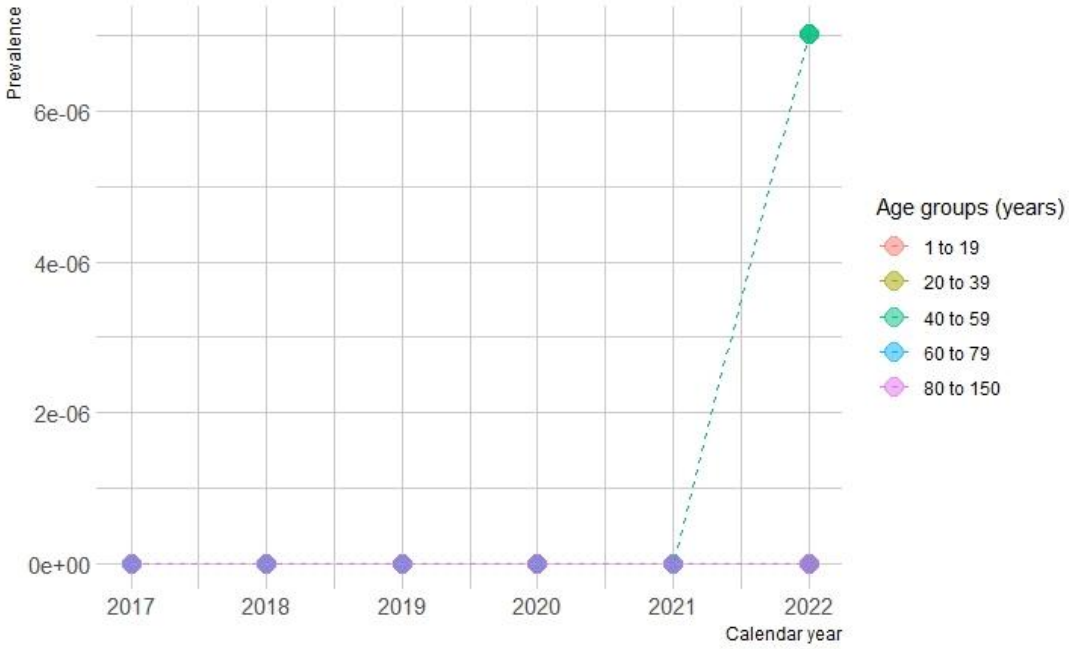
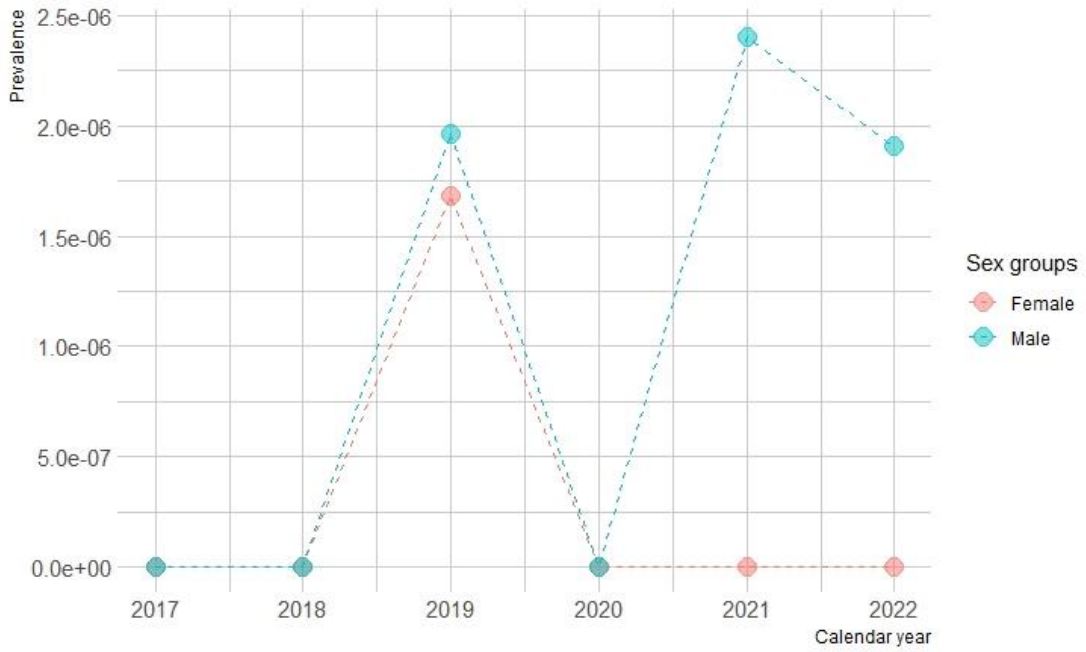
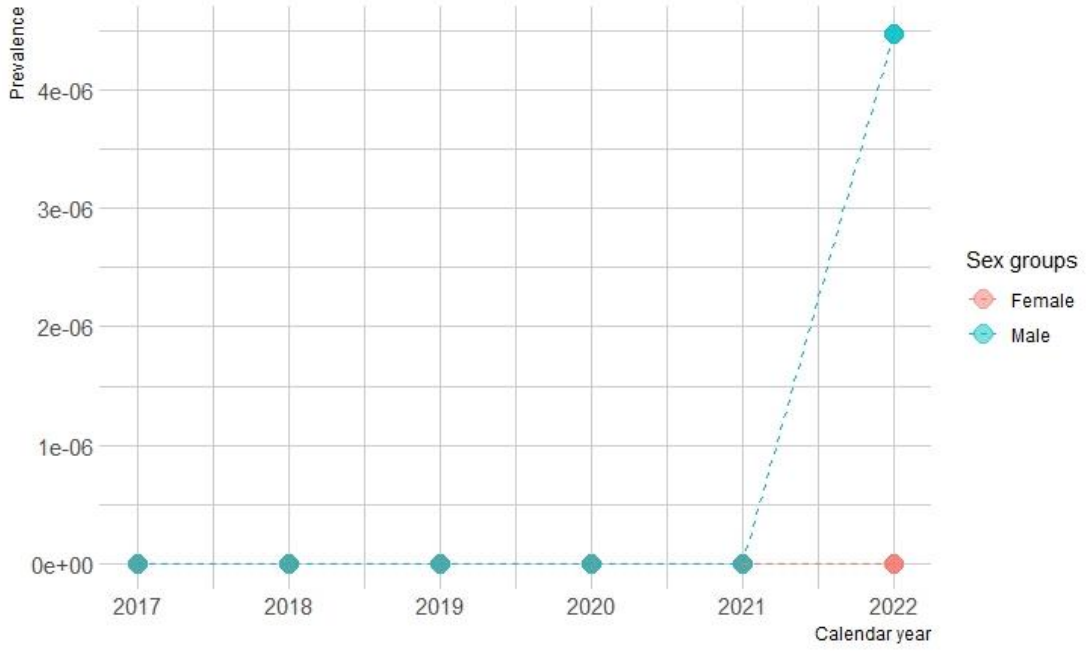


Figure 12.4 Prevalence of THN use over time, stratified by sex

IQVIA DA Germany



CPRD GOLD



12.2. Patient-level DUS

Results from patient-level DUS for THN are provided for IQVIA DA Germany and CPRD GOLD. No THN products were recorded in SIDIAP and IQVIA LPD Belgium during the study period.

12.2.1. Participants

During the entire study period, 48 (53 prescription records) and 8 (8 prescription records) new and distinct THN users were seen in IQVIA DA Germany and CPRD GOLD databases, respectively.

12.2.2. Main Results

Summary characterisation

The median age for participants was 40.0 and 45.5 years, in IQVIA DA Germany and CPRD GOLD databases, respectively. In IQVIA DA Germany cohort, 66% of the participants were male, compared to 100% in CPRD GOLD cohort. The most prevalent comorbidity observed was depressive disorder, identified in 62% of IQVIA DA Germany cohort and 62.5% of CPRD GOLD cohort. No previous records of opioid overdose were recorded in new THN users in both databases, and history of prescribed opioid use was rare.

Detailed results are presented in Table 12.7 and Table 12.8 below.

Number of prescriptions

In IQVIA DA Germany, there were 53 incident prescriptions attributed to 48 unique users. Similarly, in CPRD GOLD, there were 8 incident prescriptions recorded for 8 unique users (Table 12.9), which means most THN users were only prescribed once during the study period. For the prescribed products, there was a median of 2 nasal sprays in each package for THN prescriptions in both IQVIA DA Germany and CPRD GOLD database. Therefore, with number of nasal sprays per prescription/2 sprays per package, the median number of packages per prescriptions was 1.

Sensitivity analysis

Results from sensitivity analysis using the 180 days washout period align with the primary analysis using the 7 days washout period for defining a new user.

Table 12.7 Baseline characteristics of THN drug users in IQVIA DA Germany during the whole study period for all age groups

Characteristics	Estimate type	7 days washout	180 days washout
Number of new users based on new prescriptions	N	53	50
Age	Median [IQR]	40 [34 – 46]	40 [33 - 45]
Sex:male	N, %	35 (66%)	33 (66%)
Medical conditions			
Anxiety	N, %	9 (17%)	9 (18%)
Asthma	N, %	5 (9%)	<5
Chronic kidney disease	N, %	<5	<5
Chronic liver disease	N, %	7 (13%)	7 (14%)
COPD	N, %	10 (19%)	9 (18%)
Dementia	N, %	0 (0%)	0 (0%)
Depressive disorder	N, %	32 (60%)	31 (62%)
Diabetes	N, %	<5	<5
.GERD	N, %	<5	<5
Heart failure	N, %	0 (0%)	0 (0%)
HIV	N, %	<5	<5
Hypertension	N, %	7 (13%)	6 (12%)
Hypothyroidism	N, %	0 (0%)	0 (0%)
Inflammatory bowel disease	N, %	<5	<5
Malignant neoplastic disease	N, %	<5	<5
Myocardial infarction	N, %	0 (0%)	0 (0%)
Opioid overdose	N, %	0 (0%)	0 (0%)
Osteoporosis	N, %	0 (0%)	0 (0%)
Pneumonia	N, %	0 (0%)	0 (0%)
Rheumatoid arthritis	N, %	0 (0%)	0 (0%)
Stroke	N, %	<5	<5
Venous thromboembolism	N, %	<5	<5
Medications			
RAAS-Inhibitors	N, %	<5	<5
Antibacterials, systemic	N, %	5 (9%)	<5
Antidepressants	N, %	6 (11%)	6 (12%)
Antiepileptics	N, %	0 (0%)	0 (0%)
Anti-inflammatory, anti-rheumatic drugs	N, %	<5	<5
Antineoplastic agents	N, %	0 (0%)	0 (0%)
Antithrombotic	N, %	<5	0
Beta blocking agents	N, %	<5	<5
Calcium channel blockers	N, %	0 (0%)	0 (0%)
Diuretics	N, %	<5	<5
Drugs acid related disorder	N, %	<5	<5
Drugs obstructive airway diseases	N, %	5 (9%)	<5
Drugs used in diabetes	N, %	<5	<5

Characteristics	Estimate type	7 days washout	180 days washout
Hormonal contraceptives, systemic	N, %	0 (0%)	0 (0%)
Immunosuppressants	N, %	0 (0%)	0 (0%)
Lipid modifying agents	N, %	0 (0%)	0 (0%)
Opioids	N, %	<5	<5
Psycholeptics	N, %	6 (11%)	5 (10%)
Psychostimulants	N, %	0 (0%)	0 (0%)

Table 12.8 Baseline characteristics of THN drug users in CPRD GOLD during the whole study period for all age groups

Characteristics	Estimate type	7 days washout	180 days washout
Number of new users based on new prescriptions	N	8	8
Age	median	46 [44 - 47]	46 [44 - 47]
Sex:male	N, %	8 (100%)	8 (100%)
Medical conditions			
Anxiety	N, %	5 (63%)	5 (63%)
Asthma	N, %	<5	<5
Chronic kidney disease	N, %	0 (0%)	0 (0%)
Chronic liver disease	N, %	0 (0%)	0 (0%)
COPD	N, %	<5	<5
Dementia	N, %	0 (0%)	0 (0%)
Depressive disorder	N, %	5 (63%)	5 (63%)
Diabetes	N, %	0 (0%)	0 (0%)
Gerd	N, %	<5	<5
Heart failure	N, %	0 (0%)	0 (0%)
Hiv	N, %	0 (0%)	0 (0%)
Hypertension	N, %	0 (0%)	0 (0%)
Hypothyroidism	N, %	<5	<5
Inflammatory bowel disease	N, %	0 (0%)	0 (0%)
Malignant neoplastic disease	N, %	0 (0%)	0 (0%)
Myocardial infarction	N, %	0 (0%)	0 (0%)
Opioid overdose	N, %	0 (0%)	0 (0%)
Osteoporosis	N, %	0 (0%)	0 (0%)
Pneumonia	N, %	0 (0%)	0 (0%)
Rheumatoid arthritis	N, %	0 (0%)	0 (0%)
Stroke	N, %	0 (0%)	0 (0%)
Venous thromboembolism	N, %	0 (0%)	0 (0%)
Medications			
RAAS-Inhibitors	N, %	0 (0%)	0 (0%)
Antibacterials, systemic	N, %	0 (0%)	0 (0%)
Antidepressants	N, %	<5	<5
Antiepileptics	N, %	0 (0%)	0 (0%)
Anti-inflammatory, anti-rheumatic drugs	N, %	0 (0%)	0 (0%)

Characteristics	Estimate type	7 days washout	180 days washout
Antineoplastic agents	N, %	0 (0%)	0 (0%)
Antithrombotic	N, %	0 (0%)	0 (0%)
Beta blocking agents	N, %	0 (0%)	0 (0%)
Calcium channel blockers	N, %	0 (0%)	0 (0%)
Diuretics	N, %	0 (0%)	0 (0%)
Drugs acid related disorder	N, %	0 (0%)	0 (0%)
Drugs obstructive airway disorder	N, %	<5	<5
Drugs used in diabetes	N, %	0 (0%)	0 (0%)
Hormonal contraceptives, systemic	N, %	0 (0%)	0 (0%)
Immunosuppressants	N, %	0 (0%)	0 (0%)
Lipid modifying agents	N, %	0 (0%)	0 (0%)
Opioids	N, %	<5	<5
Psycholeptics	N, %	0 (0%)	0 (0%)
Psychostimulants	N, %	0 (0%)	0 (0%)

Table 12.9 Number of THN users and prescriptions

	IQVIA DA Germany (7 days washout)	IQVIA DA Germany (180 days washout)	CPRD GOLD (7 days washout)	CPRD GOLD (180 days washout)
Number of subjects	48	48	8	8
Number of records	53	50	8	8
Number of nasal sprays per prescription*				
Mean	2.0	2.0	1.8	1.8
Median	2	2	2	2
Q25	2	2	2	2
Q75	2	2	2	2

*For the studied THN products, each package contains 2 nasal sprays. Therefore, the median number of packages per prescription is N/2

13 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions were not collected or analyzed as part of this study. The nature of this non-interventional study, through the use of secondary data, does not fulfill the criteria for reporting adverse events, according to module VI, VI.C.1.2.1.2 of the Good Pharmacovigilance Practices (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf)

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

14 DISCUSSION

14.1 Key Results

Population level DUS

No THN prescription records were identified in IQVIA LPD Belgium or SIDIAP, and only limited recording in IQVIA DA Germany and CPRD GOLD.

In the general population cohort from IQVIA DA Germany, no THN prescriptions were recorded in 2017 and 2018, with a small number of new prescriptions recorded in the following years. The incidence rates of THN prescription ranged between 0.06 and 0.24 per 100,000 person-years. In CPRD GOLD database, 7 new THN prescriptions were recorded in 2022, equal to an incidence rate of 0.53 per 100,000 person-years. In both databases where some THN prescription records were captured, all consisted of drug forms for nasal administration with no prescription records for injectables captured.

Among 5,712 people with a recorded diagnosis of opioid use disorder in 2019, 7 new THN prescriptions were recorded in IQVIA DA Germany, resulting in an incidence rate of 197 per 100,000 person-years. However, in CPRD GOLD no THN prescription records were seen among individuals from this subpopulation.

The prevalence of THN prescription was similar to its incidence in both magnitude, pattern and trend.

Patient-level DUS

During the study, 53 new THN records were identified in IQVIA DA Germany database and 8 in CPRD GOLD database. The median age of participants was 40.0 and 45.5 years, respectively. In the IQVIA DA Germany cohort, the proportion of males was higher than females (66% vs. 34%), whereas the CPRD GOLD cohort consisted entirely of males. Depressive disorder was the most common comorbidity in both cohorts, present in 62% of the IQVIA Germany DA cohort and 62.5% of the CPRD GOLD cohort. No previous diagnosis of opioid overdose were recorded in new THN users in both databases, and history of recorded prescription for opioid use was rare.

The IQVIA DA Germany cohort had 53 incident prescriptions from 48 distinct users, while each of the 8 incident THN prescriptions in the CPRD GOLD cohort was linked to a unique user.

The sensitivity analysis supported the primary findings, showing that the results remain consistent regardless of the washout period (7 days or 180 days) used to define new users.

14.2 Limitations of the research methods

While take-home naloxone can be prescribed in primary care and outpatient specialist practices by clinicians, dispensation of THN kits via specialised support services and facilities seems to be more the routine path for dispensation. Our results demonstrate that THN is not captured by the data sources included in this study after a feasibility assessment, and in two databases it is absent. Therefore, real THN use in the populations is likely to be underestimated in this study and the results should not be interpreted as robust estimates on the incidence and prevalence of use. Also, the much larger number of naloxone ingredient records (IQVIA DA Germany 943,400, IQVIA LPD Belgium 20,700, SIDIAP 39,500, CPRD GOLD 118,576) identified for the feasibility assessment likely derived from other types of prescriptions, such as the opioid/ naloxone combinations, rather than the specific THN products being studied.

For this study we defined “take-home naloxone” as naloxone nasal spray (nasal administration), pre-filled naloxone auto-injectors or prefilled naloxone syringes (injectables) as they can be easily administered by lay people. We did not include other naloxone injectables, i.e. naloxone solutions in vials or ampoules. We acknowledge that with appropriate training, those products could also be used in naloxone programs.

However, given the absence of recording of auto-injectors or prefilled naloxone syringes in this study, it is unlikely these other injectable formulations would also be captured in the selected databases.

Additionally, our results suggest that the recording of history of 'opioid abuse' in the selected databases might potentially be incomplete. Opioid abuse is most commonly treated in specialized services or community-based public health programs, which are also not well captured in the databases included in this study.

14.3 Results in context

Take-home naloxone programs are available in Germany, Spain, Belgium and the United Kingdom[12 13].

In **Germany**, naloxone is only available on prescription issued by a physician. It has been approved in medical and non-medical settings for use in opioid overdose since 2018, and reimbursable by health insurance. Naloxone programs have currently been implemented mainly by individual addiction support facilities[14]. The programs are planned to be rolled out in a wider setting, with the aim of reaching more opioid users or people in substitution treatment after training on the appropriate use of naloxone. However, the interim report of the NALtrain project, which started in 2021, showed that the rollout of the pilot project was slower than expected. While the program aimed to have 10,000 people being dispensed naloxone nasal sprays by the end of 2024, only 1000 doses were distributed by the end of April 2023[15]. Naloxone programs are also being implemented in some prisons, psychiatric institutions, specialised practices participating in substitution programs[14].

In the **United Kingdom**, naloxone is a prescription-only medicine. However, under regulations from 2015, people "working in or for drug treatment services can, as part of their role, supply naloxone to others that their drug service has obtained, if it is being made available to save a life in an emergency". Dispensations of naloxone in this way do not require a prescription. These regulations include nasal naloxone products from 2019 onwards[13]. Types of drug treatment services that can supply naloxone include drug services provided by primary care services, secondary care services (including a range of specialised community and inpatient drug services), needle and syringe programmes as well as pharmacies providing drug treatment such as opioid substitution treatments through supervised consumption prison drug services.

Catalonia's Public Health Agency's protocol for harm reduction outlines the regional naloxone program in Spain, and highlights that "naloxone should be distributed throughout the opening of the service from doors or from the heat and coffee spaces to people" who underwent previous training on the use of naloxone and have been accepted as overdose health agents[16]. Opioid overdose prevention programs are available[17].

A THN program was available in **Belgium** in Nov 2021 according to the European Monitoring Centre for Drugs and Drug addiction[12].

Various routes for the availability and dispensation of THN are therefore available in the different countries included into this study: THN can be prescribed in primary care and outpatient specialist practices by clinicians, but dispensation of THN kits via specialised support services and facilities is common. The latter channel of distribution, however, are not documented/linked in the databases used for this study. More Information on the use of naloxone in its different forms in different European geographies would be necessary to understand further the use of this medicine in the EU.

Population-level incidence and prevalence

McDonald et al. conducted a rapid assessment of monthly THN distribution data by sending questionnaires to country experts from European countries that run naloxone programs. Average monthly distribution rates of THN kits per 100,000 people in the population of the respective country/region ranged from 0.02 in Austria and 0.12 in Catalonia, to 12.27 and 24.07 in Wales and Scotland during 2020-2021[18]. No data from Germany or Belgium were reported.

These numbers are considerably larger compared to results from our study, with our estimates of prevalence rates between 0.11 (0.06 to 0.20) and 0.18 (0.11 to 0.27) per 10,000 persons for IQVIA DA Germany and 0.22 (0.10 to 0.45) per 10,000 persons for the UK CPRD. This is likely due to the different study settings and data collection approaches, with the expert survey capturing THN kits supplied through specialised support services and facilities.

Our results show that very few prescriptions of naloxone nasal spray were prescribed in GP surgeries or specialized outpatient care practices, suggesting that the vast majority of THN preparations are being dispensed through specialised support services and facilities that take part in the regional or national THN programs.

14.4 Generalisability

The routinely collected electronic health records from primary care and outpatient specialized care settings recorded in the selected databases for this study are representative of the *general* populations for the respective countries.

However, as highlighted as a key finding in our population-level study, we acknowledge that the number of recorded THN prescription in the selected databases does *not* seem to reflect the real use of THN in the respective countries. THN kits seem to be predominantly dispensed through specialised support services and facilities, and those dispensations are not captured via primary care electronic health records.

Our results are therefore not generalisable to other health settings or countries and may only reflect a (very) limited subset of the entire population of THN users via the settings covered by the selected database. However, the lack of THN prescription records captured in the selected databases may be a generalisable finding with other databases from similar settings given the nature of THN programs.

14.5 Learnings for future studies.

In this study, there was a notable absence of data regarding THN in the included databases. The context of THN program implementation varies largely across different countries. This study emphasised the importance of considering more details on the prescribed products at the feasibility stage for future DARWIN EU® studies, including the specific ways of delivering THN programs and dispensing in specific support services and facilities. For this study, while we already expected counts for THN to be substantially smaller than the feasibility counts initially generated for all naloxone forms, actual counts of THN were not available at the feasibility stage. This study also highlights the importance of close collaboration with database partners to take into accounts the local health care delivery at feasibility stage as much as possible.

The DARWIN EU Coordination Centre has now improved the process for generating feasibility counts in the DARWIN EU Portal Dashboard, which now allows for generating feasibility counts for concept sets, such as groups of relevant products with a certain route of administration, instead of an ingredient-based search only.

The “DrugExposureDiagnostics” package has been developed specifically for DARWIN EU Drug utilisation studies and will be updated to incorporate functions so that more granular prescription information can be presented and summarised in a timely manner. Future developments will be discussed based on the experience of past/ongoing drug utilisation studies and most needs of future proposed studies.

15 CONCLUSION

Our study assessing the use of take-home naloxone for opioid overdose treatment in 4 primary care/outpatient specialised care databases from 4 European countries showed very few THN prescriptions captured in these settings. No prescriptions were seen for SIDIAP and IQVIA LPD Belgium.

With this, our study may provide useful information for future studies on take-home naloxone: based on our estimates of incompleteness and lack of generalisability, future researchers should consider the very specific regional/national distribution pathways, i.e. through specialised support services and facilities, for take-home naloxone in the context of public health programs to prevent opioid overdoses.

Limited prescriptions of THN nasal spray were recorded in the selected primary care or specialized outpatient care practices databases to quantify and characterise THN users. This suggests that take-home naloxone preparations are mostly dispensed through specialised support services and community-based facilities that take part in regional or national take-home naloxone programs and, as a consequence, are not routinely captured in the available and selected databases for this study.

This study identified important elements to consider on prescribed product information to improve the feasibility assessment process for future DARWIN EU® studies. This includes the process for generating feasibility counts, which now utilises feasibility codes for concept sets, such as groups of relevant products with a certain route of administration, instead of an ingredient-based search only. The use of "DrugExposureDiagnostics" R package, which has been developed specifically for DARWIN EU Drug utilisation studies, will be expanded to adopt these changes. Furthermore, it highlights also a potential area for improvement in data collection and/or linkage to capture more broadly data from diverse care settings, that may be relevant to real world data sources in general.

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17 ANNEXES

Appendix I: Lists with concept definition for take-home naloxone

Appendix II: Lists with concept definition for opioid use disorder

APPENDIX I: LIST WITH CONCEPT DEFINITIONS FOR TAKE HOME NALOXONE

Id	Name	Standard Concept Caption	Domain	Vocabulary
36073531	0.01 ML naloxone 18 MG/ML Nasal Spray	Standard	Drug	RxNorm Extension
36052253	0.01 ML naloxone 18 MG/ML Nasal Spray [Nyxoid]	Standard	Drug	RxNorm Extension
36052251	0.01 ML naloxone 18 MG/ML Nasal Spray [Nyxoid] Box of 2	Standard	Drug	RxNorm Extension
36052250	0.01 ML naloxone 18 MG/ML Nasal Spray [Nyxoid] Box of 2 by Napp	Standard	Drug	RxNorm Extension
36052252	0.01 ML naloxone 18 MG/ML Nasal Spray [Nyxoid] by Napp	Standard	Drug	RxNorm Extension
36073530	0.01 ML naloxone 18 MG/ML Nasal Spray Box of 2	Standard	Drug	RxNorm Extension
36808511	0.1 ML Naloxone 18 MG/ML Nasal Spray	Standard	Drug	RxNorm Extension
36808525	0.1 ML Naloxone 18 MG/ML Nasal Spray [Nyxoid]	Standard	Drug	RxNorm Extension
36808522	0.1 ML Naloxone 18 MG/ML Nasal Spray [Nyxoid] Box of 2	Standard	Drug	RxNorm Extension
36808526	0.1 ML Naloxone 18 MG/ML Nasal Spray [Nyxoid] Box of 2 by Napp	Standard	Drug	RxNorm Extension
36808491	0.1 ML Naloxone 18 MG/ML Nasal Spray [Nyxoid] by Napp	Standard	Drug	RxNorm Extension
36808506	0.1 ML Naloxone 18 MG/ML Nasal Spray Box of 2	Standard	Drug	RxNorm Extension
43037628	0.1 ML Naloxone 9 MG/ML Nasal Spray	Standard	Drug	RxNorm Extension
43037625	0.1 ML Naloxone 9 MG/ML Nasal Spray [Nalscue]	Standard	Drug	RxNorm Extension
43037626	0.1 ML Naloxone 9 MG/ML Nasal Spray [Nalscue] Box of 4	Standard	Drug	RxNorm Extension
43037627	0.1 ML Naloxone 9 MG/ML Nasal Spray [Nalscue] Box of 4 by Indivior	Standard	Drug	RxNorm Extension
43037629	0.1 ML Naloxone 9 MG/ML Nasal Spray Box of 4	Standard	Drug	RxNorm Extension
44816244	0.4 ML naloxone hydrochloride 1 MG/ML Auto-Injector	Standard	Drug	RxNorm
44816245	0.4 ML naloxone hydrochloride 1 MG/ML Auto-Injector [Evzio]	Standard	Drug	RxNorm
780226	0.4 ML naloxone hydrochloride 25 MG/ML Auto-Injector	Standard	Drug	RxNorm
1718341	0.4 ML naloxone hydrochloride 5 MG/ML Auto-Injector	Standard	Drug	RxNorm
1718343	0.4 ML naloxone hydrochloride 5 MG/ML Auto-Injector [Evzio]	Standard	Drug	RxNorm
1759246	0.5 ML naloxone hydrochloride 10 MG/ML Prefilled Syringe	Standard	Drug	RxNorm
1759247	0.5 ML naloxone hydrochloride 10 MG/ML Prefilled Syringe [Zimhi]	Standard	Drug	RxNorm
2904140	1 ACTUAT naloxone 1.8 MG/ACTUAT Nasal Spray	Standard	Drug	RxNorm Extension

2904138	1 ACTUAT naloxone 1.8 MG/ACTUAT Nasal Spray [Nyxoid]	Standard	Drug	RxNorm Extension
2904137	1 ACTUAT naloxone 1.8 MG/ACTUAT Nasal Spray [Nyxoid] Box of 2	Standard	Drug	RxNorm Extension
2904139	1 ACTUAT naloxone 1.8 MG/ACTUAT Nasal Spray Box of 2	Standard	Drug	RxNorm Extension
2904136	1 ACTUAT naloxone 2.2 MG/ACTUAT Nasal Spray	Standard	Drug	RxNorm Extension
2904133	1 ACTUAT naloxone 2.2 MG/ACTUAT Nasal Spray [Nyxoid]	Standard	Drug	RxNorm Extension
2904132	1 ACTUAT naloxone 2.2 MG/ACTUAT Nasal Spray [Nyxoid] Box of 2	Standard	Drug	RxNorm Extension
2904135	1 ACTUAT naloxone 2.2 MG/ACTUAT Nasal Spray Box of 2	Standard	Drug	RxNorm Extension
35413043	1 ML Naloxone 0.4 MG/ML Prefilled Syringe	Standard	Drug	RxNorm Extension
43163668	1 ML Naloxone 0.4 MG/ML Prefilled Syringe [NALOXONE AGUETTANT]	Standard	Drug	RxNorm Extension
43218411	1 ML Naloxone 0.4 MG/ML Prefilled Syringe [NALOXONE AGUETTANT] Box of 10	Standard	Drug	RxNorm Extension
43218412	1 ML Naloxone 0.4 MG/ML Prefilled Syringe [NALOXONE AGUETTANT] Box of 10 by Aguettant	Standard	Drug	RxNorm Extension
43196502	1 ML Naloxone 0.4 MG/ML Prefilled Syringe [NALOXONE MYLAN]	Standard	Drug	RxNorm Extension
43141452	1 ML Naloxone 0.4 MG/ML Prefilled Syringe [NALOXONE MYLAN] Box of 10	Standard	Drug	RxNorm Extension
43196503	1 ML Naloxone 0.4 MG/ML Prefilled Syringe [NALOXONE MYLAN] Box of 10 by Mylan	Standard	Drug	RxNorm Extension
21037968	1 ML Naloxone 0.4 MG/ML Prefilled Syringe [Narcan]	Standard	Drug	RxNorm Extension
21067449	1 ML Naloxone 0.4 MG/ML Prefilled Syringe [Narcan] Box of 10	Standard	Drug	RxNorm Extension
21106693	1 ML Naloxone 0.4 MG/ML Prefilled Syringe [Narcan] Box of 10 by Bristol Myers Squibb	Standard	Drug	RxNorm Extension
43141453	1 ML Naloxone 0.4 MG/ML Prefilled Syringe [Narcan] Box of 10 by SERB	Standard	Drug	RxNorm Extension
21087056	1 ML Naloxone 0.4 MG/ML Prefilled Syringe [Narcan] Box of 3	Standard	Drug	RxNorm Extension
21096838	1 ML Naloxone 0.4 MG/ML Prefilled Syringe [Narcan] Box of 3 by Bristol Myers Squibb	Standard	Drug	RxNorm Extension
21067448	1 ML Naloxone 0.4 MG/ML Prefilled Syringe [Narcan] by Bristol Myers Squibb	Standard	Drug	RxNorm Extension
21145930	1 ML Naloxone 0.4 MG/ML Prefilled Syringe Box of 1	Standard	Drug	RxNorm Extension
21077338	1 ML Naloxone 0.4 MG/ML Prefilled Syringe Box of 1 by A A H	Standard	Drug	RxNorm Extension
21155887	1 ML Naloxone 0.4 MG/ML Prefilled Syringe Box of 1 by Alliance	Standard	Drug	RxNorm Extension
21116441	1 ML Naloxone 0.4 MG/ML Prefilled Syringe Box of 1 by Hospira	Standard	Drug	RxNorm Extension
21077337	1 ML Naloxone 0.4 MG/ML Prefilled Syringe Box of 1 by UCB	Standard	Drug	RxNorm Extension
21077339	1 ML Naloxone 0.4 MG/ML Prefilled Syringe Box of 10	Standard	Drug	RxNorm Extension
21145932	1 ML Naloxone 0.4 MG/ML Prefilled Syringe Box of 10 by A A H	Standard	Drug	RxNorm Extension
43038335	1 ML Naloxone 0.4 MG/ML Prefilled Syringe Box of 10 by Aguettant	Standard	Drug	RxNorm Extension

21087055	1 ML Naloxone 0.4 MG/ML Prefilled Syringe Box of 10 by AMCo	Standard	Drug	RxNorm Extension
21175391	1 ML Naloxone 0.4 MG/ML Prefilled Syringe Box of 10 by Hameln	Standard	Drug	RxNorm Extension
43038334	1 ML Naloxone 0.4 MG/ML Prefilled Syringe Box of 10 by Mylan	Standard	Drug	RxNorm Extension
21136051	1 ML Naloxone 0.4 MG/ML Prefilled Syringe Box of 10 by Wockhardt	Standard	Drug	RxNorm Extension
21175390	1 ML Naloxone 0.4 MG/ML Prefilled Syringe Box of 3	Standard	Drug	RxNorm Extension
21155888	1 ML Naloxone 0.4 MG/ML Prefilled Syringe Box of 3 by A A H	Standard	Drug	RxNorm Extension
21096837	1 ML Naloxone 0.4 MG/ML Prefilled Syringe Box of 3 by Wockhardt	Standard	Drug	RxNorm Extension
21145931	1 ML Naloxone 0.4 MG/ML Prefilled Syringe Box of 5	Standard	Drug	RxNorm Extension
21165664	1 ML Naloxone 0.4 MG/ML Prefilled Syringe Box of 5 by Hospira	Standard	Drug	RxNorm Extension
21175389	1 ML Naloxone 0.4 MG/ML Prefilled Syringe by A A H	Standard	Drug	RxNorm Extension
21047807	1 ML Naloxone 0.4 MG/ML Prefilled Syringe by Alliance	Standard	Drug	RxNorm Extension
21028166	1 ML Naloxone 0.4 MG/ML Prefilled Syringe by AMCo	Standard	Drug	RxNorm Extension
21136050	1 ML Naloxone 0.4 MG/ML Prefilled Syringe by Hameln	Standard	Drug	RxNorm Extension
21165662	1 ML Naloxone 0.4 MG/ML Prefilled Syringe by Hospira	Standard	Drug	RxNorm Extension
21165663	1 ML Naloxone 0.4 MG/ML Prefilled Syringe by UCB	Standard	Drug	RxNorm Extension
21028167	1 ML Naloxone 0.4 MG/ML Prefilled Syringe by Wockhardt	Standard	Drug	RxNorm Extension
21107267	2 ML Naloxone 0.02 MG/ML Prefilled Syringe	Standard	Drug	RxNorm Extension
21077852	2 ML Naloxone 0.02 MG/ML Prefilled Syringe [Narcan Neonatal]	Standard	Drug	RxNorm Extension
21156455	2 ML Naloxone 0.02 MG/ML Prefilled Syringe [Narcan Neonatal] Box of 10	Standard	Drug	RxNorm Extension
21146477	2 ML Naloxone 0.02 MG/ML Prefilled Syringe [Narcan Neonatal] Box of 10 by Bristol Myers Squibb	Standard	Drug	RxNorm Extension
21166222	2 ML Naloxone 0.02 MG/ML Prefilled Syringe [Narcan Neonatal] by Bristol Myers Squibb	Standard	Drug	RxNorm Extension
21156454	2 ML Naloxone 0.02 MG/ML Prefilled Syringe Box of 10	Standard	Drug	RxNorm Extension
21146476	2 ML Naloxone 0.02 MG/ML Prefilled Syringe Box of 10 by AMCo	Standard	Drug	RxNorm Extension
21107268	2 ML Naloxone 0.02 MG/ML Prefilled Syringe by AMCo	Standard	Drug	RxNorm Extension
21175965	2 ML Naloxone 0.4 MG/ML Prefilled Syringe Box of 1	Standard	Drug	RxNorm Extension
21107269	2 ML Naloxone 0.4 MG/ML Prefilled Syringe Box of 1 by UCB	Standard	Drug	RxNorm Extension
21038540	2 ML Naloxone 0.4 MG/ML Prefilled Syringe by UCB	Standard	Drug	RxNorm Extension
21136634	2 ML Naloxone 1 MG/ML Prefilled Syringe [Prenoxad]	Standard	Drug	RxNorm Extension
21097409	2 ML Naloxone 1 MG/ML Prefilled Syringe [Prenoxad] Box of 1	Standard	Drug	RxNorm Extension

21126746	2 ML Naloxone 1 MG/ML Prefilled Syringe [Prenoxad] Box of 1 by Martindale	Standard	Drug	RxNorm Extension
21126745	2 ML Naloxone 1 MG/ML Prefilled Syringe [Prenoxad] by Martindale	Standard	Drug	RxNorm Extension
21068032	2 ML Naloxone 1 MG/ML Prefilled Syringe Box of 1	Standard	Drug	RxNorm Extension
21097407	2 ML Naloxone 1 MG/ML Prefilled Syringe Box of 1 by A A H	Standard	Drug	RxNorm Extension
21097408	2 ML Naloxone 1 MG/ML Prefilled Syringe Box of 1 by Martindale	Standard	Drug	RxNorm Extension
21166223	2 ML Naloxone 1 MG/ML Prefilled Syringe by A A H	Standard	Drug	RxNorm Extension
2029807	2 ML naloxone 1 MG/ML Prefilled Syringe by Dongkook	Standard	Drug	RxNorm Extension
21175964	2 ML Naloxone 1 MG/ML Prefilled Syringe by Martindale	Standard	Drug	RxNorm Extension
40243205	2 ML naloxone hydrochloride 0.4 MG/ML Prefilled Syringe	Standard	Drug	RxNorm
40243206	2 ML naloxone hydrochloride 1 MG/ML Prefilled Syringe	Standard	Drug	RxNorm
21146700	5 ML Naloxone 0.4 MG/ML Prefilled Syringe	Standard	Drug	RxNorm Extension
21058303	5 ML Naloxone 0.4 MG/ML Prefilled Syringe Box of 1	Standard	Drug	RxNorm Extension
21166413	5 ML Naloxone 0.4 MG/ML Prefilled Syringe Box of 1 by UCB	Standard	Drug	RxNorm Extension
21156675	5 ML Naloxone 0.4 MG/ML Prefilled Syringe by UCB	Standard	Drug	RxNorm Extension
42482092	Naloxone 0.02 MG/ML Prefilled Syringe	Standard	Drug	RxNorm Extension
21091523	Naloxone 0.02 MG/ML Prefilled Syringe [Narcan Neonatal]	Standard	Drug	RxNorm Extension
21160440	Naloxone 0.02 MG/ML Prefilled Syringe [Narcan Neonatal] Box of 10	Standard	Drug	RxNorm Extension
21150480	Naloxone 0.02 MG/ML Prefilled Syringe Box of 10	Standard	Drug	RxNorm Extension
43195673	Naloxone 0.4 MG/ML Prefilled Syringe [NALOXONE AGUETTANT]	Standard	Drug	RxNorm Extension
43184675	Naloxone 0.4 MG/ML Prefilled Syringe [NALOXONE AGUETTANT] Box of 10	Standard	Drug	RxNorm Extension
43162825	Naloxone 0.4 MG/ML Prefilled Syringe [NALOXONE MYLAN]	Standard	Drug	RxNorm Extension
43206550	Naloxone 0.4 MG/ML Prefilled Syringe [NALOXONE MYLAN] Box of 10	Standard	Drug	RxNorm Extension
42479714	Naloxone 0.4 MG/ML Prefilled Syringe [Narcan]	Standard	Drug	RxNorm Extension
21062152	Naloxone 0.4 MG/ML Prefilled Syringe [Narcan] Box of 10	Standard	Drug	RxNorm Extension
21140649	Naloxone 0.4 MG/ML Prefilled Syringe [Narcan] Box of 3	Standard	Drug	RxNorm Extension
21062151	Naloxone 0.4 MG/ML Prefilled Syringe Box of 1	Standard	Drug	RxNorm Extension
21150481	Naloxone 0.4 MG/ML Prefilled Syringe Box of 10	Standard	Drug	RxNorm Extension
21091524	Naloxone 0.4 MG/ML Prefilled Syringe Box of 3	Standard	Drug	RxNorm Extension
21022887	Naloxone 0.4 MG/ML Prefilled Syringe Box of 5	Standard	Drug	RxNorm Extension
21062150	Naloxone 1 MG/ML Prefilled Syringe [Prenoxad]	Standard	Drug	RxNorm Extension
21032651	Naloxone 1 MG/ML Prefilled Syringe [Prenoxad] Box of 1	Standard	Drug	RxNorm Extension
21170226	Naloxone 1 MG/ML Prefilled Syringe Box of 1	Standard	Drug	RxNorm Extension
2933607	naloxone 1.8 MG/ACTUAT Nasal Spray	Standard	Drug	RxNorm Extension

2933605	naloxone 1.8 MG/ACTUAT Nasal Spray [Nyxoid]	Standard	Drug	RxNorm Extension
2933604	naloxone 1.8 MG/ACTUAT Nasal Spray [Nyxoid] Box of 2	Standard	Drug	RxNorm Extension
2933606	naloxone 1.8 MG/ACTUAT Nasal Spray Box of 2	Standard	Drug	RxNorm Extension
36812243	Naloxone 18 MG/ML Nasal Spray	Standard	Drug	RxNorm Extension
36810659	Naloxone 18 MG/ML Nasal Spray [Nyxoid]	Standard	Drug	RxNorm Extension
36812405	Naloxone 18 MG/ML Nasal Spray [Nyxoid] Box of 2	Standard	Drug	RxNorm Extension
36810357	Naloxone 18 MG/ML Nasal Spray Box of 2	Standard	Drug	RxNorm Extension
2933600	naloxone 2.2 MG/ACTUAT Nasal Spray	Standard	Drug	RxNorm Extension
2933598	naloxone 2.2 MG/ACTUAT Nasal Spray [Nyxoid]	Standard	Drug	RxNorm Extension
2933597	naloxone 2.2 MG/ACTUAT Nasal Spray [Nyxoid] Box of 2	Standard	Drug	RxNorm Extension
2933599	naloxone 2.2 MG/ACTUAT Nasal Spray Box of 2	Standard	Drug	RxNorm Extension
43026214	Naloxone 9 MG/ML Nasal Spray	Standard	Drug	RxNorm Extension
43025805	Naloxone 9 MG/ML Nasal Spray [Nalscue]	Standard	Drug	RxNorm Extension
43026213	Naloxone 9 MG/ML Nasal Spray [Nalscue] Box of 4	Standard	Drug	RxNorm Extension
43026215	Naloxone 9 MG/ML Nasal Spray Box of 4	Standard	Drug	RxNorm Extension
46275772	naloxone Auto-Injector	Standard	Drug	RxNorm
46275773	naloxone Auto-Injector [Evzio]	Standard	Drug	RxNorm
42903022	naloxone hydrochloride 0.4 MG/ML Prefilled Syringe	Standard	Drug	RxNorm
46275774	naloxone hydrochloride 1 MG/ML Auto-Injector	Standard	Drug	RxNorm
44816246	naloxone hydrochloride 1 MG/ML Auto-Injector [Evzio]	Standard	Drug	RxNorm
42902833	naloxone hydrochloride 1 MG/ML Prefilled Syringe	Standard	Drug	RxNorm
1758718	naloxone hydrochloride 10 MG/ML Prefilled Syringe	Standard	Drug	RxNorm
1758723	naloxone hydrochloride 10 MG/ML Prefilled Syringe [Zimhi]	Standard	Drug	RxNorm
1592233	naloxone hydrochloride 20 MG/ML Nasal Spray	Standard	Drug	RxNorm
1592235	naloxone hydrochloride 20 MG/ML Nasal Spray [Narcan]	Standard	Drug	RxNorm
779218	naloxone hydrochloride 25 MG/ML Auto-Injector	Standard	Drug	RxNorm
35603852	naloxone hydrochloride 40 MG/ML Nasal Spray	Standard	Drug	RxNorm
35603855	naloxone hydrochloride 40 MG/ML Nasal Spray [Narcan]	Standard	Drug	RxNorm
1718344	naloxone hydrochloride 5 MG/ML Auto-Injector	Standard	Drug	RxNorm
1718345	naloxone hydrochloride 5 MG/ML Auto-Injector [Evzio]	Standard	Drug	RxNorm
1536825	naloxone hydrochloride 80 MG/ML Nasal Spray	Standard	Drug	RxNorm
1536831	naloxone hydrochloride 80 MG/ML Nasal Spray [Kloxxado]	Standard	Drug	RxNorm
35603851	naloxone Nasal Spray	Standard	Drug	RxNorm
1536828	naloxone Nasal Spray [Kloxxado]	Standard	Drug	RxNorm
43026206	Naloxone Nasal Spray [Nalscue]	Standard	Drug	RxNorm Extension
35603854	naloxone Nasal Spray [Narcan]	Standard	Drug	RxNorm
36813861	Naloxone Nasal Spray [Nyxoid]	Standard	Drug	RxNorm Extension
40141382	naloxone Prefilled Syringe	Standard	Drug	RxNorm

43162824	Naloxone Prefilled Syringe [NALOXONE AGUETTANT]	Standard	Drug	RxNorm Extension
43217555	Naloxone Prefilled Syringe [NALOXONE MYLAN]	Standard	Drug	RxNorm Extension
21101408	Naloxone Prefilled Syringe [Narcan Neonatal]	Standard	Drug	RxNorm Extension
42480283	Naloxone Prefilled Syringe [Narcan]	Standard	Drug	RxNorm Extension
21091522	Naloxone Prefilled Syringe [Prenoxad]	Standard	Drug	RxNorm Extension
1758722	naloxone Prefilled Syringe [Zimhi]	Standard	Drug	RxNorm
995258	0.1 ML Naloxone 18 MG/ML Topical Solution [Nyxoid] by Mundipharma	Standard	Drug	RxNorm Extension

APPENDIX II: LIST WITH CONCEPT DEFINITION 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