Study Protocol

P4-C2-002

DARWIN EU® – Paracetamol prescribing and paracetamol overdose in Europe: a descriptive analysis of trends and patient characteristics

Authors: B. Raventós, T. Duarte-Salles, N. Hunt, G. van Leeuwen, G. Inberg

13/05/2025

Version 2.0

CONTENTS

Study Title	DARWIN EU® – Paracetamol prescribing and paracetamol overdose in Europe: a descriptive analysis of trends and patient characteristics
Protocol version	V2.0
Date	13/05/2025
EUPAS number	EUPAS1000000584
Active substance	Paracetamol
Medicinal product	Not applicable
Research question and objectives	The aim of the study is to provide an overview of paracetamol prescribing and paracetamol overdose in Europe, and to characterise patients presenting with paracetamol overdose. The specific objectives of the study are: 1. To examine the incidence/prevalence of paracetamol prescribing (overall, and by age, sex, formulation and country/database) 2. To examine the incidence of paracetamol overdose (overall, and by age, sex, country/database) 3. To characterise patients with paracetamol overdose, in terms of comorbidities, co-prescribed medications, prior paracetamol prescription, and incidence of short-term complications and mortality.
Country(ies) of study	Denmark, France, Germany, Norway, Spain, Sweden, The Netherlands
Author	Berta Raventós, b.raventos@darwin-eu.org Talita Duarte-Salles, t.duarte@darwin-eu.org

This is a routine repeated study from P3-C1-007 with EUPAS1000000329.

LIST OF ABBREVIATIONS

Acronyms/terms	Description
APHM	Assistance Publique – Hôpitaux de Marseille
CDM	Common Data Model
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DK-DHR	Danish Data Health Registries
EHR	Electronic Health Record
EMA	European Medicines Agency
EU	European Union
GP	General Practitioner
GDPR	General Data Protection Regulation
HI-SPEED	Health Impact - Swedish Population Evidence Enabling Data-linkage
H12O	Hospital Universitario 12 de Octubre
ICD-10-GM	Classification of Diseases, version 10 in the German Modification
InGef RDB	InGef Research Database
IPCI	Integrated Primary Care Information
NAPQI	N-acetyl-p-benzoquinoneimine
NLHR	Norwegian Linked Health Registry data
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OTC	Over The Counter
SCIFI-PEARL	Swedish COVID-19 Investigation for Future Insights - a Population Epidemiology Approach using Register Linkage
SHI	Statutory Health Insurance
WHO	World Health Organization

1. TITLE

DARWIN EU® - Paracetamol prescribing and paracetamol overdose in Europe: a descriptive analysis of trends and patient characteristics

2. RESPONSIBLE PARTIES – STUDY TEAM

Study team role	Names	Organisation
Principal Investigator	Berta Raventós Talita Duarte-Salles	Erasmus MC
Data Scientist	Ger Inberg Cesar Barboza Maarten van Kessel Adam Black Ioanna Nika Ross Williams	Erasmus MC
Epidemiologist	Nicholas Hunt Guido van Leeuwen	Erasmus MC
Study Manager	Natasha Yefimenko	Erasmus MC
Data Partner*	**Names**	**Organisation**
APHM	Laurent Boyer Dorian Grousset	Assistance Publique – Hôpitaux de Marseille
DK-DHR	Claus Møldrup Elvira Bräuner Susanne Bruun	Danish Medicines Agency (DKMA)
H12O	Juan Luis Cruz Bermudez Noelia Garcia Barrio Javier de la Cruz Paula Rubio Mayo	Fundación Investigación Biomédica Hospital 12 de Octubre
InGef RDB	Raeleesha Norris Annika Vivirito Josephine Jacob Alexander Harms	Institut für angewandte Gesundheitsforschung Berlin GmbH
IPCI	Katia Verhamme Ger Inberg	Erasmus MC
NLHR	Saeed Hayati Nhung Trinh Hedvig Nordeng Maren Mackenzie Olson	University of Oslo
HI-SPEED	Huiqi Li Fredrik Nyberg Rickard Ljung Nicklas Pihlström	University of Gothenburg Swedish MPA

*Data partners' role is only to execute code at their data source, review and approve their results. They do not have an investigator role. Data analysts/programmers do not have an investigator role and thus declaration of interests (DOI) for them is not needed.

3. ABSTRACT

Title

DARWIN EU® – Paracetamol prescribing and paracetamol overdose in Europe: a descriptive analysis of trends and patient characteristics.

Rationale and background

Paracetamol (acetaminophen) is one of the most widely used medicines worldwide and is available over the counter in the European Union. It is one of the most common causes of drug poisonings and can result in severe hepatic failure. Different regulatory interventions at national level have occurred to reduce the incidence of paracetamol overdose, but it is uncertain how paracetamol is prescribed across Europe and to what extent prescription may be involved in poisonings.

Research question and objectives

The aim of the study is to provide an overview of paracetamol prescribing and paracetamol overdose trends in selected European databases, and to characterise patients presenting with paracetamol overdose.

The specific objectives of the study are:

1. To examine the incidence/prevalence of paracetamol prescribing (overall, and by age, sex, formulation and country/database).
2. To examine the incidence of paracetamol overdose (overall, and by age, sex, country/database).
3. To characterise patients with paracetamol overdose, in terms of comorbidities, co-prescribed medications, prior paracetamol prescription, and incidence of short-term complications and mortality.

Methods

Study design

Cohort studies comprising of:

1. Population-level drug utilisation study to assess incidence and prevalence of paracetamol prescribing (objective 1)
2. Population-level descriptive epidemiology study to estimate the incidence of paracetamol overdose (objective 2)
3. Patient-level characterisation study to characterise patients with a paracetamol overdose (objective 3)

Population

For objective 1 and 2, the study population will comprise all individuals present in the database at any time from 1st January 2010 to 31st of December 2023 (or the latest year with complete observation). For objective 3, the study will comprise of individuals with paracetamol overdose for the first time in their patient history during the study period.

For incidence calculations (objective 1 and 2), individuals with a record of the outcome will re-enter the study after a certain amount of time (i.e. washout window) so further occurrences of the outcome can be captured. This washout window will be defined as 60 days following the end of the prescribed treatment for paracetamol prescribing and 365 days for paracetamol overdose. For objective 3, individuals with a prior history of paracetamol overdose any time prior to index date will be excluded.

A year of observation history prior to index date will be required for all individuals within selected databases. Individuals aged less than 1 year of observation history will be excluded.

Variables

Drug of interest: Paracetamol.

Condition of interest: Paracetamol overdose.

Sample size

No sample size has been calculated.

Data sources

1. Assistance Publique – Hôpitaux de Marseille (APHM), France
2. Danish Data Health Registries (DK-DHR), Denmark
3. Hospital Universitario 12 de Octubre (H12O), Spain
4. InGef Research Database (InGef RDB), Germany
5. Integrated Primary Care Information (IPCI), The Netherlands
6. Norwegian Linked Health Registry data (NLHR), Norway
7. Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED), Sweden

Statistical analysis

Objective 1 will be conducted in all databases except for DK-DHR. Objectives 2 and 3 will be conducted in APHM, DK-DHR, InGef RDB and HI-SPEED.

Population-level drug utilisation study (objective 1): Incidence rates and period prevalence of paracetamol prescribing will be calculated overall and stratified by sex, age, and formulation. Estimates will be calculated yearly.

Population-level descriptive epidemiology (objective 2): Incidence rates of paracetamol overdose will be calculated overall and stratified by sex, age, and study period. Estimates will be calculated yearly.

Patient-level characterisation (objective 3): Characteristics will be described by means of large-scale characterisation. A prespecified list of comorbidities and concomitant medications, prior paracetamol prescriptions, short-term complications and mortality will also be described. Covariates of interest will also be reported as counts and proportions.

For all analyses, results will be reported by country/database. A sensitivity analyses excluding the prior observation requirement will be conducted. Any counts smaller than 5 will be obscured to ensure privacy and confidentiality.

4. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or Update	Reason
V2	13/05/2025	N/A	Update from initial study protocol P3-C1-007 (EUPAS1000000329)	This is a routine repeated study.

Comparision with previous protocols:

Study deliverables	P3-C1-007 (EUPAS1000000329)	P4-C2-002 (current study protocol)
Study period	2010-2023	2010-2023
Data partners:[1]		
- APHM [France]		X
- BIFAP [Spain]	X	
- CDWBordeaux [France]	X (Objective 3)	
- CPRD GOLD [UK]	X	
- DK-DHR [Denmark]	X (Objective 1)	X (Objective 2 and 3)
- EMBD-ULSEDV [Portugal]	X (Objective 1)	
- HI-SPEED [Sweden]		X
- H12O [Spain]		X (Objective 1)
- InGef RDB [Germany]		X
- IPCI [The Netherlands]		X (Objective 1)
- IQVIA DA Germany [Germany]	X (Objective 1)	
- NAJS [Croatia]	X (Objective 1)	
- NLHR [Norway]		X
- UKBB [UK]	X	
Reference study protocol	N/A	P3-C1-007 (EUPAS1000000329)
Changes from reference study protocol	N/A	Sensitivity analysis: remove the inclusion criteria of one year of prior database history analysis.

[1] Some data partners have been included to participate in specific objectives, which are noted in brackets.

5. MILESTONES

Study deliverables	Timelines*
Final Study Protocol	May 2025
Creation of Analytical code	May/June 2025
Execution of Analytical Code on the data	June 2025
Draft Study Report	July/August 2025
Final Study Report	August 2025

** The planned study timelines are subject to the availability of the data partners to initiate study activities and the timely receipt of approvals from the internal review boards governing the respective data sources.*

6. RATIONALE AND BACKGROUND

Paracetamol (acetaminophen) is one of the most widely used medicines worldwide and is listed by the World Health Organisation's (WHO) as an essential medicine.(1) It has mild analgesic and antipyretic properties, and it is generally used to treat fever and pain. Paracetamol is readily available over the counter (OTC) in European countries, and it is available through non-pharmacy outlets in some countries.(2)

Paracetamol can be found in different pharmaceutical forms and in different doses. The usual adult recommended dose is 500mg to 1000mg, with a maximum daily dose of 3000 to 4000mg/day.(3) Preparations can include paracetamol alone or in combination with other substances, such as non-steroidal anti-inflammatory drugs or opioids, and it can be found in immediate release (short-acting) and modified release (long-acting) forms in some countries. Products containing modified-release paracetamol are not available in the EU, as the European Medicines Agency (EMA) recommended suspending the marketing of these products in December 2017.(4)

Paracetamol is generally considered safe when administered in appropriate doses and for short periods of time.(5) However, toxicity is common following paracetamol overdose, and it can result in severe hepatic failure. Inadvertent overdose can result from taking additional doses, repeated supratherapeutic ingestion, and duplication of therapy.

Paracetamol is principally metabolized by glucuronidation and sulfation.(6) Small amounts are converted into the toxic metabolite N-acetyl-p-benzoquinoneimine (NAPQI), which is detoxified via conjugation with glutathione. Toxicity results in overdose when there is insufficient glutathione available for conjugation of NAPQI, which may lead to hepatotoxicity and acute kidney injury.

Hepatotoxicity following paracetamol overdose usually result from massive overdoses (>30g/day), overdose with modified-release paracetamol, and delays to treatment. Other risk factors include treatment with medications that induce the activity of the cytochrome CYP2E1 (e.g. carbamazepine, isoniazid), glutathione depletion (e.g. in patients with malnutrition or anorexia) and chronic alcohol use.(7) Chronic liver disease patients are also at increased risk for hepatoxicity.(8) N-acetylcysteine is the most widely used antidote for paracetamol overdose. It works by replenishing cysteine, a rate-limiting factor for glutathione synthesis, which is essential for detoxifying NAPQI. The risk of developing hepatotoxicity is substantially reduced when treatment is initiated within 8 hours of ingestion.(9, 10) Severe cases may require liver transplantation or result in death.(11)

Paracetamol is one of the most common causes of drug poisonings, and it is one of the most common OTC analgesics used in suicidal overdoses. Based on available data, it has been estimated that paracetamol is involved in 6% of all global poisonings, 56% of severe acute liver injury and acute liver failure and 7% of drug-induced liver injury, with 0.4% of fatal cases.(12) Different regulatory interventions at national level have occurred over many years aimed at reducing the incidence of overdose such as restriction in pack size and the total amount available to purchase OTC. However, it is uncertain how paracetamol is being

prescribed across Europe and to what extent prescription of paracetamol is involved in paracetamol poisonings.

7. RESEARCH QUESTION AND OBJECTIVES

The aim of the study is to provide an overview of paracetamol prescribing and paracetamol overdose in the selected European databases, and to characterise patients presenting with paracetamol overdose.

The specific objectives of the study are:

1. To examine the incidence/prevalence of paracetamol prescribing (overall, and by age, sex, formulation and country/database).
2. To examine the incidence of paracetamol overdose (overall, and by age, sex, country/database).
3. To characterise patients with paracetamol overdose, in terms of comorbidities, co-prescribed medications, prior paracetamol prescription, and incidence of short-term complications and mortality.

A description of the proposed objectives to be achieved in the study is described in **Table 1**. This study a routine repeated study of the DARWIN EU® P3-C1-007 study,(13) and is based on the same protocol with updated data and different data partners, with the exception of an additional sensitivity analysis, described in more detail in section "8.8 Analysis".

Table 1. Primary and secondary research questions and objective.

A. Primary research question and objective.

Objective:	Objective 1: To examine the incidence/prevalence of paracetamol prescribing Objective 2: To examine the incidence of paracetamol overdose Objective 3: To characterise patients with paracetamol overdose
Hypothesis:	n/a
Population:	Objective 1 and 2: Overall population Objective 3: Patients with paracetamol overdose
Exposure:	n/a
Comparator:	n/a
Outcome:	Objective 1: Paracetamol prescription Objective 2: Patients with paracetamol overdose Objective 3: n/a
Time *(when follow up begins and ends):*	2010-2023
Setting:	Routinely collected data from 7 databases in 7 European countries.
Main measure of effect:	Proportions, incidence and prevalence

8. RESEARCH METHODS

8.1 Study type and study design

The study types with related study designs are described in the **Table** below.

Retrospective cohort studies will be conducted using routinely collected health data from 8 databases. The study will comprise of:

1. A population-level drug utilisation study (DUS) to assess incidence/prevalence of paracetamol prescribing among the general population (objective 1).
2. A population-level descriptive epidemiology study to assess incidence of paracetamol overdose among the general population (objective 2).
3. A patient-level characterisation to characterise patients with a paracetamol overdose (objective 3).

Table 2. Description of potential study types and related study designs.

Study type	Study design	Study classification
Population Level DUS	Population Level Cohort	Off the shelf
Population-level descriptive epidemiology	Population-level cohort	Off the shelf
Patient-level characterisation	Cohort analysis	Off the shelf

8.2 Study setting and data sources

This study will be conducted using routinely collected data from 7 databases in 7 European countries selected from the DARWIN EU® Database Catalogue. All databases were previously mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM).

The selection process was based on the size of the databases, the number of individuals with the outcome of interest, geographical spread, and diversity of healthcare settings. The selection process primarily focused on databases that were recently incorporated to the DARWIN EU® network and were not part of the previous study (P3-C1-007), which included 8 databases from 7 countries (Croatia, Denmark, France, Germany, Portugal, Spain, United Kingdom).(13) Databases participating in P3-C1-007 not involved in objectives related to paracetamol overdose (objective 2 and 3) were also considered if refined mappings for paracetamol overdose were available.

Based on the feasibility assessment performed, the suggested databases are considered fit for purpose for this study at least part of the objectives:

1. Assistance Publique – Hôpitaux de Marseille (APHM), France
2. Danish Data Health Registries (DK-DHR), Denmark
3. Hospital Universitario 12 de Octubre (H12O), Spain
4. InGef Research Database (InGef RDB), Germany
5. Integrated Primary Care Information (IPCI), The Netherlands
6. Norwegian Linked Health Registry data (NLHR), Norway
7. Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED), Sweden

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 **Table .** While some databases include data extending beyond December 2023, the study data will be restricted to this time point to ensure comparability with the previous study.

All databases except DK-DHR will be used to inform objective 1. Objective 2 and 3 will be informed by APHM, DK-DHR, InGef RDB and HI-SPEED only, due to limited counts for paracetamol overdose observed in the study feasibility assessment for other databases. DK-DHR will not be considered for Objective 1, as results for this objective were already provided in the P3-C1-007 DARWIN EU® study.(13) DK-DHR will participate in the current study to support Objectives 2 and 3, as refinements in the mapping process have enabled the detection of paracetamol poisoning cases.

Table 3. Description of the selected data sources.

Country	Name of Database	Justification for Inclusion	Health Care setting[1]	Type of Data[2]	Number of active subjects[3]	Data lock for the last update
France	APHM	Contribute to the diversity of data sources in terms of geography and healthcare settings. Observed records of individuals with paracetamol overdose.	Hospital care (IP, OP)	Claims, EHRs, registries, biobank	249,900	2025-01-11
Denmark	DK-DHR	Contribute to the diversity of data sources in terms of geography and healthcare settings. Observed records of individuals with paracetamol overdose.	Hospital care (IP, OP)	EHRs, registries, others.	5,984,000	2025-1-18
Spain	H12O	Contribute to the diversity of data sources in terms of geography and healthcare settings (Objective 1 only).	Hospital care (IP, OP)	EHRs, registries	294,500	2024-09-16
Germany	InGef RDB	Contribute to the diversity of data sources in terms of geography and healthcare settings. Observed records of individuals with paracetamol overdose.	Primary care, hospital care (IP, OP)	Claims	7,658,400	2024-11-24
Netherlands	IPCI	Contribute to the diversity of data sources in terms of geography and healthcare settings (Objective 1 only).	Primary care	EHRs	1,247,900	2024-10-21
Norway	NLHR	Provide data with nation-wide coverage. Contribute to the diversity of data sources in terms of geography and healthcare settings (Objective 1 only).	Primary care, hospital care (IP, OP)	Registries	5,500,000	2024-10-29
Sweden	HI-SPEED	Provide data with nation-wide coverage. Contribute to the diversity of data sources in terms of geography and healthcare settings. Observed records of individuals with paracetamol overdose.	Primary care[5], hospital care (OP, IP)	Registries	10,563,700	2024-09-10

1. IP = inpatient, OP = outpatient, OT = other, n/a = not applicable
2. EHR = electronic health records
3. This number corresponds to the maximum number of persons in observation in the last 6 months of data.
4. Person counts provided as part of the feasibility assessment using preliminary concepts. All counts are rounded up to the nearest multiple of 100.
5. Primary care data is only available for 40% of the population.

Assistance Publique − Hôpitaux de Marseille (APHM), France

The APHM database includes all hospital stays across various care settings—acute care, psychiatric care, rehabilitation care, and home hospitalisation—capturing approximately 300,000 stays annually. In the source data, diagnoses are coded using International Classification of Diseases, version 10 (ICD-10). Drugs, procedures and measurements are recorded using terminologies in line with the French DRG system, managed via the CORA software. The APHM database also captures comprehensive drug prescription and administration data, including UCD drug codes, ATC classifications, quantities, and dosages, managed through PHARMA software. Additionally, medical and paramedical notes, such as hospitalisation reports, radiology, endoscopy, and consultation summaries, are recorded using AXIGATE software. Laboratory data, covering both prescriptions and test results, is also included.

Danish Data Health Registries (DK-DHR), Denmark

Danish health data is collected, stored and managed in national health registers at the Danish Health Data Authority and covers the entire population which makes it possible to study the development of diseases and their treatment over time. There are no gaps in terms of gender, age and geography in Danish health data due to mandatory reporting on all patients from cradle to grave, in all hospitals and medical clinics. Personal identification numbers enable linking of data across registers, so it captures data on all Danes throughout their lives, regardless of whether they have moved around the country. High data quality due to standardisation, digitisation and documentation means that Danish health data is not based on interpretation. The Danish Health Data Authority is responsible for the national health registers and for maintaining and developing standards and classifications in the Danish healthcare system. Legislation ensures balance between personal data protection and use. The current data release includes data on the entire Danish population of 5.9 million persons from 1995. It includes data from the following registries: The Central Person Registry, The National Patient Registry, The Register of Pharmaceutical Sales, The National Cancer Register, The Cause of Death registry, The Laboratory Database including Coronavirus disease 2019 test results and The Vaccination Registry (including COVID-19 vaccinations.

Hospital Universitario 12 de Octubre (H12O), Spain

The H12O data source includes hospital data from a wide range of health-related information across various domains, including laboratory results, prescriptions, treatments, administrative details, and diagnoses. Additionally, data is gathered from other systems, such as the Pathological Anatomy system, which provides insights into sample analyses, and the cost system, which tracks the expenses associated with patient interactions at the hospital. Efforts are currently underway to integrate further data sources, including radiological information and Patient-Reported Outcome Measures (PROMs).

InGef Research Database (InGef RDB), Germany

The InGef database comprises anonymized longitudinal claims data of about 10 million individuals across more than 70 statutory health insurance providers (SHIs) throughout Germany. Data are longitudinally linked over a period of currently ten years. Patients can be traced across health care sectors. All patient-level and provider-level data in the InGef research database are anonymised to comply with German data protection regulations and German federal law. German SHI claims data available in the InGef database includes information on demographics (quarter and year of birth, gender, death date if applicable, region of residence on administrative district level); hospitalisations; outpatient services (diagnoses, treatments; specialities of physicians); dispensing of drugs; dispensings of remedies and aids; and sick leave and sickness allowance times. In addition, costs or cost estimates from SHI perspective are available for all important cost elements. All diagnoses in Germany are coded using the International Classification of Diseases, version 10 in the German Modification (ICD-10-GM). The persistence (membership over time) is rather high in the InGef database. During a time period of 5 years (2009 to 2013), 70.6% of insurance members survived and remained insured with the same SHI without any gap in their observational time. Persons leaving one of the participating SHIs and entering another participating SHI, can be linked during

yearly database consistency updates and are thus not lost over time. The InGef database is dynamic in nature, i.e. claims data are updated in an ongoing process and new SHIs may join or leave the database. By law, only the last 10 years of data are allowed to be used. At every new release this window shifts, dropping older data and adding new data.

Integrated Primary Care Information (IPCI), The Netherlands

The IPCI database is a longitudinal observational database containing routinely collected data from computer-based patient records of a selected group of General Practitioners (GP) throughout the Netherlands (N=723). IPCI was started in 1992 by the department of Medical Informatics of the Erasmus University Medical Center in Rotterdam with the objective to enable better post marketing surveillance of drugs. The current database includes patient records from 2006 on, when the size of the database started to increase significantly. In 2016, IPCI was certified as Regional Data Center. Since 2019 the data is also standardized to the OMOP CDM enabling collaborative research in a large network of databases within the Observational Health Data Sciences and Informatics (OHDSI) community. The primary goal of IPCI is to enable medical research. In addition, reports are generated to inform GPs and their organizations about the provided care. Contributing GPs are encouraged to use this information for their internal quality evaluation. The IPCI database is registered on the European Medicines Agency (EMA) ENCePP resources database (http://www.encepp.eu).

Health Impact - Swedish Population Evidence Enabling Data-linkage (HI-SPEED), Sweden

The HI-SPEED study is a nationwide linked multi-register, regularly updated, observational study for timely response over time to scientific questions around effectiveness and safety of approved drugs that can arise suddenly, requiring rapid evidence for timely regulatory action - to protect patients' health and lives. The study data covers the whole Swedish population (about 10 million), with data on specialist care (National Patient Register), drug use (Prescribed Drug Register), cause of death (Cause-of-Death Register), sociodemographic data, and selected clinical data. Primary care visit diagnoses and procedures are available for 40% of the population (two largest Swedish regions). Most data start from 2015; prescription drug data on all prescriptions filled nationally are available from 2018. The study population and all data are updated quarter-yearly. HI-SPEED builds on the predecessor project “Swedish COVID-19 Investigation for Future Insights - a Population Epidemiology Approach using Register Linkage” (SCIFI-PEARL) that was initiated in 2020 to conduct research on Covid-19 and pandemic-relations (https://www.gu.se/en/research/scifi-pearl).

Norwegian Linked Health Registry data (NLHR), Norway

Norway has a universal public health care system consisting of primary and specialist health care services covering a population of approximately 5.4 million inhabitants. Many population-based health registries were established in the 1960s with use of unique personal identifiers facilitating linkage between registries. Data in these health registries are used for health analysis, health statistics, improving the quality of healthcare, research, administration and emergency preparedness. We harmonized data from the following registries: the Medical Birth Registry of Norway (i.e. pregnancy-related data), the Norwegian Prescription Registry (i.e. medications dispensed outside of hospitals), the Norwegian Patient Registry (i.e. data on diagnosis recorded in secondary care), Norway Control and Payment of Health Reimbursement (i.e. primary care data), the Norwegian Surveillance System for Communicable Diseases (i.e. data on test results of communicable diseases), the Norwegian Immunisation Registry (i.e. data on vaccination), the National Death Registry, and the National Registry. Linkage between the registries was facilitated using project-specific person ID generated from unique personal identification assigned at birth or immigration for all legal residents in Norway.

8.3 Study period

The study will span from 1st of January 2010 to 31st of December 2023. For objectives 1 and 2, incidence and prevalence will be calculated only for complete calendar years observed in the database (e.g., if the end of available data is 1st of June 2023, only data up to 31st December 2022 will be considered).

For databases with incomplete coverage for the entire study period, the study period will differ and will be defined based on data availability. This will affect InGef RDB (2015-2023) and NHRL (2018-2023). For HI-SPEED, the study period will differ across objectives, starting in 2018 (start of prescription data) for Objective 1, and 2015 (start of data availability) for Objective 2 and 3. Please see "11. Limitations of the research methods" for further details.

8.4 Follow-up

Study participants will be followed up from index date (see **Table 4**). For objective 1 and 2, index date will be defined as the latest of: study start date (1st January 2010, or start of data availability if later), or date at which they have one year of prior history. Individuals will be followed up until the earliest date of any of following events: study end (31st of December 2023 or last complete calendar year), end of data availability (end of the last year with complete observation in the database for objective 1 and 2), or loss to follow-up or date of death.

For the incidence calculations of objective 1 and 2, individuals will not contribute time to the study during a certain amount of time after the occurrence of the event. For objective 1, individuals with a paracetamol prescription will not contribute time to the study during the 60 days after the end of treatment. For objective 2, individuals with a paracetamol overdose will not contribute time to the study during the 365 days following the diagnosis of this event. For objective 3, we will only consider first-ever events (i.e. patients diagnosed for the first time with a paracetamol overdose, with this event taking place during the study period). For this objective, index date will be defined as the date of paracetamol overdose.

Table 4. Operational definition of time 0 (index date) and other primary time anchors.

Study population name(s)	Time Anchor Description (e.g. time 0, index date)	Number of entries [1]	Type of entry	Washout window	Care Setting [2]	Code Type[2]	Diagnosis position[3]	Incident with respect to…
General population (objective 1)	Study entry date	Multiple entry	Incident, prevalent	[-60, -1]	IP, OP, OT	SNOMED	Any	Paracetamol prescribing
General population (objective 2)	Study entry date	Multiple entry	Incident	[-365, -1]	IP, OP, OT	SNOMED	Any	Paracetamol overdose
Patients with paracetamol overdose (objective 3)	Date of paracetamol overdose	Single entry	Incident	[-Inf, -1]	IP, OP, OT	SNOMED	Any	Paracetamol overdose

[1] Indicate whether patients are allowed to enter the study population only once or multiple times

[2] IP = inpatient, OP = outpatient, OT = other, n/a = not applicable

[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

8.5 Study population with inclusion and exclusion criteria

The source population will comprise all individuals present in the database at any time during the period from 1st of January 2010 to 31st of December 2023 (or last year with complete observation). All patients will

need to have at least 365 days of data visibility prior to index date. Therefore, children aged <1 year will be excluded.

The operational definitions of the inclusion and exclusion criteria are presented by means of **Table** and **Table** , respectively.

Table 5. Operational definitions of inclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations:
Observation period during the study period	All individuals present in the period 01/01/2010-31/12/2023 (or last available date if earlier)	After	n/a	IP, OP, OT	n/a	n/a	All study populations
Prior database history	Study participants will be required to have 365 days of prior history observed before contributing observation time	Prior	[-365, 0]	OP	n/a	n/a	All study populations

[1] IP = inpatient, OP = outpatient, OT = other, n/a = not applicable
[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

Table 6. Operational definitions of exclusion criteria.

Criterion	Details	Order of application	Assessment window [1]	Care Settings[2]	Code Type	Diagnosis position[3]	Applied to study populations:
Washout window for paracetamol prescribing	Individuals newly prescribed with paracetamol with a previous prescription of paracetamol 60 days prior index date will be excluded	Prior	[-60, -1]	IP, OP, OT	n/a	n/a	General population (objective 1)
Washout window for paracetamol overdose (incidence)	Individuals newly diagnosed with a paracetamol overdose with previous history of that same outcome 365 days prior to index date will be excluded.	Prior	[-365, -1]	IP, OP, PT	n/a	n/a	General population (objective 2)
Washout window for paracetamol overdose (characterisation)	Individuals newly diagnosed with a paracetamol overdose with previous history of that same outcome any time prior index date will be excluded.	Prior	[-Inf, -1]	IP, OP, OT	n/a	n/a	Patients with paracetamol overdose (objective 3)

[1] Inf= Any time prior
[2] IP = inpatient, OP = outpatient, OT = other, n/a = not applicable
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter).

8.6 Variables

8.6.1 Exposure/s

This study has no exposure of interest.

8.6.2 Outcome/s

The operational definition of the outcomes is presented in the **Table** , and include paracetamol prescribing (Objective 1) and paracetamol overdose (Objective 2).

The use of paracetamol will be derived from prescription data when available. In databases lacking prescription data, dispensation records will be used. For consistency, all drug exposure data will be referred to as prescriptions in this protocol.

For paracetamol prescribing, successive individual drug records (i.e. drug exposures) separated by less than 30 days will be considered the same continuous exposure (i.e. drug era). To calculate incidence rates, multiple exposures (i.e. single or continuous) to paracetamol prescribing will be treated as separate outcomes after a washout window of 60 days following the end of the prescribed treatment. For paracetamol overdose, this window will be defined as 365 days.

A preliminary list of concept sets for paracetamol overdose can be found in the **Appendix I**.

Table 7. Operational definitions of outcome.

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care Settings[2]	Code Type	Diagnosis Position[3]	Applied to study populations
Paracetamol prescribing	A drug record of a paracetamol-containing product	Yes	Count	[-60, -1]	IP, OP, OT	RxNorm	n/a	General population (objective 1)
Paracetamol overdose	A diagnosis of paracetamol overdose or poisoning	Yes	Count	[-365, -1]	IP, OP, OT	SNOMED	Any	General population (objective 2)

[1] Inf= Any time prior
[2] IP = inpatient, OP = outpatient, OT = other, n/a = not applicable
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

8.6.3 Other covariates

The study covariates are described conceptually, and the context or rationale for the choices are provided in this section. The operational definition of the covariates is described in the **Table** .

Population-level DUS on paracetamol prescribing (objective 1):

The covariates for stratification on the population level DUS will include sex, age groups, and formulation. Age groups will include: 1-5; 6-11; 12-17; 18-29 and subsequently 10-year age bands (30-39, 40-49, etc.) up to >80 years or more. Formulations will include oral tablets, capsules, oral liquid formulations, injectable liquid formulations, and rectal suppositories.

Population level descriptive epidemiology study on paracetamol overdose (objective 2):

The covariates for stratification on the population level descriptive epidemiology study will include sex and age groups (1-17; 18-49; 50-79; >80). Given the low preliminary counts for paracetamol overdose, a broader age category will also be considered (1-17; >18).

Patient level characterisation of patients with paracetamol overdose (objective 3):

For the patient-level characterisation study, covariates will include sex, age groups (narrow: 1-17; 18-49; 50-79; >80; broad: 1-17; >18), comorbidities, concomitant medications, short-term complications of paracetamol overdose and mortality. If the number of cases allows, this analysis will be stratified by study period (2010-2016; 2017-2023).

Characteristics will be described using pre-specified comorbidities and medications, and by means of large-scale characterisation. Comorbidities will be measured for any time prior to 1 day before index date and 365 days prior to 1 day before index date. Concomitant medications will be assessed 365 days prior to 31 days before index and 30 days prior to 1 days before index date. Short-term complications will be assessed in the 30 days after index date and will include hepatic and renal toxicity. Mortality will also be assessed 0 to 30 days after index date and 31 to 365 days after index date.

Pre-specified conditions will include alcoholism, chronic kidney disease, chronic liver disease, depression, anxiety, schizophrenia, obesity, cancer, arthrosis and arthritis, pain, fever and infectious diseases. Pre-specified conditions will be assessed using the same windows as those applied for large-scale characterisation, with a few exceptions. Fever and infectious diseases will be assessed from 30 days prior to 1 day before the index date. For pain, this time window will also be applied in addition to those used for large-scale characterisation.

Pre-specified medications will include enzyme inducing medications (e.g. carbamazepine, isoniazid), and medications found in concomitant overdosing. This will include benzodiazepines, opioid analgesics, nonsteroid anti-inflammatory drugs, antipsychotics and antidepressants.(14) Prior paracetamol prescribing will also be of interest and will be reported 365 days prior to 31 days before index date, and 30 to 1 day before index date. The same assessment window will be applied for pre-specified medications.

A preliminary list of concept sets for pre-specified conditions and complications can be found in the **Appendix I**.

Table 8. Operational definitions of covariates.

Characteristic	Details	Type of variable	Assessment window [1]	Care Settings[2]	Code Type	Diagnosis Position[3]	Applied to study populations
Sex	Female, Male	Categorical	0	n/a	n/a	n/a	All
Age groups	Objective 1: 1-5; 6-11; 12-17; 18-29; 10-year bands. Objective 2 and 3: Narrow: 1-17; 18-49; 50-79; >80; Broad: 1-17; >18.	Categorical	0	n/a	n/a	n/a	All
Comorbidities	Large scale characterisation and pre-specified conditions[4]	Binary	[-Inf, -1], [-365,-1]	IP, OP, OT	SNOMED	Any	Individuals with paracetamol overdose
	Fever, infectious diseases and pain	Binary	[-30,-1]	IP, OP, OT	SNOMED	Any	Individuals with paracetamol overdose

Concomitant medications	Large scale characterisation and pre-specified medications[5]	Binary	[-365,-31], [-30,-1]	IP, OP, OT	RxNorm	Any	Individuals with paracetamol overdose
Short-term complications	Hepatic toxicity, renal toxicity and death	Binary	[0,30]	IP, OP, OT	SNOMED	Any	Individuals with paracetamol overdose
Mortality	Mortality	Binary	[0,30], [31,365]	IP, OP, OT	Date of death	n/a	Individuals with paracetamol overdose

[1] Inf= Any time prior
[2] IP = inpatient, OP = outpatient, OT = other, n/a = not applicable
[3] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)
[4] These include: alcoholism, chronic kidney disease, chronic liver disease, depression, anxiety, schizophrenia, obesity, cancer, arthrosis and arthritis, and pain.
[5] These include: carbamazepine, isoniazid, benzodiazepines, opioid analgesics, nonsteroid anti-inflammatory drugs, antipsychotics and antidepressants.

8.7 Study size

No sample size has been calculated for this study, given its descriptive nature. Our primary focus is to explore trends of paracetamol prescribing and paracetamol overdose and describe patients with paracetamol overdose.

8.8 Analysis

The type of analysis by study type is fixed as can be observed from **Table** .

Table 9. Description of study types and types of analysis.

Study type	Study classification	Type of analysis
Population Level DUS	Off-the-shelf	- Population-based incidence rates of the drug of interest - Population-based prevalence of use of the drug of interest
Population-level descriptive epidemiology	Off-the-shelf	- Population-based Incidence rates of the condition of interest
Patient-level characterisation	Off-the-shelf	- Large-scale characterisation - Patient-level characteristics

Population-level DUS on paracetamol prescribing (objective 1):

Annual incidence rates of paracetamol prescribing will be calculated as the number of new prescriptions per 100,000 person-years of the population at risk during the study period. Those study participants who experience the outcome during the study period will be able to re-enter the study and contribute time to the incidence calculations after a 60-day washout window following the end of treatment (see "8.4. Follow-up").

The period prevalence of paracetamol use will be calculated as the proportion of study participants who were prescribed a paracetamol-containing product on a yearly basis. There will be no restriction based on patients' observability within calendar years in the database (i.e., participants will be considered even if they were not present in the database for the entire year).

Analyses will be reported overall and stratified by age groups, sex and formulation (see "8.6.3 Other covariates").

Population level descriptive epidemiology study on paracetamol overdose (objective 2):

Annual incidence rates of paracetamol overdose will be calculated following the same approach as of Objective 1. Individuals will be able to re-enter the study following a 365-day washout after the occurrence of the outcome.

Analyses will be stratified by sex and age groups (see "8.6.3 Other covariates").

Patient level characterisation of patients with paracetamol overdose (objective 3):

Characteristics will be described by means of large-scale characterisation by database. Analyses will be reported overall and, if counts allow, stratified by study period (2010-2016; 2017-2023). Results by study period will be reported for databases with complete data across any of the study periods considered. As an example, for a database starting on 2015, we will report results overall and stratified by study period for 2017-2023 only. Results for 2010-2016 will be omitted to avoid misleading comparisons.

The presence of risk factors, prior paracetamol prescribing, short-term complications, and death will be reported as counts and percentages. To facilitate the reporting of the results, only the top 10 conditions and the top 10 of medications will be described in the report.

Sensitivity analysis (all objectives)

We will perform a sensitivity analysis removing the inclusion criteria of one year of prior database history (**Table 10**). This analysis is considered of interest given many databases included in the study are derived from hospital settings only and define observation periods using different approaches (e.g. first to last visit, start to end of the data availability). This will affect individuals whose index date falls within their first year of observation, which will be now included. For those patients, the lack of prior data might reduce the ability to identify prior health events, including prior history of the outcomes of interest and prior conditions and medications for characterisation. This will also impact databases whose data availability starts after the study start date (1st January 2010) and individuals aged <1 year. In both cases, data from the first year of the database/patient will be included. Results from individuals aged <1 year will be reported as an additional age category.

Table 10. Sensitivity analyses – rationale, strengths and limitations.

	What is being varied? How?	Why?	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
Prior database history (365 days)	Excluded from the sensitivity analysis.	The impact of this requirement on the included population.	- Do not exclude individuals with <365 days of prior observation.	- Less prior observation time to capture previous health events,

			- Include data from the first year of data availability.	including outcome occurrences and prior comorbidities or medication use.

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

8.9 Evidence synthesis

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

9. DATA MANAGEMENT

9.1 Data management

All databases are mapped to the OMOP CDM. 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 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 European Union (EU) member states will process personal data from individuals which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All databases used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to. In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate non-identifiable aggregate summary results.

The output files are stored in the DARWIN 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 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

Several 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, data partners are expected to 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

Concepts and phenotypes of interest will be developed and assessed using the following R packages: “CodelistGenerator”, "CohortDiagnostics”, and “DrugExposureDiagnostics”. The study code will be based on three R packages to (1) estimate incidence rates and period prevalence (“IncidencePrevalence”), and (2) characterise patients (“PatientProfiles” and “CohortCharacteristics”). These packages will include numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing.

11. LIMITATIONS OF THE RESEARCH METHODS

Database-specific limitations:

This study will be informed by 7 different data sources from 7 countries and will only reflect outcomes occurring in the healthcare settings covered by each database. Therefore, the capture of outcomes of interest, and conditions and medications for patient-level characterisation will likely differ between databases covering different health settings. It is also likely that some results will vary due to differences in how databases handle observation periods, which might vary across different database types and even within the same type. For InGef RDB, the assessment of conditions will be based on inpatient diagnoses only. For HI-SPEED, data on conditions recorded in primary care settings will be available for only 40% of the population. This is not expected to impact the capture of the condition of interest (i.e. paracetamol overdose), as most events are anticipated to be recorded in hospital settings.

Some of the databases included will not provide data for the entire study period (2010–2023) and will contribute fewer years of data based on the start of their data availability (InGef RDB: 2015; NLHR: 2018; HI-SPEED: 2015 with data on drug records starting on 2018). Note a year of observation history prior to index date will be required for all individuals included, which will reduce the study period by one year for databases starting later than 2010 for the main analysis.

Some artifact increases in incidence and prevalence (Objective 1 and 2) may be observed in the last years of available data, particularly in hospital databases where observation ends at the date of the last visit or encounter with the healthcare system, resulting in fewer people under observation in the final years.

Regarding the characterisation of patients with paracetamol overdose (Objective 3), several aspects related to the study period will need to be considered. First, the amount of data available before index date will likely affect the ability to capture prior health events, especially for conditions when assessed considering all prior data [-Inf, -1]. Second, for HI-SPEED, data on prior medication use will be incomplete for individuals diagnosed with paracetamol overdose before 2018 (data from 2015 onwards will be used for Objective 2 and 3). Third, results by study period (2010–2016 vs. 2017–2023) will be reported for strata with complete data across the time periods considered (e.g. if a database has data starting on 2015, we will report results overall and stratified by time period for 2017-2023 only).

Paracetamol prescribing:

The use of paracetamol will be derived from prescription data (or dispensation if not available). Such data might likely represent an underestimation of use, given the ease of access of paracetamol as an OTC medication. Stratification by formulation will depend on the granularity of drug records in the data and will

only be possible in cases where mappings have information on drug form (e.g. it will not be possible for drugs mapped at ingredient-level). The granularity and duration of drug records, as well as other pertinent information such as drug exposure duration, will be evaluated during the diagnostics stage.

Paracetamol overdose:

Based on the feasibility assessment, counts on paracetamol overdose are limited in some databases, and therefore, this event will only be assessed in 4 databases (APHM, DK-DHR, InGef RDB, HI-SPEED). The extent of capture of paracetamol overdose is dependent on sufficient granularity of event recording. Paracetamol overdoses recorded only as non-specific overdose will not be included.

Stratification by covariates of interest will depend on the number of cases captured and might not be possible across all databases and covariates. Similarly, complications of interest (e.g. hepatic and renal toxicity) are also rare in the selected databases, which might limit our ability to investigate the occurrence of these events following paracetamol overdose. APHM will only include data on deaths occurring in the hospital. Lastly, data on some covariates of interest (e.g. amount of paracetamol taken at overdose, overdose with modified-release formulations, delayed presentation to care) are not available and will not be described in the study. Glutathione depletion (described using codes for malnutrition or anorexia) and liver transplantation have limited counts in the selected databases and will not be able to be assessed in this study.

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

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

13. GOVERNANCE BOARD ASPECTS

APHM-Iatros, H12O, HI-SPEED and NLHR require approval from their respective IRB governance boards. DK-DHR has the umbrella approval for DARWIN EU ® studies. IPCI do not need an IRB approval for the routinely repeated studies. InGef database is anonymised and an IRB approval is therefore not required.

14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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.

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16. ANNEXES

Appendix I: List with preliminary concept definitions

Preliminary list – list to be reviewed once protocol approved and prior to parametrisation of study code.

Outcome:

Paracetamol overdose

Concept ID	Concept name
602949	Intentional acetaminophen and/or dextropropoxyphene poisoning
602950	Acetaminophen and/or dextropropoxyphene poisoning
607232	Accidental acetaminophen and/or dextropropoxyphene overdose
4322306	Poisoning caused by acetaminophen
607231	Acetaminophen and/or dextropropoxyphene overdose
4173525	Acetaminophen overdose
4166500	Accidental acetaminophen overdose
602948	Accidental acetaminophen and/or dextropropoxyphene poisoning
607233	Intentional acetaminophen and/or dextropropoxyphene overdose
4055123	Intentional paracetamol overdose
4159373	Accidental acetaminophen poisoning
4157354	Intentional paracetamol poisoning

Pre-specified conditions:

Concept ID[1]	Pre-specified comorbidity
4218106; 37017563	Alcoholism
4212540	Chronic liver disease
46271022	Chronic kidney disease
440383	Depression
442077	Anxiety
435783	Schizophrenia
4215968	Obesity
443392	Cancer
4167092	Arthritis/arthrosis
4329041	Pain
437663	Fever
432250	Infectious disease

[1] All descendants will be included.

Short-term complications:

Hepatic toxicity

Concept ID	Concept name
4026032	Acute hepatic failure
4184847	Acute hepatic failure due to drugs
4243475	Acute hepatitis
36676901	Acute infantile liver failure with multisystemic involvement syndrome
4169242	Acute toxic hepatitis
4139051	Allergic hepatitis
4318541	Cholestatic hepatitis
37396401	Decompensated cirrhosis of liver
4222609	Drug-induced cholestatic hepatitis
4342774	Drug-induced chronic hepatitis
4143008	Drug-induced cirrhosis of liver
4144765	Drug-induced disorder of liver
4231815	Drug-induced hepatic necrosis
4340942	Drug-induced hepatitis
45769564	End stage liver disease
1340280	Exacerbation of chronic active hepatitis
1340484	Exacerbation of toxic liver disease
4340389	Fulminant hepatic failure
4342883	Hepatic ascites
46273476	Hepatic ascites co-occurrent with chronic active hepatitis due to toxic liver disease
377604	Hepatic coma
46269814	Hepatic coma due to acute hepatic failure
46269949	Hepatic coma due to subacute liver failure
4029488	Hepatic encephalopathy
42710029	Hepatic encephalopathy in fulminant hepatic failure
4245975	Hepatic failure
4309163	Hepatic failure as a complication of care
196455	Hepatorenal syndrome
4308408	Hepatorenal syndrome as a complication of care
42536533	Hypersensitivity disease of liver caused by drug
4059281	Subacute hepatic failure
4342773	Subfulminant hepatic failure

4046016	Toxic cirrhosis
4055223	Toxic hepatitis
4055224	Toxic liver disease
4059297	Toxic liver disease with acute hepatitis
4058694	Toxic liver disease with cholestasis
4059299	Toxic liver disease with chronic active hepatitis
4055225	Toxic liver disease with chronic lobular hepatitis
4059298	Toxic liver disease with chronic persistent hepatitis
4058695	Toxic liver disease with fibrosis and cirrhosis of liver
4026136	Toxic liver disease with hepatic necrosis
4052963	Toxic noninfectious hepatitis
4059287	Toxic portal cirrhosis

Renal toxicity

Concept ID	Concept name
4030519	Acute drug-induced renal failure
4137752	Acute drug-induced tubulointerstitial nephritis
37116430	Acute kidney failure stage 1
37116431	Acute kidney failure stage 2
37116432	Acute kidney failure stage 3
37395516	Acute kidney injury due to acute tubular necrosis due to circulatory failure
37395521	Acute kidney injury due to acute tubular necrosis due to circulatory failure with
37395514	Acute kidney injury due to acute tubular necrosis due to hypovolaemia
37395519	Acute kidney injury due to acute tubular necrosis due to hypovolaemia with
37395518	Acute kidney injury due to acute tubular necrosis with histological evidence
36716182	Acute kidney injury due to circulatory failure
36716183	Acute kidney injury due to hypovolemia
44809061	Acute kidney injury stage 1
44809062	Acute kidney injury stage 2
44809063	Acute kidney injury stage 3
45757442	Acute nontraumatic kidney injury
197329	Acute renal failure due to acute cortical necrosis
4311129	Acute renal failure due to ischemia
45757466	Acute renal failure due to tubular necrosis
44809170	Acute renal failure induced by poison
45757398	Acute renal failure on dialysis

197320	Acute renal failure syndrome
4160274	Acute renal failure with oliguria
4126305	Acute renal impairment
36716946	Acute renal insufficiency
432961	Acute renal papillary necrosis with renal failure
4126120	Acute toxic nephropathy
444044	Acute tubular necrosis
606419	Acute tubular necrosis caused by toxin
606418	Acute tubular necrosis due to mixed ischemic and toxic causes
4128067	Acute-on-chronic renal failure
4244418	Analgesic nephropathy
37312165	Atypical hemolytic uremic syndrome
4128228	Chronic drug-induced renal disease
4128206	Chronic drug-induced tubulointerstitial nephritis
4126442	Chronic toxic interstitial nephritis
604484	Dependence on prolonged intermittent renal replacement therapy due to renal
4019967	Dependence on renal dialysis
4159967	Diarrhea-negative hemolytic uremic syndrome
36716200	Drug-induced membranous nephropathy
4043348	Drug-induced nephrogenic diabetes insipidus
4208918	Drug-induced tubulointerstitial nephritis
4030520	End stage renal failure on dialysis
4128200	End stage renal failure untreated by renal replacement therapy
4125970	End stage renal failure with renal transplant
193782	End-stage renal disease
197253	Hemolytic uremic syndrome
4267646	Hemolytic uremic syndrome of childhood
4302298	Hemolytic uremic syndrome, adult type
196455	Hepatorenal syndrome
4308408	Hepatorenal syndrome as a complication of care
4126432	Hyperkalemic renal tubular acidosis
193519	Impaired renal function disorder
42536547	Ischemia of kidney
600855	Nephritis caused by drug
4126424	Nephrotoxic acute renal failure

4048200	Nephrotoxic serum nephritis
45770903	Prerenal renal failure
4126427	Pulmonary renal syndrome
4153876	Renal failure as a complication of care
192359	Renal failure syndrome
42538752	Renal hypersensitivity caused by drug
4030518	Renal impairment
36716945	Renal insufficiency
36716169	Renal papillary necrosis caused by analgesic drug
37397038	Renal tubulopathy with encephalopathy and liver failure syndrome
4126119	Toxic nephropathy
4139414	Transient acute renal failure

Appendix II: ENCePP checklist for study protocols

Study title: DARWIN EU® – Paracetamol prescribing and paracetamol overdose in Europe: a descriptive analysis of trends and patient characteristics

EU PAS Register® number: EUPAS1000000584
Study reference number (if applicable): P4-C2-002

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, 8.2
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:	☒	☐	☐	
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)	☒	☐	☐	7, 8.5
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 generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☒	☐	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

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

Section 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?	☒	☐	☐	8.5
4.2	Is the planned study population defined in terms of:				8.3, 8.4, 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 categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5 Is exposure categorised 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?	☒	☐	☐	8.6.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.6.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

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

Comments:

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

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☐	☒	
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.2
9.1.3 Covariates and other characteristics?	☒	☐	☐	8.2
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☒	☐	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.6.2
9.3.3 Covariates and other characteristics?	☒	☐	☐	8.6.3
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	8.2

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

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
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?	☒	☐	☐	8.8

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
11.2 Are methods of quality assurance described?	☒	☐	☐	9
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:				
12.1.1 Selection bias?	☐	☒	☐	
12.1.2 Information bias?	☒	☐	☐	11
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, 11

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

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?	☒	☐	☐	

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: Berta Raventós

Date: 16/04/2025

Signature: BR