Study Protocol P2 C1-005

20/10/2023

Version 4.1

TABLE OF CONTENTS

DOCUMENT HISTORY

Version	Date	Description
V1.0	28/07/2023	**Submission to EMA**
V2.0	05/09/2023	**Second version following comments from EMA**
V3.0	22/09/2023	**Third version following comments from EMA**
V4.0	29/09/2023	**Additional clarification following comments from EMA**
V4.1	20/10/2023	**EUPAS register number added**

Study Title	DARWIN EU® - Drug utilisation study of medicines with prokinetic properties in children and adults diagnosed with gastroparesis
Protocol version identifier	V4.0
Date of last version of protocol	29th September 2023
EU PAS register number	EUPAS106798
Active substance	**Drug** / **Drug Class** / **ATC code** Erythromycin / Macrolide antibiotics / J01FA01 Metoclopramide / Prokinetic agent / A03FA01 Cisapride / Prokinetic agent / A03FA02 Domperidone / Prokinetic agent / A03FA03 Clebopride / Prokinetic agent / A03FA06 Itopride / Prokinetic agent / A03FA07 Cinitapride / Prokinetic agent / A03FA08
Medicinal product	N/A
Research question and objectives	Research question What is the real-life use of medicines with prokinetic properties in children and adults diagnosed with gastroparesis? Study objectives 1. To describe the characteristics of children and adults prescribed medications with prokinetic properties stratified by indication of use - gastroparesis yes/no. 2. To determine the dose, formulation, cumulative duration and setting ((inpatient ((P)ICU vs no (P)ICU) vs outpatient)) at time of treatment initiation of any of the prokinetic drugs of interest for patients diagnosed with gastroparesis, in children and adults separately. 3. To determine the incidence and prevalence of use of medications with prokinetics properties in the paediatric population diagnosed with gastroparesis stratified by calendar year, age categories, sex and country/database during the study period (2012 - 2022). 4. To determine the incidence and prevalence of use of medications with prokinetics properties in adults, diagnosed with gastroparesis stratified by calendar year, age categories, sex and country/database during the study period (2012 - 2022).

Countries of study	Belgium, France, Germany, Netherlands, Spain, and the United Kingdom
Author	Katia Verhamme (k.verhamme@darwin-eu.org)

LIST OF ABBREVIATIONS

Acronyms/term	Description
CDM	Common Data Model
CHUBX	Bordeaux University Hospital
CPRD GOLD	Clinical Practice Research Datalink GOLD
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real World Interrogation Network
DUS	Drug Utilization Study
EHR	Electronic Health Records
EMA	European Medicines Agency
EU	European Union
GDPR	General Data Protection Regulation
GERD	Gastro-esophageal reflux disease
GP	General Practitioner
ICU	Intensive Care Unit
PICU	Paediatric intensive care unit
ID	Index date
IMASIS	Institut Municipal Assistència Sanitària Information System
IP	Inpatient
IPCI	Integrated Primary Care Information Project
LPD	Longitudinal Patient Database
OHDSI	Observational Health Data Sciences and Informatics
OP	Outpatient
OMOP	Observational Medical Outcomes Partnership
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SNOMED	Systematized Nomenclature of Medicine
WHO	World Health Organisation

1. TITLE

DARWIN EU® - Drug utilisation study of medicines with prokinetic properties in children and adults diagnosed with gastroparesis

2. RESPONSIBLE PARTIES – STUDY TEAM

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

Table 1: Description of Study Team

Study team Role	Names	Organisation
Principal Investigator(s)/ Clinical Epidemiologists	Katia Verhamme	Erasmus MC
	Johnmary Arinze	Erasmus MC
Data Partner*	**Names**	**Organization**
Local Study Coordinator/Data Analyst	Antonella Delmestri	University of Oxford – CPRD
	James Brash	IQVIA - DA Germany/LPD Belgium
	Vianney Jouhet	University of Bordeaux - CDWBordeaux
	Núria Mercadé	IDIAPJGol - SIDIAP
	Mees Mosseveld	Erasmus MC - IPCI
	Miguel-Angel Mayer	PSMAR - IMASIS

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

3. ABSTRACT (STAND-ALONE SUMMARY OF THE STUDY PROTOCOL)

Title

DARWIN EU® - Drug utilisation study of medicines with prokinetic properties in children and adults diagnosed with gastroparesis

Rationale and Background

Gastroparesis is a medical condition characterized by delayed gastric emptying, causing symptoms like postprandial fullness, nausea, vomiting, and upper abdominal pain. It affects individuals across different age groups, encompassing both paediatric population and adults. Pharmacotherapy, particularly medication with prokinetic properties, has been used to manage symptoms, which includes off-label use.

Research question and Objectives

Research question

What is the real-life use of medicines with prokinetic properties in children and adults diagnosed with gastroparesis?

Study objectives

1. To describe the characteristics of children and adults prescribed medications with prokinetic properties stratified by indication of use - gastroparesis yes/no.
2. To determine the dose, formulation, cumulative duration and setting (inpatient ((P)ICU vs no (P)ICU) vs outpatient) at time of treatment initiation of any of the prokinetic drugs of interest where the indication of use is gastroparesis, in children and adults separately.
3. To determine the incidence and prevalence of use of medications with prokinetics properties in the paediatric population diagnosed with gastroparesis stratified by calendar year, age categories, sex and country/database during the study period (2012 - 2022).
4. To determine the incidence and prevalence of use of medications with prokinetics properties in adults, diagnosed with gastroparesis stratified by calendar year, age categories, sex and country/database during the study period (2012 - 2022).

Research Methods

Study design

- New drug user cohort study (Objective 1 and 2, Patient-level drug utilization analyses regarding summary characterization, dose, formulation, cumulative duration and setting (inpatient (paediatric) intensive care unit (P(ICU)) setting or not) vs outpatient for patients initiating treatment with a prokinetic drug.
- Population-level cohort study (Objective 3 and 4, Population-level drug utilization study of medication with prokinetic properties for patients diagnosed with gastroparesis)

Population

Patient-level drug utilization: Patent-level drug utilization analyses will include new users of medication with prokinetic properties in the period between 2012 and 180 days prior to the end of available data in each database. Patients need to have at least 1 year of data visibility prior to index date, and no use of the respective medication with prokinetic properties in the previous 1 year. This requirement of at least 1 year of prior data history will not hold for children < 1 year of age.

For objective 2, the population which will be studied for the patient level drug utilisation analysis will include new users of medication with prokinetic properties (children or adults) indicated for gastroparesis. Within this cohort, we will perform patient characterisation in terms of dose, formulation, cumulative duration and setting (inpatient ((P)ICU vs. no (P)ICU) vs outpatient).

Population-level utilization of medication with prokinetic properties: Population-level drug utilization analyses will include all individuals diagnosed with gastroparesis (objective 3 and 4) registered in the respective databases between 2012 and 2022, with at least 1 year of data visibility prior to becoming eligible for study inclusion. This requirement of at least 1 year of prior data history will not hold for children < 1 year of age.

Variables

Drug of interest:

- Macrolide antibiotics: Erythromycin
- Prokinetic agents: Metoclopramide, Cisapride, Domperidone, Clebopride, Itopride and Cinitapride

Condition of interest:

- Gastroparesis

Data sources

1. Clinical Data Warehouse of Bordeaux University Hospital (CHUBX), France
2. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
3. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
4. IQVIA LPD Belgium, Belgium
5. Institut Municipal Assistencia Sanitaria Information System (IMASIS), Spain
6. Integrated Primary Care Information Project (IPCI), The Netherlands
7. The Information System for Research in Primary Care (SIDIAP), Spain

Sample size

No sample size has been calculated for this drug utilization descriptive study, as our primary focus is to examine drug utilization of medications with prokinetics properties, irrespective of the sample size. Based on a preliminary feasibility assessment, the expected number of person counts for medication with prokinetic properties in the databases included in this study range from 60 (CHUBX) to 181,624 (CPRD GOLD) in children and from 250 (IMASIS) to 580,600 (SIDIAP) in adults.

Data analyses

Patient-level drug utilization: Large-scale patient-level characterization will be conducted at index date including patient demographics, comorbidity and comedication (objective 1). Index date will be the date of the first prescription of the specific medications with prokinetics properties for each person. Gastroparesis indication will be assessed in the period of 365 days before until 30 days after index date (i.e. date of

prescription). Frequency of comorbidities and comedication will be assessed at index date and in the period of 365 days before index date.

For objective 2, in the new users of medication with prokinetic properties indicated for gastroparesis, treatment duration will be estimated for the first treatment era of each of the respective drugs of interest and the minimum, quartiles, maximum values and proportion of longer-term use (e.g. era > 1 month) will be provided. Dose/strength of prescribed or dispensed medication with prokinetic properties will be summarised with the minimum, quartiles and maximum values. Formulation (pills, solution, solution for injection) at time of first prescription of any of the prokinetics of interest will be expressed as proportion. Different types of setting (inpatient vs. outpatient) at time of first prescription of any of the prokinetics of interest will be expressed as proportion. For inpatient setting we will stratify between (P)ICU care vs. no (P)ICU care. The statistical analyses will be performed based on OMOP-CDM mapped data using the "DrugUtilization" R package.

Population-level utilization of medication with prokinetic properties: Annual period prevalence of the use of medications with prokinetics properties and annual incidence rates per 100,000 person years will be estimated in patients diagnosed with gastroparesis, in children and adults separately. (objectives 3 and 4) The statistical analyses will be performed based on OMOP-CDM mapped data using the "IncidencePrevalence" R package.

For all analyses a minimum cell count of 5 will be used when reporting results, with any smaller counts obscured.

4. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment orupdate	Reason
1	5th September 2023	Throughout the whole protocol	Amendment of research objectives Amendments of the cohorts and creating a gastroparesis cohort Gastroparesis phenotype changed Time window for assessing the indication changed	Amendment of research objectives to be more in line with research question
V4.1	20/10/2023	Document history	Update	EUPAS register number added

5. MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE
Draft Study Protocol	24th July 2023
Final Study Protocol	September 2023
Creation of Analytical code	September 2023
Registration in ENCePP register	September 2023
Execution of Analytical Code on the data	October 2023
Interim Study Report (if applicable)	Not applicable
Draft Study Report	17th November 2023
Final Study Report	November/December 2023

6. RATIONALE AND BACKGROUND

Gastroparesis is a medical condition characterized by delayed gastric emptying of solid food in the absence of mechanical obstruction, leading to symptoms like postprandial fullness, nausea, vomiting, and upper abdominal pain.(1, 2) The condition can affect individuals across different age groups, encompassing both paediatric population and adults. Even though, gastroparesis carries a considerable health care and patient burden, associated epidemiological data are limited. Previous studies have suggested that gastroparesis may affect up to 1.8% of the adult population, whereas the prevalence in children remains unknow.(3-5) Gender distribution in gastroparesis shows a male predominance in infants (nearly 3:1 male-to-female ratio), equal likelihood in children and a clear female predominance in adolescence (2:1 female-to-male ratio) and adulthood (4:1 female-to-male ratio).

Gastroparesis arises from neuromuscular dysfunction, which may be idiopathic or associated with diabetes, medical/surgical interventions or previous infections.(4) Several gastrointestinal and systemic disease are also associated with gastroparesis including congenital defects affecting the stomach/abdomen, gastroesophageal reflux disease, dyspepsia, hypothyroidism, neurological disorders.(6) Molecular pathogenesis of gastroparesis involves mechanisms such macrophage-driven immune dysregulation (inflammatory cells around myenteric neurons with neuronal loss), oxidative stress, loss or injury to pacemaker cells (interstitial cells of Cajal) and muscle fibrosis.(7)

Primary treatment options in both children and adults with gastroparesis involve addressing fluid, electrolyte, and nutritional needs, treating any identifiable cause of the delayed gastric emptying, and managing symptoms.(4) Prokinetic and antiemetic medication have been the basis of pharmacotherapy including dopamine (D2) receptor antagonists (metoclopramide, domperidone, clebopride), serotonin (5-HT4) receptor agonists (cisapride), cholinesterase inhibitors (itopride) and motilin-like agents (macrolide antibiotic erythromycin), although many drugs have multiple mechanisms of action. Metoclopramide is generally considered first-line treatment for adults with gastroparesis, but its use in children has been limited by concerns regarding neurological side effects.(8) Additionally, metoclopramide is used as intravenous prokinetic drug for managing delayed gastric emptying and facilitating early enteral feeding in neonates.(9) Erythromycin is a macrolide antibiotic and in addition to its antimicrobial activity, erythromycin has been used as a prokinetic drug. However, it is important to note that in Europe neither erythromycin, metoclopramide or domperidone are licenced as prokinetic agents for children, and erythromycin is also not licenced as a prokinetic in adults.

As these drugs may be used off-label for gastrointestinal indications, this drug utilisation study aims to inform data on the use of medication with prokinetic properties and user characteristics in both paediatric population and adults in Europe. This study will offer detailed data on the use of these drugs including their potential indication of use, strength, formulation and duration of treatment.

7. RESEARCH QUESTION AND OBJECTIVES

Research question

What is the real-life use of medicines with prokinetic properties in children and adults diagnosed with gastroparesis?

Study objectives

1. To describe the characteristics of children and adults prescribed medications with prokinetic properties stratified by indication of use - gastroparesis yes/no
2. To determine the dose, formulation, cumulative duration and setting (inpatient ((P)ICU vs no (P)ICU) vs outpatient) at time of treatment initiation of any of the prokinetic drugs of interest where the indication of use is gastroparesis, in adults and paediatric separately.
3. To determine the incidence and prevalence of use of medications with prokinetics properties in the paediatric population diagnosed with gastroparesis stratified by calendar year, age categories, sex and country/database during the study period (2012 - 2022).
4. To determine the incidence and prevalence of use of medications with prokinetics properties in adults, diagnosed with gastroparesis stratified by calendar year, age categories, sex and country/database during the study period (2012 - 2022).

Table 2: Primary and secondary research questions and objective

A. Primary research question (objectives 2, 3 and 4)

Objective:	To determine the dose, formulation, cumulative duration and setting at time of treatment initiation of any of the prokinetic drugs of interest in new users of medication with prokinetic properties indicated for gastroparesis, in paediatric population and in adults separately (objective 2). To investigate the incidence and prevalence of use of medication with prokinetic properties in paediatric population and in adults diagnosed with gastroparesis stratified by calendar year, age categories, sex and country/database during the study period (2012-2022) (objective 3 and 4).
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	Patient-level utilization of medication with prokinetic properties: For characterisation (dose, formulation, cumulative duration and setting (inpatient ((P)ICU vs no (P)ICU) vs outpatient), we will include new users of medication with prokinetic properties indicated for gastroparesis in the period between 2012 and 180 days prior to the end of available data in each database to allow sufficient follow-up time to estimate cumulative duration of use.

	Population-level utilization of medication with prokinetic properties: Population of patients diagnosed with gastroparesis (adults and paediatric population separately) and present in the database between 1st of January 2012 and 31st of December 2022 (or the latest date of available data, whatever comes first) and at least 1 year of data visibility before they become eligible for study inclusion. This requirement of at least 1 years of data history will not hold for children <1 year of age. Within this population and during the study period we will identify: New users of medication with prokinetic properties which will be used to calculate the incidence. Prevalent use of medication with prokinetic properties in the period between 1st of January 2012 and 31st of December 2022 (or the latest date of available data, whatever comes first).
Exposure:	Medication with prokinetic properties including: • Macrolide antibiotic: Erythromycin (J01FA01) • Prokinetic agents: Metoclopramide (A03FA01), Cisapride (A03FA02), Domperidone (A03FA03), Clebopride (A03FA06), Itopride (A03FA07) and Cinitapride (A03FA08)
Comparator:	None
Outcome:	None
Time *(when follow up begins and ends):*	Follow-up will start on the respective date of the latest of the following: 1) study start date (1st January 2012), 2) date at which they have 1 year of prior history 3) diagnosis of gastroparesis (for incident gastroparesis i.e. gastroparesis diagnosed during the study period). For the patient level drug utilisation analysis, follow-up will start on the date of incident prescription and/or dispensation of medication with prokinetic properties (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), whatever comes first.
Setting:	Inpatient and outpatient setting using data from the following 7 data sources: CHUBX (France), CPRD GOLD (UK), IQVIA DA Germany (Germany), IQVIA LPD Belgium (Belgium), IMASIS (Spain), IPCI (the Netherlands) and SIDIAP (Spain).
Main measure of effect:	Incidence and prevalence of use of medication with prokinetic properties.

	Cumulative duration of use of medication with prokinetic properties expressed as minimum, p25, median, p75, maximum and proportion of longer-term use e.g. era > 1month. Dose/strength of prescribed or dispensed medication with prokinetic properties expressed as minimum, p25, median, p75, and maximum. Formulation (pills, solution, solution for injection) at time of first prescription of any of the prokinetics of interest expressed as proportion. Different types of setting (inpatient vs. outpatient) at time of first prescription of any of the prokinetics of interest expressed as proportion. For inpatient setting we will stratify between (P)ICU care vs. no (P)ICU care.

B. Secondary research question and objective 1

Objective:	To determine characteristics of new users of medication with prokinetic properties stratified by gastroparesis indication.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	Within the population of individuals present in the database between 1st of January 2012 and 31st of December 2022 (or latest date of available data, whatever comes first) and with at least 1 year of data visibility prior they become eligible for study inclusion we will identify new users of medication with prokinetic properties. New use means a prescription and/or dispensation of the prokinetic drugs of interest in the study period and no use of the respective drug in the previous 1 year. The requirement of at least 1 year of prior data history will not hold for children < 1 year of age.
Exposure:	Medication with prokinetic properties including: • Macrolide antibiotic: Erythromycin (J01FA01) • Prokinetic agents: Metoclopramide (A03FA01), Cisapride (A03FA02), Domperidone (A03FA03), Clebopride (A03FA06), Itopride (A03FA07) and Cinitapride (A03FA08)
Comparator:	None
Outcome:	None
Time *(when follow up begins and ends):*	Follow-up will start on the date of incident prescription and/or dispensation of medication with prokinetic properties (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), whatever comes first.
Setting:	Inpatient and outpatient setting using data from the following 7 data sources: CHUBX (France), CPRD GOLD (UK), IQVIA DA Germany (Germany), IQVIA LPD Belgium (Belgium), IMASIS (Spain), IPCI (the Netherlands) and SIDIAP (Spain).
Main measure of effect:	Large scale characterisation (age, sex, comorbidity and/or comedication) for new users of medication with prokinetic properties-at index date stratified by gastroparesis yes/no.

8. RESEARCH METHODS

8.1 Study Design

A cohort study will be conducted using routinely-collected health data from 7 databases. The study will comprise two consecutive parts:

- A new drug user cohort study will be used to address objective 1 and 2; to characterize patient-level drug utilization in terms of summary patient characteristics, dose, formulation, duration, and setting (inpatient ((P)ICU vs. non-(P)ICU) vs. outpatient) in paediatric population and adults diagnosed with gastroparesis.
- A population-based cohort study will be conducted to address objective 3 and 4, assessing the prevalence and incidence of the respective medication with prokinetic properties of interest in paediatric population and adults diagnosed with gastroparesis.

Table 3. Description of Potential Study Types and Related Study Designs

STUDY TYPE	STUDY DESIGN	STUDY CLASSIFICATION
Patient Level DUS	New drug/s user cohort	Off the shelf (C1)
Population Level DUS	Population Level Cohort	Off the shelf (C1)

8.2 Study Setting and Data Sources

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

1. Clinical Data Warehouse of Bordeaux University Hospital (CHUBX), France
2. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
3. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
4. IQVIA LPD Belgium, Belgium
5. Institut Municipal Assistencia Sanitaria Information System (IMASIS), Spain
6. Integrated Primary Care Information Project (IPCI), The Netherlands
7. The Information System for Research in Primary Care (SIDIAP), Spain

For this study, we have selected 7 databases from 10 databases available in the DARWIN EU® Database Catalogue. The selection process was based on the size of the databases, the number of individuals with gastroparesis and the record counts of prokinetic agents across databases, as well as the geographical spread and the experience gained from databases that participated in the DARWIN EU® WHO Watch list antibiotics study (EUPAS103381), especially on the preponderance of indications for drug use and other similar studies.(10-12) These suggested databases meet the requirements for conducting a population-level and patient-level drug utilization study, enabling us to estimate prevalence and incidence rate in paediatric population and adults and perform large scale characterization. Additionally, by including databases from different settings, we can capture both inpatient and outpatient drug prescriptions. Based on the feasibility assessment performed, the suggested databases have data on erythromycin, in addition to at least three other prokinetic agents. Use of each drug of interest is limited in children for CHUBX and IMASIS. Those two

databases were however retained as they are hospital databases where use of the drugs of interest was considerable in adults.

Information on data sources planned to be used with a justification for their choice in terms of ability to capture the relevant data is described in a **Table 4**.

When it comes to assessing the reliability of data sources, the data partners are asked to describe their internal data quality process on the source data as part of the DARWIN EU onboarding procedure. To further ensure data quality, we utilize the Achilles tool, which systematically characterizes the data and presents it in a dashboard format that is inspected. The generated data characteristics such as age distribution, condition prevalence per year, data density, measurement value distribution can be compared against expectations for the data. Additionally, the data quality dashboard (DQD) provides more objective checks on plausibility consistently across the data sources. In terms of relevance, a more general purpose diagnostic tool, CohortDiagnostics, was developed. This package evaluates phenotype algorithms for OMOP CDM datasets, offering a standard set of analytics for understanding patient capture including data generation. It provides additional insights into cohort characteristics, record counts and index event misclassification. Furthermore, timeliness is guarded by extracting the release dates for each dataset in the network and monitoring when data are out-of-date with the expected refresh cycle (typically quarterly or half-yearly). In addition, it is important to have clear understanding of the time period covered by each released database, as this can vary across different domains. To facilitate this, the CdmOnboarding (and Achilles) packages contain a 'data density' plot. This plot displays the number of records per OMOP domain on a monthly basis. This allows to get insights when data collection started, when new sources of data were added and when until when data was included.

Table 4. Description of the selected Data Sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Data lock for the last update
France	CHUBX	Database covers hospital care setting where medication with prokinetic properties may be prescribed/dispensed.	Secondary care (in and outpatients)	EHR	2.1 million	05/05/2023
UK	CPRD GOLD	Database covers primary care where medication with prokinetic properties may be prescribed/dispensed.	Primary care	EHR	3 million	20/03/2023
Germany	IQVIA DA Germany	Databases covers primary care / outpatient specialist care setting where medication with prokinetic properties may be prescribed/dispensed.	Primary care and outpatient specialist care	EHR	8.5 million	13/03/2023
Belgium	IQVIA LPD Belgium	Database covers primary care where medication with prokinetic properties may be prescribed/dispensed.	Primary care	EHR	0.4 million	31/03/2023
Spain	IMASIS	Database covers hospital care setting where medication with prokinetic properties may be prescribed/dispensed.	Secondary care (in and outpatient)	EHR	0.6 million	31/12/2022
The Netherlands	IPCI	Database covers primary care where medication with prokinetic properties may be	Primary care	EHR	1.4 million	21/03/2023

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Data lock for the last update
		prescribed/dispensed.				
Spain	SIDIAP	Database covers primary care where medication with prokinetic properties may be prescribed/dispensed.	Primary care with hospital linkage	EHR	5.8 million	31/12/2022

CHUBX = Bordeaux University Hospital; UK = United Kingdom; CPRD GOLD = Clinical Practice Research Datalink GOLD; IMASIS = Institut Municipal Assistencia Sanitaria Information System, IPCI = Integrated Primary Care Information Project; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; DA = Disease Analyzer; EHR = Electronic Heath record;

Clinical Data Warehouse of Bordeaux University Hospital (CHUBX), France

The clinical data warehouse of the Bordeaux University Hospital comprises electronic health records on more than 2 million patients with data collection starting in 2005. The hospital complex is made up of three main sites and comprises a total of 3,041 beds (2021 figures). The database currently holds information about the person (demographics), visits (inpatient and outpatient), conditions and procedures (billing codes), drugs (outpatient prescriptions and inpatient orders and administrations), measurements (laboratory tests and vital signs) and dates of death (in or out-hospital death).(13)

Clinical Practice Research Datalink GOLD (CPRD 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(14) comprises computerized records of all clinical and referral events in primary care in addition to comprehensive demographic information and medication prescription data in a sample of UK patients (predominantly from Scotland (52% of practices) and Wales (28% of practices). The prescription records include information on the type of product, date of prescription, strength, dosage, quantity, and route of administration. Data from contributing practices are collected and processed into research databases. Quality checks on patient and practice level are applied during the initial processing. Data are available for 20 million patients, including 3.2 million currently registered patients.

Access to CPRD GOLD data requires approval via the Research Data Governance Process. CPRD GOLD will be onboarded as Data Partner for DARWIN EU® in 2023.

IQVIA Disease Analyser (DA) Germany, Germany

DA Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings.(15) 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.

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.

Institut Municipal Assistència Sanitària Information System (IMASIS), Spain

The Institut Municipal Assistència Sanitària Information System (IMASIS) is the Electronic Health Record (EHR) system of Parc de Salut Mar Barcelona (PSMar) which is a complete healthcare services organisation. Currently, this information system includes and shares the clinical information of two general hospitals (Hospital del Mar and Hospital de l'Esperança), one mental health care centre (Centre Dr. Emili Mira) and one social-healthcare centre (Centre Fòrum) including emergency room settings, which are offering specific and different services in the Barcelona city area (Spain). At present, IMASIS includes clinical information more than 1 million patients with at least one diagnosis and who have used the services of this healthcare system since 1990 and from different settings such as admissions, outpatients, emergency room and major ambulatory surgery. The diagnoses are coded using The International Classification of Diseases ICD-9-CM and ICD-10-CM. The average follow-up period per patient in years is 6.37 (SD±6.82). IMASIS-2 is the anonymized relational database of IMASIS which is used for mapping to OMOP including additional sources of information such as the Tumours Registry.

Integrated Primary Care Information Project (IPCI), The Netherlands

IPCI is collected from electronic health records (EHR) of patients registered with their general practitioners (GPs) throughout the Netherlands.(16) The selection of 374 GP practices is representative of the entire country. The database contains records from 2.8 million patients out of a Dutch population of 17M starting in 1996.(16) The median follow-up is 4.7 years. The observation period for a patient is determined by the date of registration at the GP and the date of leave/death. The observation period start date is refined by many quality indicators, e.g., exclusion of peaks of conditions when registering at the GP. All data before the observation period is kept as history data. Drugs are captured as prescription records with product, quantity, dosing directions, strength and indication. Drugs not prescribed in the GP setting might be underreported. Indications are available as diagnoses by the GPs and, indirectly, from secondary care providers but the latter might not be complete. Approval needs to be obtained for each study from the Governance Board. (16)

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

SIDIAP is collected from EHR records of patients receiving primary care delivered through Primary Care Teams, consisting of GPs, nurses and non-clinical staff.(17) The Catalan Health Institute manages 328 out of 370 such Primary Care Teams with a coverage of 5.8M patients, out of 7.8M people in the Catalan population (74%). The database started to collect data in 2006. The mean follow-up is 15 years. The observation period for a patient can be the start of the database (2006), or when a person is assigned to a Catalan Health Institute primary care centre. Date of exit can be when a person is transferred-out to a primary care centre that does not pertain to the Catalan Health Institute, or date of death, or date of end of follow-up in the database. Drug information is available from prescriptions and from dispensing records in pharmacies. Drugs not prescribed in the GP setting might be underreported; and disease diagnoses made at specialist care settings are not included. Studies using SIDIAP data require previous approval by both a Scientific and an Ethics Committee.

8.3 Study Period

The study period will be from 1st of January 2012 until the earliest of 31st December 2022 or the respective data lock for the last database update see Table 4 for more details on each database's latest data).

8.4 Follow-up

For the patient-level utilization of medication with prokinetic properties, study participants will be followed up from the date of incident prescription and/or dispensation of medication with prokinetic properties (index date) until the earliest of loss to follow-up, end of data availability, death, or end of study period (31st December 2022).

For the population-level utilization of medication with prokinetic properties, study participants will be followed from the date of diagnoses of gastroparesis (if incident diagnosis during study period). For prevalent diagnosis of gastroparesis, follow-up will start when patients fulfil inclusion criteria (i.e. present in the database between 1st of January 2012 and 31st of December 2022 and with at least 1 year of data visibility (not for children < 1 year of age). 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).

Table 5: 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 Setting1	Code Type2	Diagnosis position	Incident with respect to[3]	Measurement characteristics / validation	Source of algorithm
All patients from the database eligible for the study – Analysis of prevalent use in patients diagnosed with gastroparesis	Patient present in the database during the study period (2012-2022) and with at least 1 year of valid database history (except for children < 1 year).	Patients can be considered multiple times	Prevalent	n/a	IP and OP	n/a	n/a	n/a	n/a	n/a
All patients from the database eligible for the study – Analysis of incident use in patients diagnosed with gastroparesis	Patient present in the database during the study period (2012-2022) and with at least 1 year of valid database history (except for children < 1 year).	Patients can be considered multiple times	Incident	[-365, ID]	IP and OP	n/a	n/a	Specific medication	n/a	n/a

[1]ID = index date, [3]Incident with respect to = provide a brief text description of what the patient is required to be incident to (e.g. incident user of Drug X), IP = inpatient, OP = outpatient, n/a = not applicable

Both incidence and prevalence require an appropriate denominator population and their contributed observation time to first be identified. Study participants diagnosed with gastroparesis in the denominator population will begin contributing person time on the respective date of the latest of the following: 1) study start date (1st January 2012), 2) date at which they have 1 year of prior history, 3) diagnosis of gastroparesis (for incident gastroparesis i.e. gastroparesis diagnosed during the study period). Participants will stop contributing person time at the earliest date of the following: 1) study end date (31st December 2022) or 2) end of available data in each of the data sources (date of last data extraction) or 3) date at which the observation period of the specific person ends.

An example of entry and exit into the denominator population is shown in Figure 1. In this example, person ID 1 has already sufficient prior history before the study start date and observation period ends after the study end date, so will contribute during the complete study period. Person ID 2 and 4 enter the study only when they have sufficient prior history. Person ID 3 leaves when exiting the database (the end of observation period). Lastly, person ID 5 has two observation periods in the database. The first period contributes time from study start until end of observation period, the second starts contributing time again once sufficient prior history is reached and exits at study end date.

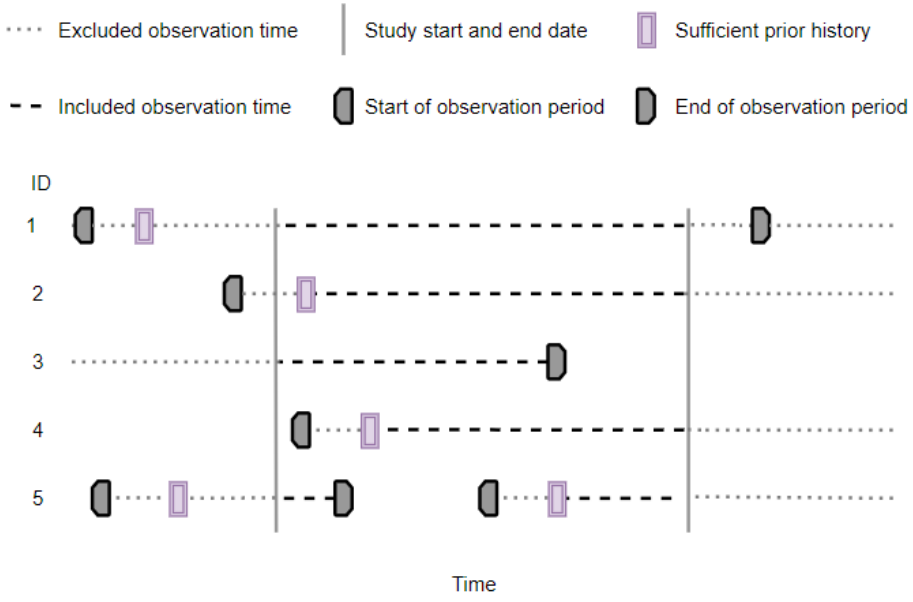


Figure 1: Included observation time for the denominator population

8.5 Study Population with inclusion and exclusion criteria

8.5.1 Patient-level utilization of medication with prokinetic properties

The description of the different cohorts of interest is described below (Figure 2).

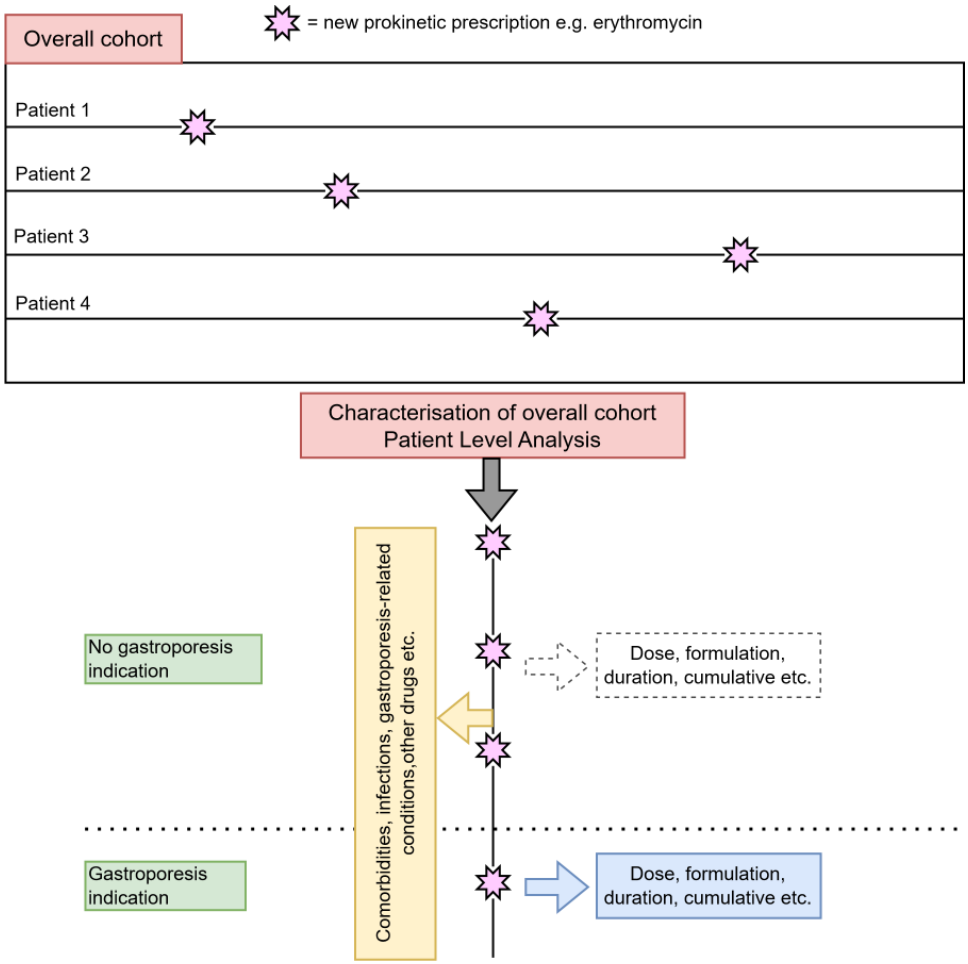


Figure 2: The description of the different cohorts of interests

All new users of medication with prokinetic properties, after 1 year of no prior use of the specific medication with prokinetic properties. The study period spans from 1st of January 2012 and 31st of December 2022 (or latest date available). Notably, all subjects have at least 1 year of data visibility prior to the date of their first prescription of medication with prokinetic properties.

For the patient level drug utilisation analysis to characterise drug use (dose, formulation, duration) within new users of medication with prokinetic properties indicated for gastroparesis (objective 2), the study period will span from 1st of January 2012 and 31st of December 2022. For this analysis, new drugs initiated for another indication than gastroparesis will not be considered (see figure 2)

8.5.2 Population-level utilization of medication with prokinetic properties

The study cohort will comprise all individuals diagnosed with gastroparesis present in the period 2012-2022 (or the latest date available, whatever comes first), with at least 1 year of data availability before the day they become eligible for study inclusion. This requirement of at least 1 year of data history will not hold for children < 1 year of age.

To identify individuals with gastroparesis, we will first define the phenotype of gastroparesis which will consist of SNOMED disease codes of gastroparesis and/or SNOMED disease codes of related conditions. The

earliest date of any of these codes will be considered as the date of diagnosis of gastroparesis. If this date falls within the study period, this will be considered as incident gastroparesis. If this date falls prior to the study period, this will be considered as prevalent gastroparesis. Preliminary codes for gastroparesis are added in the appendix.

Additional eligibility criteria will be applied for the calculation of incidence rates: The observation time of users of the medication with prokinetic properties of interest is excluded during use and 1 year afterwards.

Table 6. Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application[1]	Assessment window	Care Settings2	Code Type	Diagnosis position [3]	Applied to study populations:	Measurement characteristics / validation	Source for algorithm
Observation period in the database during the period 2012-2022 (or the latest date available)	All individuals present in the period 2012-2022 (or the latest date available)	After	n/a	IP and OP	n/a	n/a	All individuals within the selected databases	n/a	n/a
Prior database history	Study participants will be required to have a year of prior history observed before contributing observation time (except for children < 1 year of age)	After	1 year	IP and OP	n/a	n/a	All individuals within the selected databases	n/a	n/a

Diagnosed with gastroparesis	Patients diagnosed with gastroparesis#	Prior	n/a	IP and OP	SNOMED	n/a			
Washout period	New users will be required to have not used medication with prokinetic properties 1 year before a "new" prescription	After	1 year	IP and OP	n/a	n/a	All individuals within the selected databases	n/a	n/a

[1] Order of application of in and exclusion criteria before or after selection of study entry date (e.g. after = select first possible study entry date and then apply in- and/or exclusion criterion).
[2] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)
Gastroparesis phenotype will be defined following protocol approval with input from EMA.

8.6 Variables

8.6.1. Exposure

For this study, exposure of interest is use (during study period) of medication with prokinetic properties. The calculation of duration of the exposures is described in section 8.8.5 Statistical model specification and assumptions of the analytical approach considered.

The list of medication with prokinetic properties is described in Table 7.

Table 7: Exposure of interest

Drug	Drug Class	ATC code
Erythromycin	Macrolide antibiotics	J01FA01
Metoclopramide	Prokinetic agent	A03FA01
Cisapride	Prokinetic agent	A03FA02
Domperidone	Prokinetic agent	A03FA03
Clebopride	Prokinetic agent	A03FA06
Itopride	Prokinetic agent	A03FA07
Cinitapride	Prokinetic agent	A03FA08

Details of exposure are described in Table 8.

8.6.2. Outcomes

n/a

Table 8. Operational Definitions of Exposure

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type	Diagnosis position[2]	Applied to study populations:	Incident with respect to[3]...	Measurement characteristics/ validation	Source of algorithm
Medication with prokinetic properties	Preliminary code list provided in Table 7	[-365, ID]	Calendar year	Primary and secondary care	RxNorm	n/a	All individuals present in the database during the study period.	Previous use of medication with prokinetic properties of interest	n/a	n/a

[1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable; [2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter), [3] Provide brief description on what patients is required to be incident to (e.g. when identifying incident users of drug, requirement may be that the patient is incident with respect to that drug).

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

8.6.3.1. Covariates for stratification in population-level drug utilization study:

- Calendar year
- Age categories:
  - 0-<1 years
  - 1-<2 years
  - Children: 2-11 years
  - Adolescents: 12-17 years
  - Young adults: 18-44 years
  - Middle aged adults: 45-64 years
  - Older adults: 65+ years
- Sex: male of female

8.6.3.2. Covariates for patient-level drug utilization study:

- Age categories:
  - 0-<1 years
  - 1-<2 years
  - Children: 2-11 years
  - Adolescents: 12-17 years
  - Young adults: 18-44 years
  - Middle aged adults: 45-64 years
  - Older adults: 65+ years
- Sex: male of female
- Setting: inpatient vs. outpatient
- Formulation: tablets, liquid (syrup), formulation for rectal use, injection
- Indication of use: gastroparesis (it will be assessed in the period of 365 days before until 30 days after index date). Phenotype of gastroparesis will be defined following protocol approval with input from EMA.

A list of pre-specified comorbidities and comedication will be used for large-scale patient characterization.

- The following conditions will be of interest (i.e., frequency of comorbidities will be assessed at index date and in the period of 365 days before index date while frequency of infections will be assessed at index date and in the period of 7 days before index):
  - Infections
  - Gastroesophageal reflux disease
  - Dyspepsia

- Irritable bowel syndrome
- Vomiting
- Chronic constipation
- Diabetes mellitus
- Hypothyroidism
- Scleroderma
- Systemic Lupus Erythematous
- Ehlers Danlos Syndrome
- Acute migraine
- Cerebrovascular disease
- Multiple sclerosis
- Congenital defects affecting the stomach/ abdomen such as Gastroptosis

- The following medication will be of interest:
  - Opiates
  - Tricyclic antidepressants
  - L-dopa
  - Glucagon-Like Peptide 1 Receptor Agonists (Glp-1 Ras)
  - Proton pump inhibitors (PPIs)
  - Anticholinergics

Large-scale characterisation of baseline characteristics: the operational definition of the covariates is described in the Table 9 below. Index date is the start of the (first) incident prescription during the study period. From this large-scale characterisation, we will report the top 10 of most frequent comorbidities.

Table 9. Operational Definitions of Covariates

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Indication of Use – gastroparesis (yes/no)	Check for conditions of interest related to use of medication with prokinetic properties	Counts	At index date (ID), in windows around index date [-365, 30]	Primary and secondary care	SNOMED	n/a	Persons with new use during the study period	n/a	n/a
Large-scale summary characteristics of new users	Large-scale patient-level characterization with regard to baseline covariates	Counts	At index date (ID) and 365 days before ID [-365 days, ID]; for infections at ID and 7 days before ID [-7, ID]	Primary and secondary care	SNOMED	n/a	Persons with new use during the study period	n/a	n/a
Formulation	Tablets, liquid (syrup/oral suspension), injection for parenteral use, formulation for rectal use	Counts	At ID	Primary and secondary care	RxNorm	n/a	All new users	n/a	n/a

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Setting	In- or outpatient[3]	Counts	At ID	Primary and secondary care	SNOMED	n/a	All new users	n/a	n/a

[1] ID = index date, IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable
[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter); [3] For inpatient setting we will distinguish between (P)ICU care vs. no (P)ICU care.

8.7 Study size

No sample size has been calculated for this drug utilization study, as our primary focus is to examine drug utilization of medications with prokinetics properties, irrespective of the sample size. Based on a preliminary feasibility assessment, the expected number of person counts for medication with prokinetic properties in the databases included in this study range from 60 (CHUBX) to 181,624 (CPRD GOLD) in children and from 250 (IMASIS) to 580,600 (SIDIAP) in adults.

8.8 Data analysis

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

The analysis will include calculation of population-based incidence rates and prevalence, as described in section 8.8.4.

Table 10. Description of Study Types and Type of analysis

STUDY TYPE	STUDY CLASSIFICATION	TYPE OF ANALYSIS
Patient Level DUS	Off-the-shelf (C1)	- Characterisation of patient-level features - Number of persons N, with a record of setting and the respective formulation - Estimation of minimum, quartiles, and maximum values initially prescribed or dispensed dose - Estimation of minimum, quartiles, maximum treatment duration and proportion of longer-term use e.g. era > 1 month.
Population Level DUS	Off-the-shelf (C1)	- Incidence rates in the paediatric population and in adults diagnosed with gastroparesis - Prevalence of use of a drug/drug class in paediatric population and in adults diagnosed with gastroparesis

8.8.1 Federated Network Analyses

Analyses will be conducted separately for each database. Before study initiation, test runs of the analytics are performed on a subset of the data sources or on a simulated set of patients and quality control checks are performed. Once all the tests are passed, the final package is released in the version-controlled Study Repository for execution against all the participating data sources.

The data partners locally execute the analytics against the OMOP-CDM in R Studio and review and approve the by default aggregated results before returning them to the Coordination Centre. Sometimes multiple

execution iterations are performed, and additional fine tuning of the code base is needed. A service desk will be available during the study execution for support.

The study results of all data sources are checked after which they are made available to the team in the Digital Research Environment (DRE) and the Study Dissemination Phase can start. All results are locked and timestamped for reproducibility and transparency.

8.8.2 Patient privacy protection

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

8.8.3 Methods to derive parameters of interest

Drug Exposure Calculation

Drug eras will be defined as follows: Exposure starts at date of the first prescription, e.g., the index date the person entered the cohort. For each prescription, the estimated duration of use is retrieved from the drug exposure table in the CDM, using start and end date of the exposure. Subsequent prescriptions will be combined into continuous exposed episodes (drug eras) using the following specifications:

Two drug eras will be merged into one continuous drug era if the distance in days between end of the first era and start of the second era is ≤ 7 days. The time between the two joined eras will be considered as exposed by the first era as shown in Figure 2, first row.

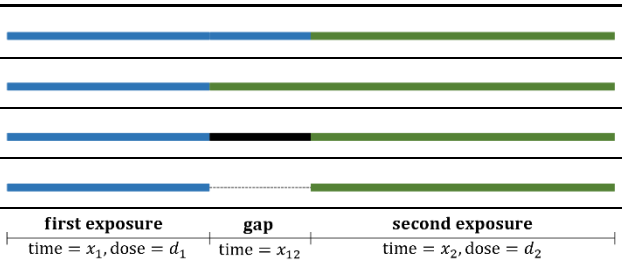
Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"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

Figure 3: Gap era joint mode

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

New user cohorts

New users will be selected based on their first prescription of the respective prokinetic drug of interest after the start of the study. For each patient, at least 1 year of data visibility will be required prior to that prescription. New users will be required to not have been exposed to the drug of interest for at least 1 year prior to the current prescription. If the start date of a prescription does not fulfil the prior exposure washout criteria of 1 year of no use, the whole exposure is eliminated. This requirement of at least 1 year of data history will not hold for children < 1 year.

Calendar time

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

Age

Age at index date will be calculated using January 1st of the year of birth as proxy for the actual birthday. Date/month is either not present or cannot be made available for governance reasons. If available, date is often set to first of the month for patient's privacy. This means that categorisation by ICH age category is difficult for the youngest age categories. The following age groups will be used for stratification for population-level analyses:

- 0-<1 years

- 1-<2 years
- Children: 2-11 years
- Adolescents: 12-17 years
- Young adults: 18-44 years
- Middle aged adults: 45-64 years
- Older adults: 65+ years

Sex

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

Indication

Indication will be determined based on a predefined definition of gastroparesis, looked up in the assessment window (365 before and 30 days after prescription).

Setting

Inpatient vs outpatient. Whether or not patient was an in- or outpatient will be assessed at index date (date of first prescription of the prokinetic drug of interest). For inpatient visits, we will further stratify in patients admitted to (P)ICU at time of prescription and patients not admitted to (P)ICU.

Formulation

Formulation will be assessed at the date of the first prescription of the respective drug (index date).

Characterization of patient-level features

Large-scale patient-level characterisation will be conducted. Co-variates will be extracted for the following time intervals: Concepts in the “condition” domain will be assessed for 365 days before index date, and at index date. The top-10 for both time windows will be presented.

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

8.8.4.1 Population-level drug utilization study

Prevalence and incidence calculations will be conducted separately for each medication with prokinetic properties of interest.

Prevalence calculations

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

An illustration of the calculation of period prevalence is shown below in **Figure 4**. Between time t+2 and t+3, two of the five study participants are users of medication with prokinetics properties giving a prevalence of 40%. Meanwhile, for the period t to t+1 all five also have some observation time during the year with one of the five study participants being a user of medication with prokinetic properties, giving a prevalence of 20%.

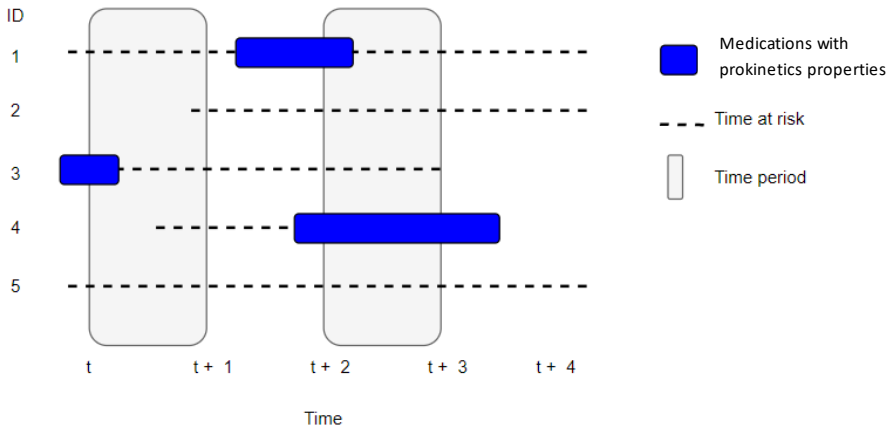


Figure 4: Period prevalence example

Incidence calculations

Annual incidence rates of the medication with prokinetics properties of interest will be calculated as the of number of **new users** after 1 year of no use per 100,000 person-years of the population at risk of getting exposed during the period for each calendar year. Any study participants with use of the medication of interest prior to the date at which they would have otherwise satisfied the criteria to enter the denominator population (as described above) will be excluded. Those study participants who enter the denominator population will then contribute time at risk up to their first prescription during the study period. Or if they do not have a drug exposure, they will contribute time at risk up as described above). Time-at-risk of subjects who die will be censored at the time of death. Similarly, time at risk of subjects who are lost to follow-up will be censored at the time of loss to follow-up [last contact]. Subjects with data until the end of the study period

without experiencing exposure will be administratively censored at the end of the study period. Incidence rates will be given together with 95% Poisson confidence intervals.

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

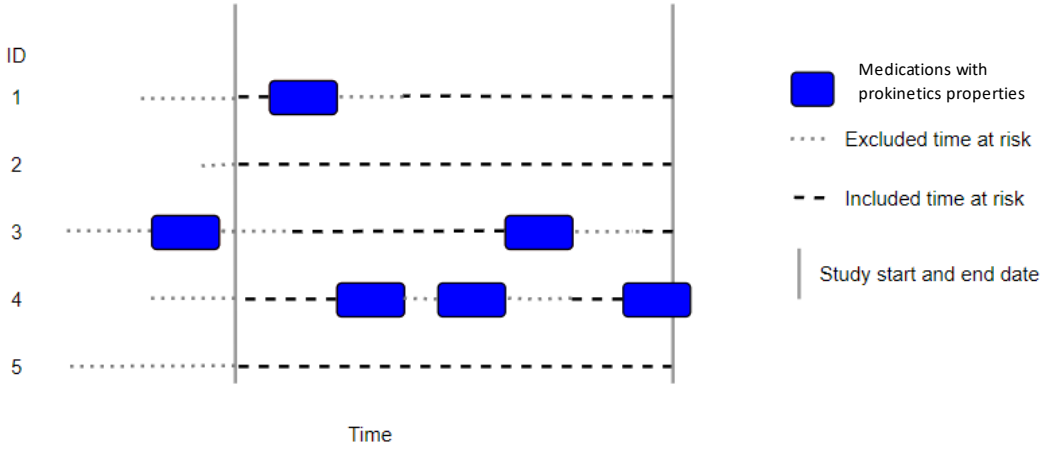


Figure 5: Incidence example

8.8.4.2 Patient-level drug utilization study

New drug user patient-level characteristics on index date

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

Formulation

The number of persons (N, %) with a record of the respective formulation will be provided.

Treatment duration

Treatment duration will be calculated as the duration of the first treatment era of the medication with prokinetic properties of interest during the study period. Treatment duration will be summarized providing the minimum, quartiles, maximum treatment duration and proportion of longer-term use e.g. era > 1month. For databases, where duration cannot be calculated due to e.g., missing information on quantity or dosing, treatment duration will not be provided.

Setting

Inpatient vs outpatient. Whether or not patient was an in- or outpatient will be assessed at index date (date of first prescription of the prokinetic drug of interest). For inpatient visits, we will further stratify in patients admitted to (P)ICU at time of prescription and patients not admitted to (P)ICU. The number of persons (N, %) with a record of the respective setting at time of treatment initiation will be provided.

Dose

For each prescription at index date, the prescribed dose/strength will be retrieved from the drug_exposure and drug_strength tables, where the amount quantity and units are available.
From this, the initial dose/strength in the cohort will be characterised by the minimum dose/strength, p25, median, p75, and maximum dose/strength.

8.8.5 Statistical model specification and assumptions of the analytical approach considered

R-packages

We will use the R packages "IncidencePrevalence"(18) package for the population-level estimation of drug utilization and "DrugUtilization" for the patient-level drug utilization analyses including patient characterization.

8.8.6 Evidence synthesis

Results from analyses described in section 8.8 Data analysis will be presented separately for each database and no meta-analysis of results will be conducted.

9. DATA MANAGMENT

9.1 Data management

All databases are mapped to the OMOP common data model. This enables the use of standardised analytics and tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM is developed and maintained by the Observational Health Data Sciences and Informatics (OHDSI) initiative and is described in detail on the wiki page of the CDM: https://ohdsi.github.io/CommonDataModel and in The Book of OHDSI: http://book.ohdsi.org

The analytic code for this study will be written in R. Each data partner will execute the study code against their database containing patient-level data and will then return the results set which will only contain aggregated data. The results from each of the contributing data sites will then be combined in tables and figures for the study report.

9.2 Data storage and protection

For this study, participants from various EU member states will process personal data from patients which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All databases used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate non-identifiable aggregate summary results.
The output files are stored in the DARWIN Digital Research Environment. These output files do not contain any data that allow identification of subjects included in the study. The DRE implements further security measures in order to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

10. QUALITY CONTROL

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

Study specific quality control
When defining cohorts for drugs, a systematic search of possible codes for inclusion will be identified using CodelistGenerator R package (https://github.com/darwin-eu/CodelistGenerator). A pharmacist will review the codes of the opioids of interest. This software allows the user to define a search strategy and using this will then query the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, DrugExposureDiagnostics (19) will be run if needed to assess the use of different codes across the databases contributing to the study.

The study code will be based on two R packages currently being developed to (1) estimate Incidence and Prevalence and (2) characterize drug utilization using the OMOP common data model. These packages will include numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R package will be made publicly available via GitHub.

11. LIMITATION OF THE RESERACH METHODS

The study will be informed by routinely collected health care data and several considerations should be mentioned. There is variability in database setting, notably the differences between primary care database and hospital databases and absence of linked data that restricts the ability to establish comprehensive connections between various patient records and outcomes. Furthermore, a recording of a prescription or

dispensation does not mean that the patient actually took the drug. In addition, for databases where duration of drug use cannot be calculated due to e.g. missing information on quantity or dosing, treatment duration will not be provided. For data governance reasons, exact date of birth is not available limiting how narrow age groups can be defined in infants.

In addition, the quality of condition recording used for patient characterization and identification of the (potential) indication may vary across the databases included in this study selected from those currently available in the DARWIN EU network and recording of some conditions linked to indication may be incomplete. Indications are not linked to prescriptions at the time they are issued or dispensed in the databases. Indications will be inferred by the proximity of codes for gastroparesis or conditions associated with gastroparesis and some misclassification may occur. Validation of code lists by individual patient health record review will not be performed.

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions will not be collected or analyzed as part of this evaluation. The nature of this non-interventional evaluation, 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.

13. GOVERNANCE BOARD ASPECTS

All data sources require approval from their respective IRB board, with the exception of IQVIA DA Germany and Belgium which will not require any further specific approvals to undertake this study.

A PDF report including an executive summary, and the specified tables and/or figures will be submitted to EMA by the DARWIN EU® CC upon completion of the study.

14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

14.1 Study Report

A study report including an executive summary, and the specified tables and/or figures will be submitted to EMA by the DARWIN EU® CC upon completion of the study.

An interactive dashboard incorporating all the results (tables and figures) will be provided alongside the study report. The full set of underlying aggregated data used in the dashboard will also be made available if requested.

15. OTHER RESULTS

n/a

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17. ANNEXES

Appendix I: List with preliminary concept definitions (exposure)

Appendix II: List with preliminary concept definitions for indication of use

Appendix III: ENCePP checklist for study protocols

APPENDIX I – LIST WITH PRELIMINARY CONCEPT DEFINITIONS

CONCEPT ID	Name	ATC code
21602970	Erythromycin	J01FA01
21600484	Metoclopramide	A03FA01
21600485	Cisapride	A03FA02
21600486	Domperidone	A03FA03
21600489	Clebopride	A03FA06
45893516	Itopride	A03FA07
21602970	Cinitapride	J01FA01

APPENDIX II – LIST WITH PRELIMINARY CONCEPT DEFINITIONS FOR INDICATION OF USE

Preliminary list – list to be reviewed once protocol approved and prior to parametrisation of study code (using phenotype deck)

Gastroparesis

concept_id	concept_name
195847	Gastroparesis syndrome
37017429	Gastroparesis due to type 1 diabetes mellitus
37018728	Gastroparesis due to type 2 diabetes mellitus
37017430	Gastroparesis due to diabetes mellitus
4295558	Nondiabetic gastroparesis

Gastroesophageal reflux disease

concept_id	concept_name
4010501	Alkaline reflux disease
42535063	Gastroesophageal reflux disease in pregnancy
36687117	Paraesophageal hernia with gastroesophageal reflux disease
765110	Diaphragmatic hernia with gastroesophageal reflux disease
318800	Gastroesophageal reflux disease
4076267	Gastro-esophageal reflux disease with ulceration
30437	Gastro-esophageal reflux disease with esophagitis
4144111	Gastroesophageal reflux disease without esophagitis
4159148	Gastroesophageal reflux disease with apnea
4159156	Gastroesophageal reflux disease with hiatal hernia
36713492	Non-erosive gastro-esophageal reflux disease
36713493	Erosive gastro-esophageal reflux disease
36713494	Ulcer of esophagus due to gastro-esophageal reflux disease with complication
36717641	Ulcer of esophagus due to gastro-esophageal reflux disease without complication

Dyspepsia

concept_id	concept_name
4100532	Psychogenic dyspepsia
44790450	Undiagnosed dyspepsia
4091959	Flatulent dyspepsia
4114304	Drug-induced dyspepsia
4289526	Nonulcer dyspepsia

Irritable bowel syndrome

concept_id	concept_name
1340381	Exacerbation of irritable bowel syndrome
75576	Irritable bowel syndrome
4057826	Irritable bowel syndrome with diarrhea
4341644	Irritable bowel syndrome variant of childhood
4341645	Irritable bowel syndrome variant of childhood with diarrhea
4340374	Irritable bowel syndrome variant of childhood with constipation
4234788	Irritable bowel syndrome characterized by alternating bowel habit
4261072	Irritable bowel syndrome characterized by constipation

Vomiting

concept_id	concept_name
3175765	Postprandial vomiting
3183009	Recurrent vomiting
1340502	Exacerbation of vomiting
4012877	Vertigo, acute onset with vomiting and inability to stand
4024560	Hypertension AND/OR vomiting complicating pregnancy childbirth AND/OR puerperium
4037774	Bilious vomiting following gastrointestinal surgery
760991	Morning vomiting
45757414	Vomiting fecal matter
45757468	Vomiting without nausea
4032472	Postoperative nausea and vomiting
27674	Nausea and vomiting
4077584	Cyclical vomiting syndrome
40385744	Chemotherapy-induced nausea and vomiting
4103552	Psychogenic cyclical vomiting
4102984	Vomiting associated with other psychological disturbances
27321	Persistent vomiting
22666	Vomiting after gastrointestinal tract surgery
4023182	Vomiting food
4340522	Intermittent vomiting
4083547	Acute vomiting
4096715	Vomiting symptom
4091511	Effortless vomiting
4091519	Diarrhea and vomiting
4145805	Vomiting blood - fresh
4170302	Diarrhea and vomiting, symptom
4121590	Diarrhea and vomiting after gastrointestinal tract surgery
4104544	Nausea, vomiting and diarrhea
42535473	Intractable cyclical vomiting syndrome
4101344	Finding of vomiting

concept_id	concept_name
4149594	Vomiting in infants AND/OR children
4222657	Uncontrollable vomiting
4143327	Decreased nausea and vomiting
4147910	Self-induced vomiting
441546	Psychogenic vomiting
4299836	Concealed vomiting
4294425	Purpura due to prolonged vomiting and/or coughing
4246979	Coffee ground vomiting
4188573	Tendency to nausea and vomiting
4170402	Drug-induced nausea and vomiting
441408	Vomiting
4311574	Post-tussive vomiting
4169915	Vomiting in newborn
4170551	Habit vomiting
4170729	Jamaican vomiting sickness
4179793	Vomiting due to organic disease during pregnancy
4180241	Erosion of teeth due to persistent vomiting
4274327	Chronic vomiting
44783646	Intractable nausea and vomiting
45767105	At risk of vomiting
45767550	Self-induced vomiting to lose weight
4323686	Bilious vomiting
4216862	Postoperative vomiting
36716760	Bilious vomiting of newborn
37109979	Nausea and vomiting following administration of anesthetic agent
4247894	Increased nausea and vomiting
201218	Epidemic vomiting syndrome
35623148	Vomiting co-occurrent and due to infectious disease
35625971	Vomiting during third trimester of pregnancy
4312477	Projectile vomiting
440785	Vomiting of pregnancy
4239207	Radiation-induced nausea and vomiting
42598804	Vomiting AND wasting disease of piglet

Chronic constipation

concept_id	concept_name
4026011	Chronic constipation without overflow
4340520	Chronic constipation
4135220	Chronic constipation with overflow
4306923	Chronic idiopathic constipation

Diabetes mellitus

concept_id	concept_name
201820	Diabetes mellitus
4322638	Diabetes mellitus AND insipidus with optic atrophy AND deafness
4143529	Diabetes mellitus associated with cystic fibrosis
4245270	Diabetes mellitus associated with genetic syndrome
4240589	Diabetes mellitus associated with hormonal etiology
4178452	Diabetes mellitus associated with pancreatic disease
4178790	Diabetes mellitus associated with receptor abnormality
42537681	Diabetes mellitus caused by chemical
765478	Diabetes mellitus caused by drug without complication
4144583	Diabetes mellitus due to cystic fibrosis
43531011	Diabetes mellitus due to genetic defect in beta cell function
43531642	Diabetes mellitus due to genetic defect in insulin action
4192852	Diabetes mellitus due to insulin receptor antibodies
45757077	Diabetes mellitus due to pancreatic injury
4237068	Diabetes mellitus due to structurally abnormal insulin
443012	Diabetes mellitus during pregnancy - baby delivered
192691	Diabetes mellitus during pregnancy - baby not yet delivered
4058243	Diabetes mellitus during pregnancy, childbirth and the puerperium
45757129	Diabetes mellitus in mother complicating childbirth
194700	Diabetes mellitus in mother complicating pregnancy, childbirth AND/OR puerperium
4079850	Diabetes mellitus in neonate small for gestational age
45766050	Diabetes mellitus in remission
4062685	Diabetes mellitus in the puerperium - baby delivered during current episode of care
4062686	Diabetes mellitus in the puerperium - baby delivered during previous episode of care
4235410	Diabetes mellitus induced by non-steroid drugs
4136889	Diabetes mellitus induced by non-steroid drugs without complication
45757674	Diabetes mellitus type 1 without retinopathy
36684827	Diabetes mellitus type 2 with periodontal disease
45757474	Diabetes mellitus type 2 without retinopathy
44793113	Diabetes mellitus with multiple complications
4008576	Diabetes mellitus without complication
43531645	Diabetes mellitus, transient neonatal 1
43531019	Diabetes mellitus, transient neonatal 2
43531020	Diabetes mellitus, transient neonatal 3
4129516	Diabetes-deafness syndrome maternally transmitted
4046332	Diabetic acute painful polyneuropathy
37312019	Diabetic cardiomyopathy
35625719	Diabetic cataract of bilateral eyes

4033942	Diabetic dermopathy
4087682	Diabetic foot
4159742	Diabetic foot ulcer
4137220	Diabetic glomerulonephritis
4114426	Diabetic hand syndrome
37018912	Diabetic hand syndrome due to type 2 diabetes mellitus
4164175	Diabetic intraretinal microvascular anomaly
443727	Diabetic ketoacidosis
4009303	Diabetic ketoacidosis without coma
37110068	Diabetic mastopathy
4048028	Diabetic mononeuropathy
4262282	Diabetic mononeuropathy multiplex
4234742	Diabetic neuropathy with neurologic complication
4151453	Diabetic optic papillopathy
4311708	Diabetic peripheral neuropathy
44805628	Diabetic retinopathy detected by national screening programme
4082347	Diabetic thick skin syndrome
4047906	Insulin dependent diabetes mellitus type 1A
4102018	Insulin dependent diabetes mellitus type 1B
45769875	Insulin reactive hypoglycemia due to type 2 diabetes mellitus
4129524	Insulin resistance - type A
4129525	Insulin resistance - type B
4130162	Insulin treated type 2 diabetes mellitus
43531006	Maturity onset diabetes of the young, type 1
4130164	Maturity onset diabetes of the young, type 2
43531640	Maturity-onset diabetes of the young
43531017	Maturity-onset diabetes of the young, type 10
43531018	Maturity-onset diabetes of the young, type 11
43531012	Maturity-onset diabetes of the young, type 3
43531013	Maturity-onset diabetes of the young, type 4
43531014	Maturity-onset diabetes of the young, type 5
43531643	Maturity-onset diabetes of the young, type 6
43531015	Maturity-onset diabetes of the young, type 7
43531644	Maturity-onset diabetes of the young, type 8
43531016	Maturity-onset diabetes of the young, type 9
37204818	Myopathy and diabetes mellitus
193323	Neonatal diabetes mellitus
44793114	Pre-existing diabetes mellitus
45757079	Pre-existing diabetes mellitus in mother complicating childbirth
43531007	Pre-existing diabetes mellitus in pregnancy
4062687	Pre-existing malnutrition-related diabetes mellitus
606039	Pre-existing malnutrition-related diabetes mellitus in pregnancy
4063042	Pre-existing type 1 diabetes mellitus

43531008	Pre-existing type 1 diabetes mellitus in pregnancy
4063043	Pre-existing type 2 diabetes mellitus
43531010	Pre-existing type 2 diabetes mellitus in pregnancy
201254	Type 1 diabetes mellitus
4099215	Type 1 diabetes mellitus maturity onset
40484648	Type 1 diabetes mellitus uncontrolled
40484649	Type 1 diabetes mellitus well controlled
4152858	Type 1 diabetes mellitus with arthropathy
4099214	Type 1 diabetes mellitus with ulcer
443412	Type 1 diabetes mellitus without complication
201826	Type 2 diabetes mellitus
45757508	Type 2 diabetes mellitus controlled by diet
4230254	Type 2 diabetes mellitus in nonobese
4304377	Type 2 diabetes mellitus in obese
40485020	Type 2 diabetes mellitus well controlled
4200875	Type 2 diabetes mellitus with peripheral angiopathy
4099651	Type 2 diabetes mellitus with ulcer
4193704	Type 2 diabetes mellitus without complication
45766051	Type I diabetes mellitus in remission
45766052	Type II diabetes mellitus in remission
40482801	Type II diabetes mellitus uncontrolled

Hypothyroidism

concept_id	concept_name
3171361	Lithium induced hypothyroidism
45757058	Hypothyroidism due to thyroiditis
45757193	Hypothyroidism in childbirth
138384	Acquired hypothyroidism
4009783	Hyperthermia-hyperphagia-hypothyroidism syndrome
605667	Hypothyroidism due to and following radiotherapy
606080	Transient congenital hypothyroidism due to dual oxidase 2 mutation
37016177	Cerebral degeneration due to hypothyroidism
4032331	Hypothyroidism following external radiotherapy
133728	Congenital hypothyroidism
4099205	Irradiation hypothyroidism
140062	Iodine hypothyroidism
4095912	Hypothyroidism resulting from para-aminosalicylic acid
4095913	Hypothyroidism resulting from phenylbutazone
4095914	Hypothyroidism resulting from resorcinol
4099644	Premature puberty due to hypothyroidism
4101898	Myasthenic syndrome due to hypothyroidism
4071079	Neonatal jaundice with congenital hypothyroidism

concept_id	concept_name
4065088	Congenital hypothyroidism with ectopic thyroid
4130017	Congenital hypothyroidism without goiter
4034815	Autoimmune hypothyroidism
4130018	Hypothyroidism due to Hashimoto's thyroiditis
4030047	Hypothyroidism due to TSH receptor blocking antibody
132583	Postablative hypothyroidism
4030049	Post-infectious hypothyroidism
4129369	Hypothyroidism due to iodide trapping defect
4034824	Hypothyroidism due to iodide organification defect
4130027	Subclinical iodine deficiency hypothyroidism
4132435	Central hypothyroidism
137820	Postoperative hypothyroidism
4173188	Transient neonatal hypothyroidism
4081998	Congenital hypothyroidism with diffuse goiter
4104540	Transient hypothyroidism
4147364	Hypothyroidism due to infiltrative disease
44796355	Congenital hypothyroidism not screened for or screening incomplete
37016342	Hypothyroidism caused by drug
37208050	Hypothyroidism caused by amiodarone
4291925	Hypothalamic hypothyroidism
4192649	Hypothyroidism due to fibrous invasive thyroiditis
4296343	Hypertrichosis in hypothyroidism
4231548	Hypothyroidism following radioiodine therapy
4236858	Infant hypothyroidism
4236859	Infant hypothyroidism to 24 months of age
140673	Hypothyroidism
4175837	Hypothyroidism due to cystinosis
4176015	Hypothyroidism in pregnancy
4172443	Hypothyroidism due to food stuff
4183422	Subclinical hypothyroidism
4185526	Athyrotic hypothyroidism sequence
4210299	Hypothyroidism due to defect in thyroid hormone synthesis
40609121	Primary hypothyroidism
4245619	Hypothyroidism due to amyloidosis
4268472	Hypothyroidism due to systemic sclerosis
44782482	Infant hypothyroidism due to maternal drug
4289921	Hypothyroidism due to iodide excess
37397258	Congenital hypothyroidism due to transplacental passage of maternal thyroid stimulating hormone binding inhibitory antibody
37399723	Idiopathic congenital hypothyroidism
37397535	Hypothyroidism due to mutation in transcription factor of pituitary development
36713742	Congenital hypothyroidism due to absence of thyroid gland

concept_id	concept_name
36717199	Obesity, colitis, hypothyroidism, cardiac hypertrophy, developmental delay syndrome
36716764	Congenital central hypothyroidism
36716765	Congenital hypothyroidism due to iodine deficiency
36717595	Acquired central hypothyroidism
37110062	Neonatal diabetes, congenital hypothyroidism, congenital glaucoma, hepatic fibrosis, polycystic kidney syndrome
37110922	Congenital central hypothyroidism due to thyrotropin-releasing hormone receptor deficiency
36674793	Genetic transient congenital hypothyroidism
36675175	X-linked central congenital hypothyroidism with late-onset testicular enlargement
37204507	Congenital hypothyroidism due to maternal intake of antithyroid drug
4303055	Hypothyroidism due to sarcoidosis
4220368	Secondary hypothyroidism
4309027	Idiopathic atrophic hypothyroidism
4223217	Severe hypothyroidism
134312	Iatrogenic hypothyroidism

Scleroderma

concept_id	concept_name
4033497	Sclerodermatomyositis
4299985	Drug-induced pseudoscleroderma
4221675	Pseudoscleroderma due to rheumatoid disease
4223504	Pseudoscleroderma due to cytotoxic therapy
4299967	Pseudoscleroderma due to silicon/paraffin implant
4224630	Pseudoscleroderma due to amyloid light-chain amyloidosis
441928	Localized scleroderma
36674475	Neonatal scleroderma
4291432	Occupational scleroderma
4331739	Linear scleroderma
4270880	Porphyria-induced scleroderma
4295306	Scleroderma-associated calcinosis
4296511	Scleroderma-associated telangiectasia
4296514	Scleroderma-associated poikiloderma
4299827	Scleroderma-associated hypermelanosis
4027230	Systemic sclerosis sine scleroderma
4126439	Acute scleroderma renal crisis
4128222	Renal involvement in scleroderma
4196974	Coup de sabre scleroderma
4296512	Scleroderma-associated nailfold telangiectasia

4296513	Scleroderma-associated necrotizing vasculitis
4296515	Scleroderma-associated nail dystrophy
4337524	Pericarditis secondary to scleroderma
44811612	Polymyositis/scleroderma overlap syndrome
4301143	Scleroderma-like secondary cutaneous sclerosis
4300100	Scleroderma-like reaction due to poison
37397763	Glomerulonephritis co-occurrent and due to scleroderma

Systemic Lupus Erythematous

concept_id	concept_name
4295179	Acute systemic lupus erythematosus
36676444	Autosomal systemic lupus erythematosus
4346976	Bullous systemic lupus erythematosus
46270532	Cheilitis due to lupus erythematosus
37110504	Chorea co-occurrent and due to systemic lupus erythematosus
4044056	Chorea in systemic lupus erythematosus
37110517	Demyelination of central nervous system co-occurrent and due to systemic lupus erythematosus
4269448	Dilated cardiomyopathy due to systemic lupus erythematosus
46273369	Endocarditis due to systemic lupus erythematosus
4296502	Fulminating systemic lupus erythematosus
37019030	Gingival disease co-occurrent and due to lupus erythematosus
37016279	Glomerular disease due to systemic lupus erythematosus
4055640	Lung disease with systemic lupus erythematosus
4299106	Lupus disease of the lung
255891	Lupus erythematosus
45768793	Lupus erythematosus of oral mucous membrane
4291306	Lupus erythematosus overlap syndrome
4301142	Lupus erythematosus-associated necrotizing vasculitis
4295305	Lupus erythematosus-associated urticarial vasculitis
4057084	Lupus hepatitis
4344399	Lupus panniculitis
4344495	Lupus vasculitis
4105023	Myopathy due to disseminated lupus erythematosus
4316373	Neonatal lupus erythematosus
46270384	Nephropathy co-occurrent and due to systemic lupus erythematosus
37399735	Nephrosis co-occurrent and due to systemic lupus erythematosus
37395585	Nephrotic syndrome co-occurrent and due to systemic lupus erythematosus
4101469	Pericarditis secondary to systemic lupus erythematosus
4105637	Polyneuropathy in disseminated lupus erythematosus
4319305	Rash of systemic lupus erythematosus

4145240	Renal tubulo-interstitial disorder in systemic lupus erythematosus
4217054	Retinal vasculitis due to systemic lupus erythematosus
37117740	Secondary autoimmune hemolytic anemia co-occurrent and due to systemic lupus erythematosus
4285717	SLE glomerulonephritis syndrome
4250483	SLE glomerulonephritis syndrome, WHO class I
4186940	SLE glomerulonephritis syndrome, WHO class II
4297164	SLE glomerulonephritis syndrome, WHO class III
4267801	SLE glomerulonephritis syndrome, WHO class IV
4178133	SLE glomerulonephritis syndrome, WHO class V
4002526	SLE glomerulonephritis syndrome, WHO class VI
257628	Systemic lupus erythematosus
4318863	Systemic lupus erythematosus encephalitis
44784527	Systemic lupus erythematosus in remission
4301051	Systemic lupus erythematosus of childhood
4344400	Systemic lupus erythematosus with multisystem involvement
4344158	Systemic lupus erythematosus with organ/system involvement
4149913	Systemic lupus erythematosus with pericarditis
44814064	Systemic lupus erythematosus/Sjogren's overlap syndrome
4300204	Systemic lupus erythematosus-associated antiphospholipid syndrome
4219859	Systemic lupus erythematosus-related syndrome

Ehlers Danlos Syndrome

concept_id	concept_name
79145	Ehlers-Danlos syndrome
4307651	Ehlers-Danlos syndrome, dysfibronectinemic
4049487	Ehlers-Danlos syndrome, type 2
4062070	Ehlers-Danlos syndrome, type 4
4106173	Ehlers-Danlos syndrome, hydroxylysine-deficient
4148925	Ehlers-Danlos syndrome, type 3
4176273	Ehlers-Danlos syndrome, type 8
36676402	Ehlers-Danlos syndrome spondylocheirodysplastic type
4284819	Ehlers-Danlos syndrome, type 5
4307510	Ehlers-Danlos syndrome, type 1
37395762	Ehlers-Danlos syndrome classic type
37397547	Ehlers-Danlos syndrome kyphoscoliotic type
36715309	Ehlers-Danlos syndrome musculocontractural type
36715310	Ehlers-Danlos syndrome progeroid type
4205583	Ehlers-Danlos syndrome, procollagen proteinase deficient
4213256	Ehlers-Danlos syndrome, procollagen proteinase resistant
4315048	Ehlers-Danlos syndrome, dominant type 4

4320939	Ehlers-Danlos syndrome, recessive type 4
36715308	Ehlers-Danlos syndrome cardiac valvular type
4324953	Ehlers-Danlos syndrome, familial joint laxity type
36717138	Ehlers-Danlos syndrome kyphoscoliotic and deafness type
4002589	Ehlers-Danlos syndrome, non hydroxylysine deficient ocular type
36674514	Ehlers-Danlos syndrome due to tenascin-X deficiency
46271476	Periodontitis co-occurrent with Ehlers-Danlos syndrome type 4

Acute migraine

concept_id	concept_name
762580	Refractory acute confusional migraine
601849	Acute migraine
4318866	Acute confusional migraine

Parkinson disease

concept_id	concept_name
44782422	Dementia due to Parkinson's disease
46269696	Restrictive lung disease due to Parkinson disease
608033	Progressive supranuclear palsy parkinsonism syndrome
608078	Autosomal recessive familial Parkinson disease
608851	Fluency disorder due to Parkinson disease
4049300	MPTP-induced parkinsonism
4064308	Postencephalitic parkinsonism
4047751	Juvenile Parkinson's disease
374013	Secondary parkinsonism
4046092	Carbon monoxide-induced parkinsonism
4044052	Manganese-induced parkinsonism
4043380	Parkinsonism with calcification of basal ganglia
4046093	Vascular parkinsonism
4086836	Parkinsonian facies
4095182	Parkinsonian ataxia
4088333	Type A Wolff-Parkinson-White pattern
4088494	Type B Wolff-Parkinson-White pattern
4140881	Symptomatic parkinsonism
4098286	Parkinson's facies
4155897	Parkinsonian flexion posture
4126631	Parkinsonian features
4204820	Parkinsonian tremor
4140090	Parkinsonism

concept_id	concept_name
44792293	Cerebral degeneration in Parkinson's disease
373139	Syphilitic parkinsonism
4171569	Parkinsonism due to drug
4314734	Dementia associated with Parkinson's Disease
4231949	Cerebral degeneration due to Parkinson's disease
40485457	Multiple system atrophy, Parkinson's variant
441458	Poisoning by anti-parkinsonism drug
381270	Parkinson's disease
4177039	Hypokinetic parkinsonian dysphonia
44784241	X-linked dystonia parkinsonism
45765396	Rapid onset dystonia parkinsonism
45765480	Frontotemporal dementia with parkinsonism-17
37395785	Young onset Parkinson disease
37396063	Parkinsonism with dementia of Guadeloupe
37399497	Early onset parkinsonism and intellectual disability syndrome
37396747	Autosomal dominant late onset Parkinson disease
36713737	Orthostatic hypotension co-occurrent and due to Parkinson's disease
36714473	Psychosis co-occurrent and due to Parkinson's disease
36715010	Adult-onset dystonia parkinsonism
36716523	Parkinsonism co-occurrent and due to acute infection
36716524	Parkinsonism due to human immunodeficiency virus infection
36716525	Parkinsonism following infection
36716557	Parkinsonism due to hereditary spastic paraplegia
36716783	Atypical Parkinsonism
36716784	Parkinsonism due to heredodegenerative disorder
37117203	Infection causing parkinsonism
37110499	Sporadic Parkinson disease
37110500	Parkinsonism due to and following injury of head
37110501	Parkinsonism due to mass lesion of brain
37110549	Functional parkinsonism
37110776	Atypical juvenile parkinsonism
4219273	Parkinsonian syndrome with idiopathic orthostatic hypotension
4248716	Neuroleptic-induced parkinsonism
42537905	Hemiparkinsonism hemiatrophy syndrome
4253363	Wolff-Parkinson-White pattern
35624223	Parkinsonism caused by cyanide
36674193	X-linked parkinsonism with spasticity syndrome
37204371	Parkinsonian pyramidal syndrome
37311987	Dissociative neurological symptom disorder co-occurrent with Parkinsonism
3654598	Amyotrophic lateral sclerosis, parkinsonism, dementia complex
3655826	Parkinsonism caused by methanol
3655832	Parkinsonism caused by carbon disulfide

Cerebrovascular disease

concept_id	concept_name
381591	Cerebrovascular disease
4046444	Asymptomatic cerebrovascular disease
4121341	Diffuse cerebrovascular disease
45773166	Secondary cerebrovascular disease
40484120	Small vessel cerebrovascular disease
374060	Acute ill-defined cerebrovascular disease
434056	Late effects of cerebrovascular disease
4100231	Cerebral degeneration due to cerebrovascular disease
43531621	Vertigo as sequela of cerebrovascular disease
43531622	Ataxia as sequela of cerebrovascular disease
40479575	Dysphasia as late effect of cerebrovascular disease
40480002	Aphasia as late effect of cerebrovascular disease
40481762	Hemiplegia as late effect of cerebrovascular disease
43530679	Apraxia as late effect of cerebrovascular disease
43530687	Dysarthria as late effects of cerebrovascular disease
43530688	Fluency disorder as sequela of cerebrovascular disease
43531583	Visual disturbance as sequela of cerebrovascular disease
44782427	Hemiparesis as late effect of cerebrovascular disease
37309663	Memory deficit due to and following cerebrovascular disease
42539256	Cognitive deficit due to and following cerebrovascular disease
40480449	Sensory disorder as a late effect of cerebrovascular disease
40480475	Abnormal vision as a late effect of cerebrovascular disease
40480938	Monoplegia of lower limb as late effect of cerebrovascular disease
40481842	Monoplegia of upper limb as late effect of cerebrovascular disease
40484513	Hemiplegia of nondominant side as late effect of cerebrovascular disease
40484522	Hemiplegia of dominant side as late effect of cerebrovascular disease
43530702	Monoplegia of leg dominant side as sequela of cerebrovascular disease
43530703	Monoplegia of arm dominant side as sequela of cerebrovascular disease
42535100	Weakness of left facial muscle as sequela of cerebrovascular disease
42539254	Weakness of right facial muscle as sequela of cerebrovascular disease

Multiple sclerosis

concept_id	concept_name
374919	Multiple sclerosis
4231948	Benign multiple sclerosis
4258676	Malignant multiple sclerosis
37311816	Progressive multiple sclerosis
4046108	Acute relapsing multiple sclerosis
4102337	Exacerbation of multiple sclerosis

4137855	Secondary progressive multiple sclerosis
4145049	Relapsing remitting multiple sclerosis
35623817	Marburg acute multiple sclerosis
4178929	Primary progressive multiple sclerosis
37110514	Progressive relapsing multiple sclerosis
4105353	Multiple sclerosis of the brainstem
44784474	Dementia associated with multiple sclerosis
761978	Cognitive impairment due to multiple sclerosis
765565	Functional quadriplegia due to multiple sclerosis
4101729	Multiple sclerosis of the spinal cord
37116351	Multiple sclerosis, ichthyosis, factor VIII deficiency syndrome
44782559	Dementia due to multiple sclerosis with altered behavior

Gastroptosis

concept_id	concept_name
201898	Gastroptosis

Infection

Indication of use	Concept ID Included	Concept ID Excluded
Cardiovascular System Infection	4028265	42537043, 42537216, 4119591, 4193175, 42537495, 4103844, 4207188
Bloodstream infection	132736, 132797, 4331670,	42537043, 42537216, 42537495, 45757222
Catheter-related Infection	42537043, 42537216, 42537495	
Central Nervous System Infection	4028070	4027382, 4237782, 4266366, 374278, 381783
Gastrointestinal System Infection	37396146	4112288, 4341228, 3655333, 37116438, 37017318, 4207191, 36716496, 42537647, 4345693, 196620, 4340791, 36717503, 4340113, 37110318, 36716876, 196347, 4341225
Pneumonia	255848	4049965, 4050872, 261326
Lower Respiratory Tract Infection other than pneumonia	256451, 4270490	4278083, 4058712
Bone and Joint Infection	4253010, 42536600, 4309315, 40483549, 40481969, 40481970, 40480732, 40480731, 40482509, 4003305, 4001293, 4003303, 4001965, 4001294, 4003306, 36715562, 4151843, 141663, 74862, 80626, 4152591, 4002794, 761909, 37309799,	4157481, 37017284, 4343916, 80184

	37309829, 37309798, 37309800, 37309830, 37309779, 37309778, 37309854, 37309869, 36717458, 607418, 4334028, 4262590, 4308690, 4291175, 762781, 72410	
Eye, Ear, Nose, Throat or Mouth Infection	4181583, 437486, 4110027, 4309954, 4122755, 37312548, 4066144, 4309214, 4336548, 4065984, 4042997, 4185761, 4136096, 4051481, 619673, 4185273, 4093433, 4171577, 4134613	4208666, 4085100, 4122211, 4149910, 4122756, 37396756, 4208812, 4220916
Genitourinary Tract Infection	4193167	
Skin and Soft Tissue Infection	4029803, 4058352, 193353, 43530817, 4050695, 4318386, 4029803, 439417, 4130006, 4116986, 4152958, 4155028, 4151520, 4095409, 36715560, 4110712, 37395724, 4327871, 4201370, 40483694, 4280729, 40547222, 4316194, 4048751, 4287930, 619669, 443858, 4220824, 4170730, 4146602, 4087572, 444193, 4190297, 444237, 4105482, 196849, 4185273, 443772, 78916, 442542, 444111, 76848, 4245384, 4161947, 4266814, 4127735, 4047351, 4084286, 3655670, 40489336, 201093, 4174406, 4308468, 4306831, 4347179, 607157, 4180168, 4322630, 443796, 4043900, 4027538, 37017777, 4043718, 4344254, 200644, 133566, 37395594, 40484119, 4034650, 4121790, 761859, 4345453, 4180772, 4345448, 4173075, 36675187, 36675189, 76032, 4124848, 4080337, 4121789, 4120281	4290719, 42536747, 37017777, 37396839, 4341774, 4342877, 3655664, 3655670, 3655330, 4030291, 3655666, 3655610, 607399
Surgical Site Infection	437474	
Other Infection	432250	4028265, 132736, 4331670, 42537043, 42537216, 42537495, 4028070, 37396146, 255848, 256451, 4270490, 4253010, 42536600, 4309315, 40483549, 40481969, 40481970, 40480732, 40480731, 40482509, 4003305, 4001293, 4003303, 4001965,

		4001294, 4003306, 36715562, 4151843, 141663, 74862, 80626, 4152591, 4002794, 761909, 37309799, 37309829, 37309798, 37309800, 37309830, 37309779, 37309778, 37309854, 37309869, 36717458, 607418, 4334028, 4262590, 4308690, 4291175, 762781, 4181583, 437486, 4110027, 4309954, 4122755, 37312548, 4066144, 4309214, 4336548, 4065984, 4042997, 4185761, 4136096, 4051481, 619673, 4185273, 4093433, 4171577, 4134613, 4193167, 4029803, 4058352, 193353, 43530817, 4050695, 4318386, 4029803, 439417, 4130006, 4116986, 4152958, 4155028, 4151520, 4095409, 36715560, 4110712, 37395724, 4327871, 4201370, 40483694, 4280729, 40547222, 4316194, 4048751, 4287930, 619669, 443858, 4220824, 4170730, 4146602, 4087572, 444193, 4190297, 444237, 4105482, 196849, 4185273, 443772, 78916, 442542, 444111, 76848, 4245384, 4161947, 4266814, 4127735, 4047351, 4084286, 3655670, 40489336, 201093, 4174406, 4308468, 4306831, 4347179, 607157, 4180168, 4322630, 443796, 4043900, 4027538, 37017777, 4043718, 4344254, 200644, 133566, 37395594, 40484119, 4034650, 4121790, 761859, 4345453, 4180772, 4345448, 4173075, 36675187, 36675189, 76032, 4124848, 4080337, 4121789, 4120281, 437474, 432251, 440029, 763528, 3654645, 3655580, 3655670, 4030507, 4080879, 4105474, 4188426, 4193174, 4193987, 4208780, 4249564, 4249828, 4270602, 4345236, 4345692, 36715551, 36715566, 36717290, 37017777, 37394534, 37394535, 37394536, 42536622

Infection

Infection	Concept ID Included	Concept ID Excluded
Cardiovascular System Infection	4028265	42537043, 42537216, 4119591, 4193175, 42537495, 4103844, 4207188
Bloodstream infection	132736, 132797, 4331670,	42537043, 42537216, 42537495, 45757222
Catheter-related Infection	42537043, 42537216, 42537495	
Central Nervous System Infection	4028070	4027382, 4237782, 4266366, 374278, 381783
Gastrointestinal System Infection	37396146	4112288, 4341228, 3655333, 37116438, 37017318, 4207191, 36716496, 42537647, 4345693, 196620, 4340791, 36717503, 4340113, 37110318, 36716876, 196347, 4341225
Pneumonia	255848	4049965, 4050872, 261326
Lower Respiratory Tract Infection other than pneumonia	256451, 4270490	4278083, 4058712
Bone and Joint Infection	4253010, 42536600, 4309315, 40483549, 40481969, 40481970, 40480732, 40480731, 40482509, 4003305, 4001293, 4003303, 4001965, 4001294, 4003306, 36715562, 4151843, 141663, 74862, 80626, 4152591, 4002794, 761909, 37309799, 37309829, 37309798, 37309800, 37309830, 37309779, 37309778, 37309854, 37309869, 36717458, 607418, 4334028, 4262590, 4308690, 4291175, 762781, 72410	4157481, 37017284, 4343916, 80184
Eye, Ear, Nose, Throat or Mouth Infection	4181583, 437486, 4110027, 4309954, 4122755, 37312548, 4066144, 4309214, 4336548, 4065984, 4042997, 4185761, 4136096, 4051481, 619673, 4185273, 4093433, 4171577, 4134613	4208666, 4085100, 4122211, 4149910, 4122756, 37396756, 4208812, 4220916
Genitourinary Tract Infection	4193167	
Skin and Soft Tissue Infection	4029803, 4058352, 193353, 43530817, 4050695, 4318386, 4029803, 439417, 4130006, 4116986, 4152958, 4155028, 4151520, 4095409, 36715560, 4110712, 37395724, 4327871, 4201370, 40483694, 4280729, 40547222, 4316194, 4048751, 4287930, 619669, 443858,	4290719, 42536747, 37017777, 37396839, 4341774, 4342877, 3655664, 3655670, 3655330, 4030291, 3655666, 3655610, 607399

Infection	Concept ID Included	Concept ID Excluded
	4220824, 4170730, 4146602, 4087572, 444193, 4190297, 444237, 4105482, 196849, 4185273, 443772, 78916, 442542, 444111, 76848, 4245384, 4161947, 4266814, 4127735, 4047351, 4084286, 3655670, 40489336, 201093, 4174406, 4308468, 4306831, 4347179, 607157, 4180168, 4322630, 443796, 4043900, 4027538, 37017777, 4043718, 4344254, 200644, 133566, 37395594, 40484119, 4034650, 4121790, 761859, 4345453, 4180772, 4345448, 4173075, 36675187, 36675189, 76032, 4124848, 4080337, 4121789, 4120281	
Surgical Site Infection	437474	
Other Infection	432250	4028265, 132736, 4331670, 42537043, 42537216, 42537495, 4028070, 37396146, 255848, 256451, 4270490, 4253010, 42536600, 4309315, 40483549, 40481969, 40481970, 40480732, 40480731, 40482509, 4003305, 4001293, 4003303, 4001965, 4001294, 4003306, 36715562, 4151843, 141663, 74862, 80626, 4152591, 4002794, 761909, 37309799, 37309829, 37309798, 37309800, 37309830, 37309779, 37309778, 37309854, 37309869, 36717458, 607418, 4334028, 4262590, 4308690, 4291175, 762781, 4181583, 437486, 4110027, 4309954, 4122755, 37312548, 4066144, 4309214, 4336548, 4065984, 4042997, 4185761, 4136096, 4051481, 619673, 4185273, 4093433, 4171577, 4134613, 4193167, 4029803, 4058352, 193353, 43530817, 4050695, 4318386, 4029803, 439417, 4130006, 4116986, 4152958, 4155028, 4151520, 4095409, 36715560, 4110712, 37395724, 4327871, 4201370, 40483694, 4280729, 40547222,

Infection	Concept ID Included	Concept ID Excluded
		4316194, 4048751, 4287930, 619669, 443858, 4220824, 4170730, 4146602, 4087572, 444193, 4190297, 444237, 4105482, 196849, 4185273, 443772, 78916, 442542, 444111, 76848, 4245384, 4161947, 4266814, 4127735, 4047351, 4084286, 3655670, 40489336, 201093, 4174406, 4308468, 4306831, 4347179, 607157, 4180168, 4322630, 443796, 4043900, 4027538, 37017777, 4043718, 4344254, 200644, 133566, 37395594, 40484119, 4034650, 4121790, 761859, 4345453, 4180772, 4345448, 4173075, 36675187, 36675189, 76032, 4124848, 4080337, 4121789, 4120281, 437474, 432251, 440029, 763528, 3654645, 3655580, 3655670, 4030507, 4080879, 4105474, 4188426, 4193174, 4193987, 4208780, 4249564, 4249828, 4270602, 4345236, 4345692, 36715551, 36715566, 36717290, 37017777, 37394534, 37394535, 37394536, 42536622

Preliminary code list for medication of interest

Class	Treatment	ConceptID
Opiates	codeine	1201620
	fentanyl	1154029
	hydrocodone	1174888
	hydromorphone	1126658
	morphine	1110410
	oxycodone	1124957
	oxymorphone	1125765
	tramadol	1103314
Tricyclic antidepressants	amitriptyline	710062
	clomipramine	798834
	doxepin	738156
	imipramine	778268
	trimipramine	705755
	amoxapine	713109
	desipramine	716968

	nortriptyline	721724
	protriptyline	754270
L-dopa	levodopa	789578
	etilevodopa	43527177
PPIs	omeprazole	923645
	pantoprazole	948078
	esomeprazole	904453
	dexlansoprazole	19039926
	lansoprazole	929887
	Rabeprazole	911735
Anticholinergics	atropine	914335
	scopolamine	965748
	methylscopolamine	19065868
	cyclopentolate	910232
	homatropine	1101703
	tropicamide	906072
Glp-1 Ras	exenatide	1583722
	liraglutide	40170911
	albiglutide	44816332
	taspoglutide	36850415
	lixisenatide	44506754
	dulaglutide	45774435

APPENDIX III – ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title:
DARWIN EU® - DUS of medicines with prokinetic properties in children and adults diagnosed with gastroparesis

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

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

Comments:

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

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g., cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.2
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.8
3.4	Does the protocol specify measure(s) of association? (e.g., risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	8.2/8.5
4.2	Is the planned study population defined in terms of:				8.5
	4.2.1 Study time period	☒	☐	☐	
	4.2.2 Age and sex	☒	☐	☐	
	4.2.3 Country of origin	☒	☐	☐	
	4.2.4 Disease/indication	☒	☐	☐	
	4.2.5 Duration of follow-up	☒	☐	☐	
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	8.5

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.6
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorized according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☒	☐	☐	
5.5	Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☐	☐	☒	8.6
6.2	Does the protocol describe how the outcomes are defined and measured?	☐	☐	☒	
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☐	☐	☒	

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.6
	9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☐	☐	☒	8.6
	9.1.3 Covariates and other characteristics?	☒	☐	☐	8.6
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.6
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	8.6
	9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.6
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.6
	9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	8.6

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.3 Covariates and other characteristics?	☒	☐	☐	8.6
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.8
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	8.7
10.3 Are descriptive analyses included?	☒	☐	☐	8.8
10.4 Are stratified analyses included?	☒	☐	☐	8.8
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.2
11.2 Are methods of quality assurance described?	☒	☐	☐	10.0
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

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

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.1 Selection bias?	☒	☐	☐	11
12.1.2 Information bias?	☒	☐	☐	
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.2

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	13
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	9.2

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	4

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	14
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	14

Comments:

Name of the main author of the protocol: Katia Verhamme

Date: 29th September 2023

Signature: