



Study Protocol

P3-C2-001

DARWIN EU® - Monitoring prescription of essential medicines administered in ICU

12/12/2025

Version 3.0

	P3-C2-001 Study Protocol	
	Author(s): G. van Leeuwen, K. Verhamme	Version: V3.0
		Dissemination level: Public

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Study title	DARWIN EU® - Monitoring prescription of essential medicines administered in ICU																																																					
Protocol version identifier	V3.0																																																					
Date	12/12/2025																																																					
EU PAS number	EUPAS1000000534																																																					
Active substance	The following medicines are of interest: <table><tr><th>Drug</th><th>Drug class</th><th>ATC code</th></tr><tr><td>Ketamine</td><td>Anesthetics</td><td>N01AX03</td></tr><tr><td>Propofol</td><td>Anesthetics</td><td>N01AX10</td></tr><tr><td>Heparin</td><td>Anticoagulants</td><td>B01AB01</td></tr><tr><td>Diazepam</td><td>Benzodiazepines</td><td>N05BA01</td></tr><tr><td>Lorazepam</td><td>Benzodiazepines</td><td>N05BA06</td></tr><tr><td>Midazolam</td><td>Benzodiazepines</td><td>N05CD08</td></tr><tr><td>Dexamethasone</td><td>Corticosteroids</td><td>H02AB02</td></tr><tr><td>Prednisolone</td><td>Corticosteroids</td><td>H02AB06</td></tr><tr><td>Cisatracurium</td><td>Neuromuscular Blockers</td><td>M03AC11</td></tr><tr><td>Rocuronium</td><td>Neuromuscular Blockers</td><td>M03AC09</td></tr><tr><td>Fentanyl</td><td>Opioids</td><td>N01AH01</td></tr><tr><td>Remifentanil</td><td>Opioids</td><td>N01AH06</td></tr><tr><td>Esketamine</td><td>Anesthetics</td><td>N01AX14</td></tr><tr><td>Sufentanil</td><td>Opioids</td><td>N01AH03</td></tr><tr><td>Suxametonium (Succinylcholine)</td><td>Neuromuscular Blockers</td><td>M03AB01</td></tr><tr><td>Atracurium</td><td>Neuromuscular Blockers</td><td>M03AC04</td></tr></table>			Drug	Drug class	ATC code	Ketamine	Anesthetics	N01AX03	Propofol	Anesthetics	N01AX10	Heparin	Anticoagulants	B01AB01	Diazepam	Benzodiazepines	N05BA01	Lorazepam	Benzodiazepines	N05BA06	Midazolam	Benzodiazepines	N05CD08	Dexamethasone	Corticosteroids	H02AB02	Prednisolone	Corticosteroids	H02AB06	Cisatracurium	Neuromuscular Blockers	M03AC11	Rocuronium	Neuromuscular Blockers	M03AC09	Fentanyl	Opioids	N01AH01	Remifentanil	Opioids	N01AH06	Esketamine	Anesthetics	N01AX14	Sufentanil	Opioids	N01AH03	Suxametonium (Succinylcholine)	Neuromuscular Blockers	M03AB01	Atracurium	Neuromuscular Blockers	M03AC04
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Countries of study	France: CDW Bordeaux, Greece: PGH, Hungary: SUCD, Spain: IMASIS
Author(s)	G. van Leeuwen (g.vanleeuwen@darwin-eu.org) K. Verhamme (k.verhamme@darwin-eu.org)

This is a routine repeated study from [P3-C1-014 with EUPAS1000000089](#)

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LIST OF ABBREVIATIONS

Acronyms/term	Description
CC	Coordination Centre
CDM	Common Data Model
CDW Bordeaux	Clinical Data Warehouse of Bordeaux University Hospital
DARWIN EU®	Data Analysis and Real World Interrogation Network
DRE	Digital Research Environment
DQD	Data Quality Dashboard
DOI	Declaration of Interests
DUS	Drug Utilisation Study
EEA	European Economic Area
EHR	Electronic Health Records
EMA	European Medicines Agency
EU	European Union
GDPR	General Data Protection Regulation
ICD	International Classification of Diseases
ICU	Intensive Care Unit
ID	Index date
IMASIS	Institut Municipal Assistència Sanitària Information System
IP	Inpatient
NAJS	Croatian National Public Health Information System
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
PGH	Papageorgiou General Hospital
PHE	Public health emergencies
SD	Standard deviation
SNOMED	Systematized Nomenclature of Medicine
SUCD	Semmelweis University Clinical Data
ULSM-RT	Unidade Local de Saúde de Matosinhos Realtime Database
WHO	World Health Organisation

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1. TITLE

DARWIN EU® - Monitoring prescription of essential medicines administered in ICU

2. RESPONSIBLE PARTIES – STUDY TEAM

Study team role	Names	Organisation
Principal Investigator	Guido van Leeuwen Katia Verhamme	Erasmus MC
Data Scientist	César Barboza Maarten van Kessel Ger Inberg	Erasmus MC
Epidemiologist/ Clinical Domain Expert	Guido van Leeuwen Katia Verhamme	Erasmus MC
Study Manager	Natasha Yefimenko	Erasmus MC
Data Partner*	Names	Organisation
CDW Bordeaux	Guillaume Verdy Romain Griffier	Chu de Bordeaux
IMASIS	Juan Manuel Ramírez-Anguita Angela Leis Miguel-Angel Mayer	Consorti Mar Parc de Salut Barcelona
PGH	Pantelis Natsiavas Alexandros Rekkas Anastasia Farmaki Achilles Chytas	Papageorgiou General Hospital
SUCD	Bagyura Zsolt István Mészáros Ágota	Semmelweis University

*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 scientists do not have an investigator role and thus declaration of interests (DOI) for them is not needed.

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3. ABSTRACT

Title

DARWIN EU® – Monitoring prescription of essential medicines administered in ICU - a routine repeated study

Rationale and background

The European Medicines Agency (EMA) recently expanded its mandate to include crisis preparedness and management of medicinal products and medical devices, particularly focusing on monitoring and reporting shortages during public health emergencies (PHE). This extended responsibility encompasses coordinating responses to shortages of critical medical devices and in-vitro diagnostics across European Union (EU) and European Economic Area (EEA) countries. Recognising the importance of robust scientific and commercial data, there is a growing emphasis on analysing prescriptions of critical medicines in hospital settings, particularly Intensive Care Units (ICUs), to provide valuable insights into usage patterns. This systematic analysis enhances EMA's ability to proactively monitor and respond quicker to potential public health emergencies, ensuring continued access to essential healthcare resources during crises.

This is a routine repeated study of a population- and patient-level drug utilisation study previously performed within DARWIN EU® ([EUPAS1000000089](#)) to report the annual prescription rate of selected medicines of importance for public health emergencies, specifically used in ICU.

Research question and objectives

1. To estimate the annual proportion of prescribing of selected medicines in a cohort of patients being hospitalised, stratified by ICU admission (yes/no).
2. To characterise the two cohorts of hospitalised patients (ICU admission (yes/no) who initiated treatment with drug of interest in terms of demographics, presence of COVID-19 infection (yes/no), and use of mechanical ventilation (yes/no) at time of first prescribing of drug of interest.
3. To determine the duration of treatment in the cohort of hospitalised patients being treated with drug of interest, stratified by ICU admission (yes/no) and mechanical ventilation (yes/no).
4. To determine the consumption of the specified drugs at hospital level: median cumulative dose and median number of prescriptions per patient, cumulative median dose, and cumulative number of prescriptions per hospital. Dose is stratified by route (all/parenteral/non-parenteral/unknown).

Methods

Study design

- Population-level cohort study (Objective 1). Population-level drug utilisation study of selected medicines of importance for public health emergencies, specifically used in hospital/ICU.
- New drug user cohort (Objectives 2, 3 and 4), Patient-level drug utilisation study regarding characterisation, dose and duration of treatment).

Population

Population-level drug utilisation: Population-level drug utilisation study will include all patients being hospitalised in the respective databases in the period between 1st of January 2015 and 31st of December 2024 (or the latest date of data availability of respective database, whatever comes first). The population will be further stratified based on ICU admission status (yes/no).

Patient-level drug utilisation: Patient-level drug utilisation study will include hospitalised patients (ICU admission (yes/no)) who are initiating treatment with selected prespecified medication, in the period

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between 1st of January 2015 and 31st of December 2024 (or the latest date of data availability of respective database, whatever comes first).

Variables

Drugs of interest:

- Propofol
- Rocuronium
- Heparin
- Fentanyl
- Dexamethasone
- Prednisone
- Ketamine
- Cisatracurium
- Remifentanyl
- Diazepam
- Midazolam
- Lorazepam
- Esketamine
- Sufentanyl
- Suxametonium (Succinylcholine)
- Atracurium

Data source

1. Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux), France
2. Institut Municipal Assistencia Sanitaria Information System (IMASIS), Spain
3. Papageorgiou General Hospital (PGH), Greece
4. Semmelweis University Clinical Data (SUCD), Hungary

Statistical analysis

Population-level drug utilisation: The proportion of patients who are prescribed pre-specified selected medicines of importance for public health emergencies will be estimated in a cohort of patients being hospitalised, stratified by ICU admission (yes/no) (Objective 1). For patients admitted to ICU, the prescription of pre-selected medications will be examined during the ICU admission period. The statistical analyses will be performed based on OMOP-CDM mapped data using “PatientProfiles” R package and stratified by calendar year and country/database.

Patient-level drug utilisation: Characterisation will be conducted in two cohorts of hospitalised patients (ICU admission (yes/no)) who initiated treatment with drug of interest. This characterisation will include describing demographic characteristics (age, sex), determining whether patients have COVID-19 infection (yes/no), and whether they are receiving mechanical ventilation (yes/no) (Objective 2). These characteristics will be reported as counts and proportions. The statistical analyses will be performed based on OMOP-CDM mapped data using “PatientProfiles” R package stratified by calendar year and country/database.

For objective 3 and 4, duration (objective 3) and dose per patient and per hospital and number of prescriptions (objective 4) of prescribed pre-specified selected medicines of importance for public health emergencies will be summarised with the median cumulative value of the dose of each drug episode of drug of interest in a cohort of hospitalised patients. The duration of treatment will be estimated using

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descriptive statistics for the first treatment episode for each of the respective medicines of interest in the cohort of hospitalised patients and stratified by admission to ICU and mechanical ventilation. The statistical analyses will be performed based on OMOP-CDM mapped data using the "PatientProfiles" and "DrugUtilization" R packages.

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4. AMENDMENTS AND UPDATES

This is a routine repeated study of a population- and patient-level drug utilisation study previously performed within DARWIN EU® ([EUPAS1000000089](#)) into the annual rate of prescription of selected medicines of importance for public health emergencies, specifically used in ICU.

Amendments to the approved study protocol 17-11-2025:

Amendment number	Previous approved version of the report	Date	Section of the study	Amendment or update	Reason
1	Not applicable	17-11-2025	Objectives	Change of median cumulative dose on hospital level to cumulative median dose	More appropriate wording.
2	Not applicable	17-11-2025	Data partners	FinOMOP-HUS excluded from study	Had data access and governance board issues during study and did not execute any cohort diagnostics or study code. Therefore, not feasible to be included in time for report.
3	Not applicable	17-11-2025	Data partners	ULSM-RT excluded from study	Had data access issues during study and could not provide results for cohort diagnostics or study code. Despite much debugging, the issues could not be solved in time for the report.
4	Not applicable	17-11-2025	Analysis	Better description of analysis per objective	More clarity was needed to specify the analysis and stratification per objective.

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5. MILESTONES

Study milestones and deliverables	Planned dates
Draft Study Protocol	7 th March 2025
Final Study Protocol	31 st March 2025
Creation of Analytical code	18 th April 2025
Execution of Analytical Code on the data	2 nd May 2025
Draft Study Report	16 th May 2025
Final Study Report	26 th November 2025

6. RATIONALE AND BACKGROUND

The European Medicines Agency's (EMA) expanded mandate, effective from March 1, 2022, emphasises its role in crisis preparedness and the management of medicinal products and medical devices.(1, 2) Under this extended mandate, EMA now holds responsibility for monitoring and reporting shortages of critical medicine during public health emergencies (PHE). Such shortages have the potential to hinder the fulfilment of treatment requirements for both individual patients and entire populations.(1, 2) Furthermore, the Agency has also mandate to coordinate responses from European Union (EU) and European Economic Area (EEA) countries to shortages of critical medical devices and in-vitro diagnostics during crisis situations.(1, 2)

To enhance EMA's capacity for effective monitoring and response coordination, there is a recognised need for robust scientific and commercial data. Specifically, prescriptions of medicines deemed critical in hospital and more specifically Intensive Care Unit (ICU) settings can offer valuable insights into trends and seasonal variations and shortages in this area have a high public health impact. The systematic analysis of such data contributes substantively to the ongoing efforts of EMA, enabling a more comprehensive understanding of medicine usage patterns in critical care settings. This, in turn, facilitates EMA's ability to proactively monitor, assess, and coordinate responses to potential shortages of critical medicines, aligning with the overarching goal of ensuring continued and uninterrupted access to essential healthcare resources during crises.

7. RESEARCH QUESTION AND OBJECTIVES

1. To estimate the annual proportion of prescribing of selected medicines in a cohort of patients being hospitalised, stratified by ICU admission (yes/no).
2. To characterise the two cohorts of hospitalised patients (ICU admission (yes/no) who initiated treatment with drug of interest in terms of demographics, presence of COVID-19 infection (yes/no), and use of mechanical ventilation (yes/no) at time of first prescribing of drug of interest.
3. To determine the duration of treatment of selected medications in the cohort of hospitalised patients being treated with drug of interest, stratified by ICU admission (yes/no) and mechanical ventilation (yes/no).

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4. To determine the consumption of the specified drugs at hospital level: median cumulative dose and median number of prescriptions per patient, cumulative median dose, and cumulative number of prescriptions per hospital. Dose is stratified by route (all/parenteral/non-parenteral/unknown).

Description of the proposed objectives to be achieved in the study is displayed in [Table 1](#).

Table 1. Primary and secondary research questions and objective.

A. Primary research question and objective.

Objective:	To estimate the annual proportion of prescribing of selected medicines in a cohort of patients being hospitalised, stratified by ICU admission (yes/no) (Objective 1).
Hypothesis:	N/A
Population (<i>mention key inclusion-exclusion criteria</i>):	All patients hospitalised in the respective databases between 1 st of January 2015 and 31 st of December 2024 (or the latest date of data availability of respective database, whatever comes first). The population will be stratified into two cohorts based on ICU admission status (yes/no): those admitted to ICU (ICU cohort) and those hospitalised without ICU admission during their respective hospital stay (Non-ICU cohort).
Exposure:	Selected medicines: • Propofol • Rocuronium • Heparin • Fentanyl • Dexamethasone • Prednisolone • Ketamine • Cisatracurium • Remifentanyl • Diazepam • Midazolam • Lorazepam • Esketamine • Sufentanil • Suxametonium

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	Atracurium
Comparator:	None
Outcome:	None
Time (when follow up begins and ends):	Follow-up will start on the date of admission to ICU (ICU cohort) or the hospital (Non-ICU cohort). End of follow-up is defined as the earliest of discharge from ICU or hospital, death during admission, end of data availability in each of data sources or end of study period (31 st December 2024).
Setting:	Inpatient setting using data from the following 6 data sources: CDW Bordeaux (France), IMASIS (Spain), PGH (Greece), SUCD (Hungary)
Main measure of effect:	Proportion summarising the total number of ICU prescriptions of pre-selected medications over total number of ICU admissions. Proportion summarising the total number of prescriptions of pre-selected medications during hospitalisation over total number of records of hospitalised patients without ICU admission.

B. Secondary research questions and objectives.

Objective:	To characterise the two cohort of hospitalised patients (ICU admission yes/no) who initiate treatment with drug of interest in terms of demographics, presence of COVID-19 infection and use of mechanical ventilation (Objective 2). To determine the duration of treatment with selected medications in the overall cohort of hospitalised patients being treated with drug of interest as well as in groups stratified by admission to ICU and mechanical ventilation (Objective 3). To determine the consumption of the specified drugs at hospital level: median cumulative dose and median number of prescriptions per patient, cumulative median dose, and cumulative number of prescriptions per hospital. Dose is stratified by route (all/parenteral/non-parenteral/unknown) (Objective 4).
Hypothesis:	N/A
Population (mention key inclusion-exclusion criteria):	Hospitalised patients who are initiating treatment with selected prespecified medication, stratified by ICU admission (yes/no) at time of treatment initiation, in the period between 1 st of January 2015 and 31 st of December 2024 (or the latest date of data availability of respective database, whatever comes first).
Exposure:	Selected medicines:

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	• Propofol • Rocuronium • Heparin • Fentanyl • Dexamethasone • Prednisolone • Ketamine • Cisatracurium • Remifentanyl • Diazepam • Midazolam • Lorazepam • Esketamine • Sufentanil • Suxametonium (succinylcholine) • Atracurium
Comparator:	None
Outcome:	None
Time (<i>when follow up begins and ends</i>):	Follow-up will start on the date of first prescription of medication of interest in hospitalised patients (ICU admission yes/no) (index date). End of follow-up will be defined as the earliest of discharge from hospital/ICU, death during admission, end of data availability or end of study period (31 st December 2024). For stratified cohort of patients admitted to ICU, end of follow up will be defined as discharge from ICU, death during ICU admission, end of data availability in each of data sources or end of study period (31 st December 2024) whichever comes first.
Setting:	Inpatient setting using data from the following 6 data sources: CDW Bordeaux (France), IMASIS (Spain), PGH (Greece), SUCD (Hungary)
Main measure of effect:	Characteristics of interest (demographics, presence of COVID-19 infection and use of mechanical ventilation) expressed as counts and proportions, stratified by ICU admission (yes/no).

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	Duration of treatment with pre-specified medication of interest expressed as minimum, quartiles and maximum values, stratified by ICU admission (yes/no) and mechanical ventilation. Median cumulative dose (by patient) and cumulative median dose (by hospital) of pre-specified medication of interest expressed as median and interquartile range in mg/day or mg/month, stratified by administration route (all/parenteral/non-parenteral/other (unknown)) Cumulative and median number of prescriptions per patient and per hospital.
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8. RESEARCH METHODS

8.1 Study type and study design

The Study Types with related Study Designs are described in the [Error! Not a valid bookmark self-reference.](#) below and are selected from the DARWIN EU Catalogue of Data analytics.

A cohort study will be conducted, with a population based cohort to address objective 1 and a new drug user cohort to address objective 2 and 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
Patient Level DUS	New drug/s user cohort	Off the shelf

8.2 Study setting and data sources

This study will be conducted using routinely collected data from 4 databases in 4 EU countries. All databases were previously mapped to the OMOP Common Data Model (CDM).

1. Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux), France
2. Institut Municipal Assistencia Sanitaria Information System (IMASIS), Spain
3. Papageorgiou General Hospital (PGH), Greece
4. Semmelweis University Clinical Data (SUCD), Hungary

For this study, 4 databases in the DARWIN EU® Database Catalogue were considered fit for purpose. The selection process was based on the size of the databases, the setting covered (hospital and have at least partial information regarding the ICU admission which is highly relevant for this study), the number of individuals prescribed/administered medication of interest, as well as the geographical spread.

Based on the feasibility assessment performed, the suggested databases have enough data on medicines of interest.

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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 3**.

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 utilise the Achilles tool (<https://github.com/ohdsi/achilles>), which systematically characterises the data and presents it in a dashboard format that is inspected (<https://github.com/darwin-eu/DashboardExport>). 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 tools, *CohortDiagnostics* (<https://github.com/darwin-eu-dev/CohortDiagnostics>) and *DrugExposureDiagnostics* (<https://darwin-eu.github.io/DrugExposureDiagnostics/>) were developed. *CohortDiagnostics* 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. *DrugExposureDiagnostics* package assesses ingredient specific diagnostics for drug exposure records. 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* (<https://github.com/darwin-eu/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.

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Table 3. Description of the selected data sources and justification for inclusion.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Data lock for the last update
France	CDW Bordeaux	Database covers inpatient hospital care setting where selected pre-specified medicines of interest are prescribed/administered*. ICU admission also present in the data.	Inpatient (Hospital) Care	EHR	2.3m	22-02-2024
Spain	IMASIS	Database covers inpatient hospital care setting where selected pre-specified medicines of interest are prescribed/administered*. ICU admission also present in the data.	Inpatient (Hospital) Care	EHR	1.8m	13-07-2024
Greece	PGH	Database covers inpatient hospital care setting where selected pre-specified medicines of interest are prescribed/administered*.	Inpatient (Hospital) Care	EHR, claims	1.4m	18-03-2024
Hungary	SUCD	Database covers inpatient hospital care setting where selected pre-specified medicines of interest are prescribed/administered*.	Inpatient (Hospital) Care	EHR, claims, registry	1.9m	30-11-2024

*Referring to medication actions as administration in the inpatient setting accurately reflects the process of delivering prescribed medications to patients under direct supervision.

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[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).(3)

The data from the hospital production information system are loaded daily into a CDW in i2b2 format. A specific ETL from i2b2 to OMOP has been set up to standardise the data in OMOP-CDM format. Currently, this ETL from i2b2 to OMOP is launched manually when needed (this ETL can be scheduled regularly if necessary). The data is integrated in the OMOP Common Data Model version 5.3.1 and is stored in Oracle version 19c.

[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 anonymised relational database of IMASIS which is used for mapping to OMOP including additional sources of information such as the Tumours Registry.

[Papageorgiou General Hospital \(PGH\), Greece](#)

PGH, situated in Thessaloniki—the second-largest city in Greece—began operations in 1999. By 2004, it had formed a partnership with Aristotle University of Thessaloniki's School of Medicine, hosting its Teaching Clinics. The hospital boasts 30 clinics, including 2 Internal Medicine clinics, 2 Surgery clinics, 10 collaborative departments, and 8 laboratory centers. With a capacity of 745 beds, PGH employs 1.939 staff members and supports over 200,000 hospitalisation days annually, conducts 20,000 surgeries, and manages approximately 1,000 daily visits to outpatient departments. The eHealth Lab at the Institute of Applied Biosciences, part of the Centre for Research and Technology Hellas (INAB|CERTH), focuses on developing software for medical informatics applications. INAB|CERTH, certified by EHDEN for its proficiency in Extract-Transform-Load (ETL) operations for OMOP-CDM, serves as a subcontractor managing PGH's OMOP-CDM instance on its behalf. PGH's information system integrates multiple databases—including Electronic Healthcare Records and Laboratory Information Systems—and aligns with international medical vocabularies and standards. It also encompasses an imaging system (PACS) to handle the extensive daily diagnostic imaging. Furthermore, PGH utilises specialised software for logistical management, blood transfusion services, and more. The hospital's significant daily patient influx results in the production of a vast and diverse array of medical data.

[Semmelweis University Clinical Data \(SUCD\), Hungary](#)

Semmelweis University is the largest provider of health care services in Hungary. Most of the departments cater for the most serious cases and patients requiring complex treatment, thus making the university a

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

8.3 Study period

The study period is from 1st of January 2015 until 31st of December 2024 or the latest date of data availability of respective database, whatever comes first ([Table 3](#)).

8.4 Follow-up

Participants will be followed up from the date of admission to the hospital until the earliest of the following: discharge from hospital, death during admission, end of data availability in each of data sources or end of study period (31st December 2024). For stratified cohort of patients admitted to ICU, end of follow up will be defined as discharge from ICU, death during ICU admission, end of data availability in each of data sources or end of study period (31st December 2024) whichever comes first.

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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)	Number of entries	Type of entry	Washout window	Care Setting ¹	Code Type ²	Diagnosis position	Incident with respect to...	Measurement characteristics/ validation	Source of algorithm
All hospitalised patients in the database during the study period	Date of admission to ICU or hospital during the study period	Multiple	Prevalent	None	IP	n/a	n/a	n/a	n/a	n/a
Hospitalised patients initiating treatment with the selected pre-specified medicines - characterisation	Date of treatment initiation medication of interest	Multiple	Incident	None	IP	RxNorm	n/a	Use of medication of interest	n/a	n/a

¹ IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable

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8.5 Study population with inclusion and exclusion criteria

For population level drug utilisation (Objective 1), study population will include all patients being hospitalised in the respective database, in the study period. The population will be stratified based on ICU admission status (yes/no): those admitted to ICU (ICU cohort) and those hospitalised without ICU admission during their respective hospitalisation (Non-ICU cohort) (**Figure 1**).

For patient-level drug utilisation (Objective 2 and 3), the study population will include all hospitalised patients who were initiating treatment with selected pre-specified medicines in the study period. These patients will be categorised by ICU admission (yes/no) at the time of treatment initiation. This will result in two cohorts: patients who initiate treatment during ICU visit (ICU cohort) and patients who begin treatment during hospital stay outside of ICU, regardless of any prior or subsequent ICU admission during respective hospitalisation (Non-ICU cohort) (**Figure 2**).

The operational definitions of the inclusion criteria are presented in **Table 5**.

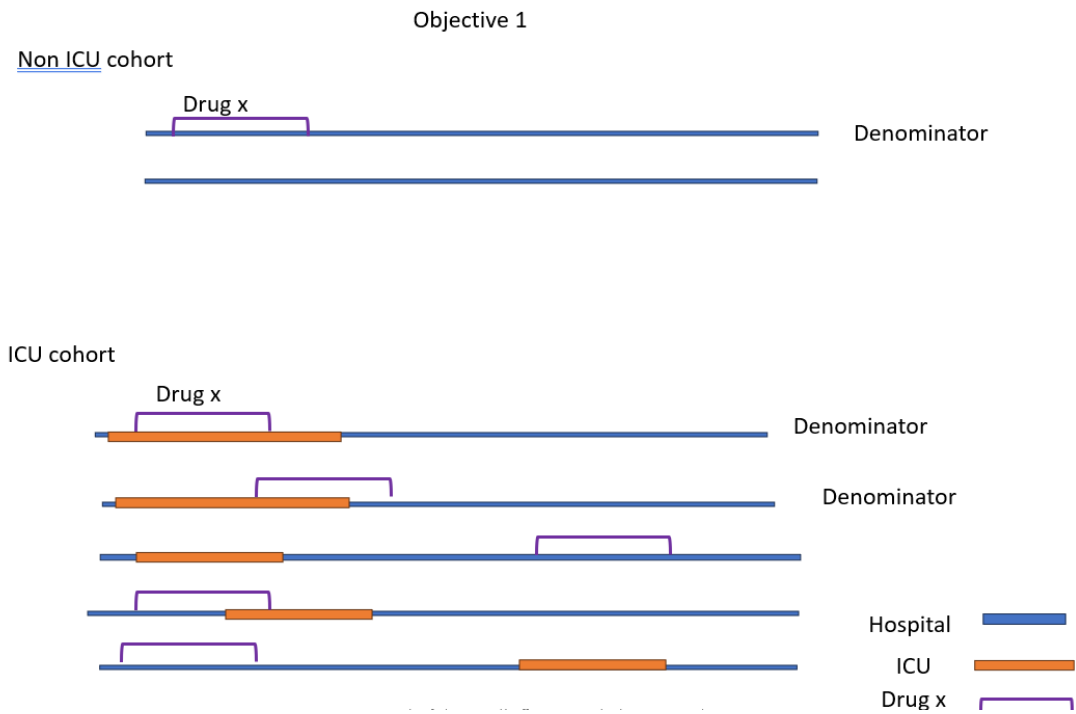


Figure 1. Visualisation of ICU and Non-ICU cohorts for Objective 1.

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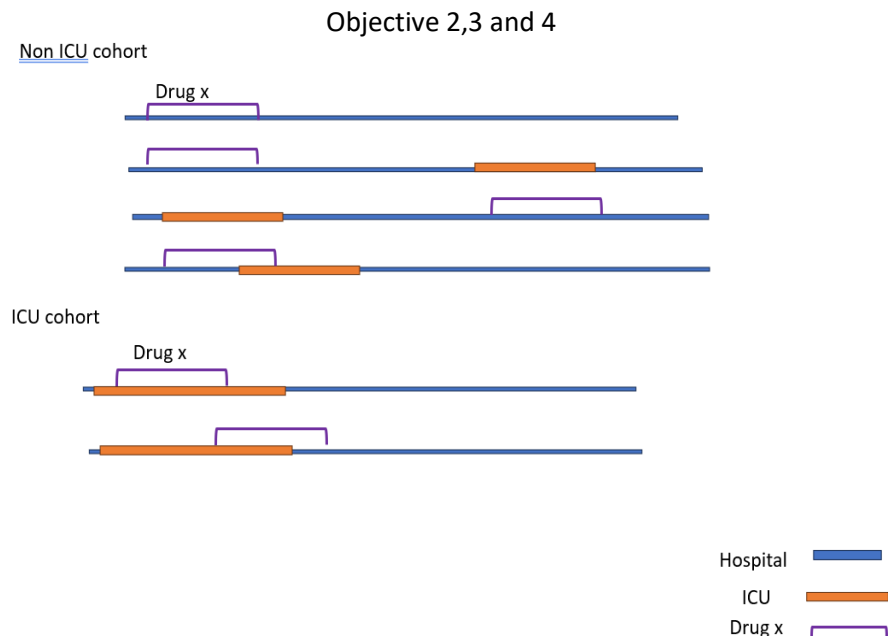


Figure 2. Visualisation of ICU and Non-ICU cohorts for Objective 2,3 and 4.

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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:	Measurement characteristics/validation	Source for algorithm
Observation period in the database during the study period	Patient present in the respective database from 2015 to 2024	n/a	n/a	IP	n/a	n/a	All hospitalised patients in the database	n/a	n/a
Incident drug use (Objective 2-4)	New user of prespecified drugs during hospitalisation (both ICU and Non-ICU)	n/a	n/a	IP	n/a	n/a	All hospitalised patients in the database	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)

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8.6 Variables

8.6.1 Exposure/s

For this study, the exposure of interest is use (during the study period) of pre-specified medications. The list of medications of interest is described in [Table 7](#), and a preliminary list of concepts is presented in [Appendix I](#).

Table 6. Exposure of interest.

Drug	Drug class	ATC code
Ketamine	Anaesthetics	N01AX03
Propofol	Anaesthetics	N01AX10
Heparin	Anticoagulants	B01AB01
Diazepam	Benzodiazepines	N05BA01
Lorazepam	Benzodiazepines	N05BA06
Midazolam	Benzodiazepines	N05CD08
Dexamethasone	Corticosteroids	H02AB02
Prednisolone	Corticosteroids	H02AB06
Cisatracurium	Neuromuscular Blockers	M03AC11
Rocuronium	Neuromuscular Blockers	M03AC09
Fentanyl	Opioids	N01AH01
Remifentanyl	Opioids	N01AH06
Esketamine	Anaesthetics	N01AX14
Sufentanil	Opioids	N01AH03
Suxametonium (Succinylcholine)	Neuromuscular Blockers	M03AB01
Atracurium	Neuromuscular Blockers	M03AC04

The operational definitions of exposure are described [Table 7](#).

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Table 7. Operational definitions of exposure.

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting ¹	Code Type	Applied to study populations
Selected pre-specified medication of importance for public health emergencies	Preliminary code list provided in Table 6 and Appendix I	none	Calendar year	IP including ICU	RxNorm	All hospitalised patients

¹ IP = inpatient, , n/a = not applicable

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8.6.2 Outcome/s

None.

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

Covariates for stratification in population-level drug utilisation study (objective 1):

- Calendar year
- ICU admission (yes/no):
 - ICU admission (yes) meaning that patient was admitted to the ICU during hospitalisation (ICU cohort).
 - ICU admission (no) meaning that patients was not admitted to the ICU during hospitalisation (Non-ICU cohort).

The evaluation of prescribing practices for pre-specified selected medicines of interest will be conducted as follows:

- For patients admitted to the ICU: From the start of ICU admission to discharge from the ICU.
- For patients not admitted to the ICU: From hospital admission to discharge from the hospital.

Other variables in patient-level drug utilisation study:

Operational definition of other variables in patient-level drug utilisation study is described in [Table 8](#).

Covariates for stratification and other variables in patient-level drug utilisation study (objective 2, 3, and 4):

Covariate for stratification (objective 2, 3, and 4):

- ICU admission (yes/no) at time of treatment initiation (index date):
 - ICU admission (yes) indicates treatment initiation during ICU (ICU cohort).
 - ICU admission (no) indicates treatment initiation during hospitalisation but outside of ICU, regardless of any prior or subsequent ICU admission during respective hospitalisation (Non-ICU cohort).

Characterisation of hospitalised patients at the time of treatment initiation of selected medicines stratified by ICU admission (yes/no) was done in terms of:

- Sex (female/male/unknown) (Objective 2)
- Age (Median (IQR) and range) (Objective 2)
- COVID-19 infection (yes/no) (Objective 2), defined as either positive test results for SARS-CoV-2 or a clinical diagnosis of COVID-19 infection (both as defined below) 14 days before or at the moment of prescription/administration.

Positive test result for SARS-CoV-2: typically detected using RT-PCR tests, known for their high sensitivity and specificity. Due to variations in the availability of population-wide RT-PCR and self-reported lateral flow tests, relying solely on RT-PCR may not always be feasible across all data sources. Therefore, all positive test results for SARS-CoV-2 observed in the data source were included for analysis.

Clinical diagnosis of COVID-19: diagnostic codes indicative of COVID-19 were identified with the recorded date being used in the analyses.

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- COVID-19 infection (yes) and mechanical ventilation (yes) (objective 2): defined as either positive test results for SARS-CoV-2 or a clinical diagnosis of COVID-19 infection and use of mechanical ventilation or tracheostomy.
- Mechanical ventilation (yes/no) (Objective 2 and 3): defined as use of mechanical ventilation or tracheostomy 7 days before or at the moment of prescription. Narrow and broad definitions w be used.

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Table 8. Operational definitions of covariates.

Characteristic	Details	Type of variable	Assessment window	Care Settings ¹	Code Type	Applied to study populations	Measurement characteristics/ validation	Source for algorithm
COVID-19 infection	Defined as either positive test results for SARS-CoV-2 or a clinical diagnosis of COVID-19 infection	Counts	At index date (ID) and 14 days before ID	IP	SNOMED	Hospitalised patients at the time of treatment initiation	n/a	n/a
Mechanical ventilation (narrow)	Mechanical ventilation or tracheostomy	Counts	At index date (ID) and 7 days before ID	IP	SNOMED	Hospitalised patients at the time of treatment initiation	n/a	n/a
Mechanical ventilation (broad)	Narrow definition and/or proxy defined by continuous use of more than 1 day of anaesthetics (Propofol) used for sedation during ventilation or tracheostomy.	Counts	At index date (ID) and 7 days before ID	IP	SNOMED	Hospitalised patients at the time of treatment initiation	n/a	n/a
Setting for objective 1	ICU admission	Counts	During hospitalisation	IP	SNOMED	Hospitalised patients	n/a	n/a
Setting for objective 2 and 3	ICU admission	Counts	At the time of treatment initiation	IP	SNOMED	Hospitalised patients at the time of treatment initiation	n/a	n/a

¹ IP = inpatient, , n/a = not applicable

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8.7 Study size

No sample size has been calculated for this drug utilisation descriptive study, as our primary focus is to examine drug utilisation of selected medicines of importance for public health emergencies in the hospital setting, irrespective of the sample size. Based on a preliminary feasibility assessment, the expected number of person counts for a selection of the pre-specified list of medications in the hospital databases included in this study for example propofol ranged from no counts in SUCD to 87,800 (IMASIS) for heparin from 300 (SUCD) to 45,900 (CDW Bordeaux), fentanyl ranged from no counts in PGH to 124,300 (InGef RDB) and ketamine ranged from no counts in PGH, SUCD to 9800 (CDW Bordeaux).

8.8 Analysis

This section describes the details of the analysis approach and rationale for the choice of analysis, with reference to the DARWIN EU® Catalogue of Data Analysis which describes the type of analysis in function of the study type. [Error! Not a valid bookmark self-reference. 9.](#)

Table 8. Description of study types and type of analysis.

Study type	Study classification	Type of analysis
Population Level DUS	Off-the-shelf	- Proportion of pre-specified selected medicines in a cohort of patients being hospitalised, stratified by ICU admission (yes/no) - Median and interquartile range of cumulative dose and cumulative number prescriptions of the specified drugs at hospital level in mg/day or mg/month.
Patient Level DUS	Off-the-shelf	- Characterisation of pre-specified patient-level features - Estimation of minimum, p25, median, p75, and maximum treatment duration - Median and interquartile range of cumulative dose and cumulative number of prescriptions of the specified drugs at patient level in mg/day or mg/month.

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 and the Study Dissemination Phase can start. All results are locked and timestamped for reproducibility and transparency.

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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 Main statistical methods

R-packages

We will use the R package "PatientProfiles" for the population-level estimation of drug utilisation and "PatientProfiles" and "DrugUtilization" for the patient-level drug utilisation analyses.

Drug exposure calculations

Drug eras will be defined as follows: Exposure starts at date of the first prescription, e.g., the index date the person entered the cohort of drug exposure. For each prescription, the estimated duration of use is retrieved from the drug exposure table in the CDM, using the 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 3**, first row.

<i>Gap era joint mode</i>	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	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$

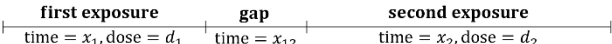


Figure 3. Gap era joint mode

New user cohort

New users will be selected based on their first prescription of selected pre-specified medicines of interest during hospitalisation/ICU within the study period.

8.8.4 Methods to derive parameters of interest

Calendar time

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

ICU setting

See section 8.6.3 for details.

Prescription rate

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The annual rate of prescription of the selected pre-specified medicines of importance for public health emergencies will be calculated separately for each selected pre-specified medication, stratified by ICU admission (yes/no).

To calculate the annual prescription rate, the total number of prescriptions for the selected pre-specified medicines during a given year will be divided by the total number of records within that year in each data source, throughout the specified time period, taking into account ICU admission status. Therefore, for patients admitted to ICU, the annual rate of prescription will be calculated as proportion summarising the total number of ICU prescriptions for the selected medications (from start of ICU admission to discharge from ICU) during a given year over the total number of ICU admissions in that year. For patients not admitted to ICU during their hospitalisation, the annual rate of prescription will be calculated as proportion representing the total number of prescriptions for selected medication during hospitalisation without ICU admission in a given year over the total number of records within the cohort of hospitalised patients without ICU admission during their hospitalisation for that year in each data source.

Characterisation of patient-level features

For each concept extracted at index date (i.e. data of start of the prescription), the number of persons (N, %) with a record within the study period will be provided.

Characterisation in terms of care setting and patient characteristics including presence of COVID-19 infection and use of mechanical ventilation at index date will be provided for each of selected pre-specified medicines. Count of prescriptions for each individual drug will also be reported at patient and hospital level.

Dose

The dose used for cumulative dose administered will be the dose during the treatment episodes for each medication of interest in hospitalised patients. Median and IQR range of the cumulative dose of the specified drugs at hospital level in mg/day or mg/month will be provided.

For each prescription at index date, the prescribed dose/strength will be retrieved from the drug_exposure and drug_strength tables, where the quantity and units are available.

Cumulative median dose was calculated by multiplying number of users in ICU/Non-ICU setting and respective cumulative dose at the patient level.

The quality of recordings of drug use and drug dose might be of varying quality for different databases. Therefore, data quality checks (using exposure diagnostics) will be conducted prior to study code execution to evaluate the quality of recording of units, dosage and strength for the selected pre-specified medicines of importance for public health emergencies in the databases this study will be conducted in. Only for those databases where we have good quality on dosing and strength, the daily dose and cumulative dose will be reported.

Treatment duration

Treatment duration will be calculated as the duration of the first treatment era of the selected pre-specified medications of importance for public health emergencies in a cohort of hospitalised patients during the study period. Treatment duration will be summarised providing the minimum, quartiles and maximum values. For databases, where duration cannot be calculated due to e.g., missing information on quantity or dosing, treatment duration will not be provided.

8.8.5 Missing values

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For the drug utilisation studies we assumed that the absence of a prescription records means that the person did not receive the respective drug.

8.8.6 Description of sensitivity analysis

None.

8.9 Evidence synthesis

Results from analyses described in section 6.8 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 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.

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, data partners 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

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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 specific drugs, conditions, and co-morbidities, a systematic search of possible codes for inclusion was previously identified using CodelistGenerator R package (<https://github.com/darwin-eu/CodelistGenerator>). This software allows the user to define a search strategy and, using this will then query the vocabulary tables of the OMOP CDM to find potentially relevant codes. The codes returned will then be reviewed by two clinical epidemiologists to consider their relevance.

In addition, the CohortDiagnostics R package (<https://github.com/OHDSI/CohortDiagnostics>) and DrugExposure (<https://darwin-eu.github.io/DrugExposureDiagnostics/>) Diagnostics R package will be run to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error. This will allow for a consideration of the validity of the study cohort of patients with the selected conditions, drugs, and co-morbidities in each of the databases and inform decisions around whether.

11. LIMITATIONS OF THE RESEARCH METHODS

General limitations:

Drug prescriptions: A recording of a prescription does not mean that the patient took the drug. Therefore, assumptions of actual use will be made. secondly, ICU drug prescriptions might not yet be fully integrated, and this is particularly true for medication administrations during surgeries. Lastly, this study will be informed by 6 different data sources from 6 countries and will only reflect drug use occurring in the healthcare settings covered by each database. Results obtained will likely differ across countries and health settings. It is also likely that some results will vary due to differences in how databases handle observations periods, which might vary across different database types.

Database specific limitations:

In CDWBordeaux data has been collected from intensive care units (ICUs) since 2010. However, for a subset of ICUs that manage the most critical patients, data is only available from 2020 onwards, with a gradual increase in completeness until near 2021. ICU drug prescriptions might not be fully integrated, and some CDWBordeaux made it clear that portion of the care provided in these ICUs is still recorded on paper and therefore not available in data warehouse and that they do not have dose data available for medication use in ICU.

IMASIS in the previous study identified an inconsistency in the units associated with midazolam and propofol. They have two presentations where the quantity units (bottles or vials) may not align with their corresponding quantity values, which might instead be expected to be expressed in terms of millilitres (ml). This could lead to unexpectedly high values in the observed ranges. However, at this moment they have found a solution to distinguish between bottles and vials and therefore hope to have solved the problem.

PGH only has the drugs mapped to the ingredient level and therefore no information on dosing. Moreover, The ICU of the hospital uses a separate EHR system that hasn't been mapped yet, so not all drugs, procedures, and measurements provided to the ICU patients are available in the current dataset and only have information on the length of stay in the ICU.

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SUCD do not have information on all the pre-specified medications, and it seems that not all prescriptions are picked up. However, of the prescriptions that are picked up the duration and dosing is present. Furthermore, there is both hospital and ICU data.

Study-specific limitations:

Duration of drug use and dose might not be complete for selected pre-specified medication of interest due to missing information on quantity, dosing or end date or continuous infusion rate.

Despite criteria adopted to differentiate ICU and non-ICU units, there remains a possibility of misclassification between settings.

Also, there might be database specific differences regarding recording and completeness of recording of mechanical ventilation.

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

All data sources require approval from their respective IRB board.

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.

15. OTHER ASPECTS

None.

16. REFERENCES

1. Agency EM. Regulation on EMA's extended mandate becomes applicable 2022 [Available from: <https://www.ema.europa.eu/en/news/regulation-emas-extended-mandate-becomes-applicable>].

	P3-C2-001 Study Protocol	
	Author(s): G. van Leeuwen, K. Verhamme	Version: V3.0
		Dissemination level: Public

2. Agency EM. Medicines shortages and availability issues [Available from: <https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/medicine-shortages-availability-issues>].
3. Palmaro A, Gauthier M, Conte C, Grosclaude P, Despas F, Lapeyre-Mestre M. Identifying multiple myeloma patients using data from the French health insurance databases: Validation using a cancer registry. *Medicine (Baltimore)*. 2017;96(12):e6189.

17. ANNEXES

Appendix I:

Table S1. Code list for exposure definitions. (preliminary codes – might change during study execution based on drug exposure diagnostics).

Drug	Drug class	ATC code	Concept ID	Descendants
Ketamine	Anaesthetics	N01AX03	785649	Yes
Propofol	Anaesthetics	N01AX10	753626	Yes
Heparin	Anticoagulants	B01AB01	1367571	Yes
Diazepam	Benzodiazepines	N05BA01	723013	Yes
Lorazepam	Benzodiazepines	N05BA06	791967	Yes
Midazolam	Benzodiazepines	N05CD08	708298	Yes
Dexamethasone	Corticosteroids	H02AB02	1518254	Yes
Prednisolone	Corticosteroids	H02AB06	1550557	Yes
Cisatracurium	Neuromuscular Blockers	M03AC11	19015726	Yes
Rocuronium	Neuromuscular Blockers	M03AC09	19003953	Yes
Fentanyl	Opioids	N01AH01	1154029	Yes
Remifentanyl	Opioids	N01AH06	19016749	Yes
Esketamine	Anaesthetics	N01AX14	1366610	Yes
Sufentanyl	Opioids	N01AH03	19078219	Yes
Suxametonium (Succinylcholine)	Neuromuscular Blockers	M03AB01	836208	Yes
Atracurium	Neuromuscular Blockers	M03AC04	19014341	Yes

Table S2. Code list for characterisation

	P3-C2-001 Study Protocol	
	Author(s): G. van Leeuwen, K. Verhamme	Version: V3.0
	Dissemination level: Public	

Concept name		Domain	Concept ID
Acute bronchitis caused by SARS-CoV-2	COVID Diagnosis	Condition	3661405
Acute hypoxemic respiratory failure due to disease caused by severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition	3655976
Acute kidney injury due to disease caused by severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition	3661748
Acute respiratory distress syndrome due to disease caused by severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition	3661406
Asymptomatic SARS-CoV-2	COVID Diagnosis	Condition	3662381
Bronchitis caused by COVID-19	COVID Diagnosis	Condition	756031
Cardiomyopathy due to disease caused by severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition	3656667
Conjunctivitis due to disease caused by severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition	3656668
Coronavirus infection	COVID Diagnosis	Condition	439676
COVID-19	COVID Diagnosis	Condition	37311061
Disease due to Coronaviridae	COVID Diagnosis	Condition	4100065
Dyspnea caused by severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition	3656669
Encephalopathy due to disease caused by severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition	37310284
Fever caused by severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition	3661885
Gastroenteritis caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2)	COVID Diagnosis	Condition	37310283

	P3-C2-001 Study Protocol	
	Author(s): G. van Leeuwen, K. Verhamme	Version: V3.0
	Dissemination level: Public	

Concept name		Domain	Concept ID
Infection of upper respiratory tract caused by severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition	37310286
Lower respiratory infection caused by SARS-CoV-2	COVID Diagnosis	Condition	3663281
Lymphocytopenia due to severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition	3661631
Myocarditis due to disease caused by severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition	37310287
Otitis media due to disease caused by severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition	37310254
Patient meets COVID-19 clinical diagnostic criteria	COVID Diagnosis	Observation	704995
Patient meets COVID-19 laboratory confirmation criterion (detection of specific RNA in a clinical specimen using a molecular amplification detection test)	COVID Diagnosis	Observation	700297
Patient meets COVID-19 laboratory diagnostic criteria	COVID Diagnosis	Observation	704996
Patient meets COVID-19 presumptive laboratory evidence criteria (detection of specific antigen in a clinical specimen, OR detection of specific antibody in serum, plasma, or whole blood indicative of a new or recent infection)	COVID Diagnosis	Observation	700296
Pneumonia caused by Human coronavirus	COVID Diagnosis	Condition	37016927
Pneumonia caused by SARS-CoV-2	COVID Diagnosis	Condition	3661408
Pneumonia due to severe acute respiratory syndrome coronavirus	COVID Diagnosis	Condition	40479642
Respiratory infection caused by COVID-19	COVID Diagnosis	Condition	756039

	P3-C2-001 Study Protocol	
	Author(s): G. van Leeuwen, K. Verhamme	Version: V3.0
	Dissemination level: Public	

Concept name		Domain	Concept ID
Rhabdomyolysis due to disease caused by severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition	3655977
Sepsis due to disease caused by severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition	3655975
Severe acute respiratory syndrome	COVID Diagnosis	Condition	320651
Severe acute respiratory syndrome of upper respiratory tract	COVID Diagnosis	Condition	37396171
Suspected COVID-19	COVID Diagnosis	Observation	37311060
Thrombocytopenia due to severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Condition	3661632
Suspected coronavirus infection	COVID Diagnosis	Observation	45763724
2019-ncov coronavirus, sars-cov-2/2019-ncov (covid-19), any technique, multiple types or subtypes (includes all targets), non-cdc	COVID19 positive test	Measurement	40218804
Cdc 2019 novel coronavirus (2019-ncov) real-time rt-pcr diagnostic panel	COVID19 positive test	Measurement	40218805
Coronavirus nucleic acid detection	COVID19 positive test	Measurement	44789510
Coronavirus nucleic acid detection assay	COVID19 positive test	Measurement	44811805
Coronavirus RNA (ribonucleic acid) detection assay	COVID19 positive test	Measurement	45770687
Coronavirus RNA (ribonucleic acid) measurement by NAAT (nucleic acid amplification test)	COVID19 positive test	Measurement	44807536
Detection of ribonucleic acid of severe acute respiratory syndrome coronavirus 2 using polymerase chain reaction	COVID19 positive test	Observation	3667069
Human coronavirus 229E RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection	COVID19 positive test	Measurement	36660491

	P3-C2-001 Study Protocol	
	Author(s): G. van Leeuwen, K. Verhamme	Version: V3.0
	Dissemination level: Public	

Concept name		Domain	Concept ID
Human coronavirus HKU1 RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection	COVID19 positive test	Measurement	36659667
Human coronavirus NL63 RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection	COVID19 positive test	Measurement	36660329
Human coronavirus OC43 RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection	COVID19 positive test	Measurement	36660364
Infectious agent antigen detection by immunoassay technique, qualitative or semiquantitative, multiple-step method; severe acute respiratory syndrome coronavirus (eg, SARS-CoV, SARS-CoV-2 [COVID-19]) (Coronavirus disease [COVID-19])	COVID19 positive test	Measurement	742224
Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]), amplified probe technique	COVID19 positive test	Measurement	700360
Infectious disease (bacterial or viral respiratory tract infection), pathogen-specific nucleic acid (DNA or RNA), 22 targets including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), qualitative RT-PCR, nasopharyngeal swab	COVID19 positive test	Measurement	742218
Infectious disease (bacterial or viral respiratory tract infection), pathogen-specific nucleic acid (DNA or RNA), 22 targets including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), qualitative RT-PCR, nasopharyngeal swab	COVID19 positive test	Measurement	742219
Influenza virus A and B and SARS-CoV-2 (COVID-19) and SARS-related CoV RNA panel - Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement	36661384

	P3-C2-001 Study Protocol	
	Author(s): G. van Leeuwen, K. Verhamme	Version: V3.0
	Dissemination level: Public	

Concept name		Domain	Concept ID
Influenza virus A and B and SARS-CoV-2 (COVID-19) identified in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement	36661375
Influenza virus A and B RNA and SARS-CoV-2 (COVID-19) N gene panel - Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement	36661376
Measurement of Coronavirus (Coronavirinae subfamily species)	COVID19 positive test	Measurement	705104
Measurement of Coronavirus (Coronavirinae subfamily species) antigen	COVID19 positive test	Measurement	705105
Measurement of Severe acute respiratory syndrome coronavirus 2 antigen	COVID19 positive test	Measurement	37310257
Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	COVID19 positive test	Measurement	756055
Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Genetic material using Molecular method	COVID19 positive test	Measurement	586310
Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Blood	COVID19 positive test	Measurement	704991
Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Respiratory specimen	COVID19 positive test	Measurement	756029
Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Saliva	COVID19 positive test	Measurement	586307
Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Sample from nose	COVID19 positive test	Measurement	705107
Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Sample from oropharynx	COVID19 positive test	Measurement	704976

	P3-C2-001 Study Protocol	
	Author(s): G. van Leeuwen, K. Verhamme	Version: V3.0
	Dissemination level: Public	

Concept name		Domain	Concept ID
Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Specified specimen	COVID19 positive test	Measuremen t	586309
Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Unspecified specimen	COVID19 positive test	Measuremen t	756065
Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) specific cell-mediated immune response in Blood	COVID19 positive test	Measuremen t	702834
Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Culture method	COVID19 positive test	Measuremen t	704992
Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique	COVID19 positive test	Measuremen t	705001
Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Blood	COVID19 positive test	Measuremen t	705000
Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Respiratory specimen	COVID19 positive test	Measuremen t	756085
Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Saliva	COVID19 positive test	Measuremen t	586308
Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Sample from nose	COVID19 positive test	Measuremen t	705106
Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	COVID19 positive test	Measuremen t	704975

	P3-C2-001 Study Protocol	
	Author(s): G. van Leeuwen, K. Verhamme	Version: V3.0
	Dissemination level: Public	

Concept name	Domain		Concept ID
using Nucleic acid amplification technique in Sample from oropharynx			
Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Unspecified specimen	COVID19 positive test	Measurement	756084
Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Sequencing	COVID19 positive test	Measurement	704993
SARS-CoV-2 (COVID-19) Ag [Presence] in Respiratory specimen by Rapid immunoassay	COVID19 positive test	Measurement	723477
SARS-CoV-2 (COVID-19) N gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement	706167
SARS-CoV-2 (COVID-19) N gene [Cycle Threshold #] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N1	COVID19 positive test	Measurement	706157
SARS-CoV-2 (COVID-19) N gene [Cycle Threshold #] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N2	COVID19 positive test	Measurement	706155
SARS-CoV-2 (COVID-19) N gene [Presence] in Nasopharynx by NAA with probe detection	COVID19 positive test	Measurement	715272
SARS-CoV-2 (COVID-19) N gene [Presence] in Nose by NAA with probe detection	COVID19 positive test	Measurement	757678
SARS-CoV-2 (COVID-19) N gene [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement	706161
SARS-CoV-2 (COVID-19) N gene [Presence] in Respiratory specimen by	COVID19 positive test	Measurement	586524

	P3-C2-001 Study Protocol	
	Author(s): G. van Leeuwen, K. Verhamme	Version: V3.0
	Dissemination level: Public	

Concept name		Domain	Concept ID
Nucleic acid amplification using CDC primer-probe set N1			
SARS-CoV-2 (COVID-19) N gene [Presence] in Respiratory specimen by Nucleic acid amplification using CDC primer-probe set N2	COVID19 positive test	Measurement	586525
SARS-CoV-2 (COVID-19) N gene [Presence] in Saliva (oral fluid) by NAA with probe detection	COVID19 positive test	Measurement	36661378
SARS-CoV-2 (COVID-19) N gene [Presence] in Serum or Plasma by NAA with probe detection	COVID19 positive test	Measurement	586520
SARS-CoV-2 (COVID-19) N gene [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement	706175
SARS-CoV-2 (COVID-19) N gene [Presence] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N1	COVID19 positive test	Measurement	706156
SARS-CoV-2 (COVID-19) N gene [Presence] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N2	COVID19 positive test	Measurement	706154
SARS-CoV-2 (COVID-19) ORF1ab region [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement	723469
SARS-CoV-2 (COVID-19) ORF1ab region [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement	706168
SARS-CoV-2 (COVID-19) ORF1ab region [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement	723478
SARS-CoV-2 (COVID-19) ORF1ab region [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement	723464

	P3-C2-001 Study Protocol	
	Author(s): G. van Leeuwen, K. Verhamme	Version: V3.0
	Dissemination level: Public	

Concept name		Domain	Concept ID
SARS-CoV-2 (COVID-19) [Presence] in Unspecified specimen by Organism specific culture	COVID19 positive test	Measurement	586516
SARS-CoV-2 (COVID-19) RdRp gene [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement	723471
SARS-CoV-2 (COVID-19) RdRp gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement	723470
SARS-CoV-2 (COVID-19) RdRp gene [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement	706160
SARS-CoV-2 (COVID-19) RdRp gene [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement	706173
SARS-CoV-2 (COVID-19) RNA [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement	586528
SARS-CoV-2 (COVID-19) RNA [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement	586529
SARS-CoV-2 (COVID-19) RNA [Log #/volume] (viral load) in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement	715262
SARS-CoV-2 (COVID-19) RNA panel - Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement	706158
SARS-CoV-2 (COVID-19) RNA panel - Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement	706169
SARS-CoV-2 (COVID-19) RNA [Presence] in Nasopharynx by NAA with non-probe detection	COVID19 positive test	Measurement	723476

	P3-C2-001 Study Protocol	
	Author(s): G. van Leeuwen, K. Verhamme	Version: V3.0
	Dissemination level: Public	

Concept name		Domain	Concept ID
SARS-CoV-2 (COVID-19) RNA [Presence] in Nasopharynx by NAA with probe detection	COVID19 positive test	Measurement	586526
SARS-CoV-2 (COVID-19) RNA [Presence] in Nose by NAA with probe detection	COVID19 positive test	Measurement	757677
SARS-CoV-2 (COVID-19) RNA [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement	706163
SARS-CoV-2 (COVID-19) RNA [Presence] in Respiratory specimen by Sequencing	COVID19 positive test	Measurement	36661377
SARS-CoV-2 (COVID-19) RNA [Presence] in Saliva (oral fluid) by NAA with probe detection	COVID19 positive test	Measurement	715260
SARS-CoV-2 (COVID-19) RNA [Presence] in Saliva (oral fluid) by Sequencing	COVID19 positive test	Measurement	715261
SARS-CoV-2 (COVID-19) RNA [Presence] in Serum or Plasma by NAA with probe detection	COVID19 positive test	Measurement	723463
SARS-CoV-2 (COVID-19) RNA [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement	706170
SARS-CoV-2 (COVID-19) S gene [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement	723467
SARS-CoV-2 (COVID-19) S gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement	723468
SARS-CoV-2 (COVID-19) S gene [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement	723465
SARS-CoV-2 (COVID-19) S gene [Presence] in Serum or Plasma by NAA with probe detection	COVID19 positive test	Measurement	586519

	P3-C2-001 Study Protocol	
	Author(s): G. van Leeuwen, K. Verhamme	Version: V3.0
	Dissemination level: Public	

Concept name		Domain	Concept ID
SARS-CoV-2 (COVID-19) S gene [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement	723466
SARS-CoV-2 (COVID-19) whole genome [Nucleotide sequence] in Isolate by Sequencing	COVID19 positive test	Measurement	586517
SARS-CoV+SARS-CoV-2 (COVID-19) Ag [Presence] in Respiratory specimen by Rapid immunoassay	COVID19 positive test	Measurement	757685
SARS-like coronavirus N gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement	706172
SARS-like coronavirus N gene [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement	706171
SARS-related coronavirus E gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement	706166
SARS-related coronavirus E gene [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement	586523
SARS-related coronavirus E gene [Presence] in Serum or Plasma by NAA with probe detection	COVID19 positive test	Measurement	586518
SARS-related coronavirus E gene [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement	706174
SARS-related coronavirus+MERS coronavirus RNA [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement	706159
SARS-related coronavirus RNA [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Measurement	706165

	P3-C2-001 Study Protocol	
	Author(s): G. van Leeuwen, K. Verhamme	Version: V3.0
	Dissemination level: Public	

Concept name	Domain		Concept ID
SARS-related coronavirus RNA [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Measurement	723472

Table S3. Code list for mechanical ventilation

Concept name	Domain		Concept ID	Descendants
Artificial respiration	Ventilation	Procedure	4230167	Yes
Assisted breathing	Ventilation	Procedure	4145647	Yes
Intubation of respiratory tract	Ventilation	Procedure	40487536	Yes

	P3-C2-001 Study Protocol	
	Author(s): G. van Leeuwen, K. Verhamme	Version: V3.0
	Dissemination level: Public	

Appendix II: ENCePP checklist for study protocols

Study title: DARWIN EU® - Monitoring prescription of essential medicines administered in ICU – a routine repeated study

EU PAS Register® number: EUPAS1000000534 Study reference number (if applicable): P3-C2-001

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

Comments:

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<u>Section 2: Research question</u>	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	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 generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no <i>a priori</i> hypothesis?	☒	☐	☐	

Comments:

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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.

	P3-C2-001 Study Protocol		
	Author(s): G. van Leeuwen, K. Verhamme		Version: V3.0
	Dissemination level: Public		

<u>Section 3: Study design</u>	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:

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<u>Section 4: Source and study populations</u>	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:				8.3, 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:

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<u>Section 5: Exposure definition and measurement</u>	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

	P3-C2-001 Study Protocol	
	Author(s): G. van Leeuwen, K. Verhamme	Version: V3.0
	Dissemination level: Public	

<u>Section 5: Exposure definition and measurement</u>	Yes	No	N/A	Section Number
5.2 Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorized according to time windows?	☐	☐	☒	
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:

<u>Section 6: Outcome definition and measurement</u>	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:

<u>Section 7: Bias</u>	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)	☐	☐	☒	

	P3-C2-001 Study Protocol	
	Author(s): G. van Leeuwen, K. Verhamme	Version: V3.0
	Dissemination level: Public	

Comments:

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<u>Section 8: Effect measure modification</u>	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:

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<u>Section 9: Data sources</u>	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 events, 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
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:

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	Dissemination level: Public	

<u>Section 10: Analysis plan</u>	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?	☒	☐	☐	8.8

Comments:

<u>Section 11: Data management and quality control</u>	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:

<u>Section 12: Limitations</u>	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? 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).	☒ ☒ ☐	☐ ☐ ☐	☐ ☐ ☒	11
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

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Comments:

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<u>Section 13: Ethical/data protection issues</u>	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:

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

Comments:

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<u>Section 15: Plans for communication of study results</u>	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:

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Name of the main author of the protocol: Guido van Leeuwen

Date: 27/03/2025

Signature: _____