Study Protocol

P4-C1-020

DARWIN EU® - Assessment of immunoglobulin use in clinical practice

19/01/2026

Version 4.0

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Public

CONTENTS

Study title	DARWIN EU® - Assessment of immunoglobulin use in clinical practice
Protocol version	V4.0
Date	19/01/2026
EUPAS number	EUPAS1000000823
Active substance	Immunoglobulins: respiratory syncytial virus immune globulin intravenous, immunoglobulin G, freeze-dried pepsin-treated human normal immunoglobulin, ph4-treated acidic human normal immunoglobulin, ph4-treated acidic human normal immunoglobulin (for s.c. injection), polyethylene glycol-treated human normal immunoglobulin, freeze-dried ph4-treated human normal immunoglobulin, freeze-dried sulfonated human normal immunoglobulin, freeze-dried polyethylene glycol-treated human normal immunoglobulin, immunoglobulin M human, immunoglobulin A, Rho(D) immune globulin, tetanus immune globulin, varicella-zoster immune globulin, hepatitis B immune globulin, rabies immune globulin human, Immunoglobulin Anti-Rubella, human vaccinia immune globulin, staphylococcus epidermidis immunoserum rabbit, staphylococcus aureus immunoserum, cytomegalovirus immune globulin, diphtheria antitoxin, hepatitis A immunoglobulin (systemic), Immunoglobulin Anti-Tickborne Encephalitis, pertussis immunoglobulin; systemic, measles immunoglobulin; systemic mumps immunoglobulin; systemic, anthrax immune globulin, Bacillus anthracis immunoserum rabbit, Nebacumab, raxibacumab, bezlotoxumab, obiltoxaximab, palivizumab, MOTAVIZUMAB, tixagevimab, ansuvimab, sotrovimab, REGDANVIMAB, casirivimab, nirsevimab, Sipavibart
Medicinal product	Immunoglobulin brands: Flebogamma DIF, Kiovig, Privigen, Octagam, Yimmugo, Ig vena, Intratect, Iqymune, Panzyga/Globiga, Gamunex, Hizentra, Hyqvia, Cuvitru, Cutaquig, Xembify, Gammagard, Nanogam/Optiglobin, Clairyg, Tegeline, Pentaglobin, Keycute/Naxiglo, Gammaplex, Beriglobin, Rhesonativ, Rhophylac
Research question and objectives	Research question: What are the treatment and patient characteristics of individuals receiving immunoglobulins across European countries? Study objectives: 1. To estimate the overall and annual prevalence of immunoglobulin use in the general population, overall and stratified by i) type of immunoglobulin, and ii) route of administration. Estimates will be stratified by age and sex. 2. To describe the distribution and quarterly trends of prespecified immunoglobulin brands among prevalent immunoglobulin users (if available). 3. To estimate the number of immunoglobulin prescriptions, treatment duration, and dose (initial, cumulative) of immunoglobulin use during the study period. 4. To characterise patients initiating treatment with prespecified immunoglobulins in terms of i) demographics at index date, ii) indication for use, iii) comorbidities, iv) common infections post-index, and v) antibiotics post-index.
Countries of study	France, Germany, United Kingdom
Authors	Ellen Gerritsen, e.gerritsen@darwin-eu.org Dina Vojinovic, d.vojinovic@darwin-eu.org

LIST OF ABBREVIATIONS

Acronyms/terms	Description
ATC	Anatomical Therapeutic Chemical
CC	Coordinating centre
CDM	Common Data Model
CDW Bordeaux	Clinical Data Warehouse of Bordeaux University Hospital
CPRD GOLD	Clinical Practice Research Datalink GOLD
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DDD	Defined daily doses
DOI	Declaration of Interests
DQD	Data Quality Dashboard
DRE	Digital Research Environment
DTZ	Data Transfer Zone
EHR	Electronic Health Records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EUPAS	EU Post-Authorisation Studies Register
GDPR	General Data Protection Regulation
GP	General Practitioner
ICD	International Classification of Diseases
IG	Immunoglobulin
IP	Inpatient
IRB	Institutional Review Board
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OP	Outpatient
RxNorm	Medical prescription normalised
SNOMED	Systemised Nomenclature of Medicine
WHO	World Health Organisation

1. TITLE

DARWIN EU® - Assessment of immunoglobulin use in clinical practice

2. DESCRIPTION OF THE STUDY TEAM

Study team role	Names	Organisation
Principal Investigators	Ellen Gerritsen Dina Vojinovic	IQVIA
Data Scientists	Akram Mendez Gargi Jadhav	IQVIA
Study Manager	Natasha Yefimenko	Erasmus MC
Data source	**Names**	**Data Partner Organisation***
Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux)	Guillaume Verdy Loïc Ronflette	Centre Hospitalier Universite de Bordeaux
IQVIA Disease Analyzer Germany (IQVIA DA Germany)	James Brash	IQVIA
Clinical Practice Research Datalink GOLD (CPRD GOLD)	Antonella Delmestri Marta Pineda Moncusí Mandickel Kamtengeni Hezekiah Omulo	University of Oxford

*Data partners do not have an investigator role. Data partners execute code at their data source, review, and approve their results.

3. ABSTRACT

Title

DARWIN EU® - Assessment of immunoglobulin use in clinical practice

Rationale and background

Immunoglobulins can be routinely administered as replacement therapy in immunodeficient patients or are used as immunomodulating doses to treat various immune-related and inflammatory diseases. The global demand of immunoglobulins increases every year, resulting in intermittent shortages that could affect individuals with conditions that have limited alternative treatments. Prolonged low levels of certain immunoglobulins can increase the risk of certain infections and replenishment of these immunoglobulins can reduce this risk. This study aims to generate real-world evidence on the treatment and characteristics of individuals receiving immunoglobulins.

Research question and objectives

Research question

What are the treatment and patient characteristics of individuals receiving immunoglobulins across European countries?

Objectives

The specific objectives of this study are:

1. To estimate the overall and annual prevalence of immunoglobulin use in the general population, overall and stratified by i) type of immunoglobulin, and ii) route of administration. Estimates will be stratified by age and sex.
2. To describe the distribution and quarterly trends of prespecified immunoglobulin brands among prevalent immunoglobulin users (if available).
3. To estimate the number of immunoglobulin prescriptions, treatment duration, and dose (initial, cumulative) of immunoglobulin use during the study period.
4. To characterise patients initiating treatment of prespecified immunoglobulins in terms of i) demographics at index date, ii) indication for use, iii) comorbidities, iv) common infections post-index, and v) antibiotics post-index.

Methods

Study design

A descriptive retrospective cohort study will be conducted to estimate the prevalence of individuals with a recorded immunoglobulin prescription in the general population, to estimate the prevalence of individuals with a record of a prespecified immunoglobulin brand among prevalent immunoglobulin users, and to characterise individuals receiving immunoglobulin treatment, using routinely collected health data from 3 data sources from 3 countries across Europe for the period from 2017 to 2024.

Population

Objective 1

The study population will include all individuals who are present in the data source during the study period between 01/01/2017 and 31/12/2024.

Objective 2

The study population will include all individuals who have a drug prescription or dispensing record of immunoglobulin and are present in the data source during the study period between 01/01/2017 and 31/12/2024.

Objectives 3–4

For primary care data sources, the study population will include all individuals who initiate immunoglobulin treatment with prespecified immunoglobulin brands and are present in the data source during the study period. Individuals are required to have 180 days data visibility prior to study inclusion and should not have a record of an immunoglobulin prescription in the 180 days prior to study inclusion. To ensure sufficient follow-up time, only individuals who initiated immunoglobulin treatment at least 180 days before the end of the available data will be included.

For hospital care data settings, the study population will include all individuals who have an immunoglobulin record and are present in the data source during the study. Individuals are not required to have prior data availability, and no washout period will be applied prior to study inclusion. To ensure sufficient follow-up time, only individuals who initiated immunoglobulin treatment at least 180 days before the end of the available data will be included.

Variables

Drug of interest: immunoglobulins

Relevant covariates and other variables: demographics, prespecified indication for use, comorbidities, prespecified common infections, and prespecified antibiotics

Data sources

1. France: Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux)
2. Germany: IQVIA Disease Analyzer Germany (IQVIA DA Germany)
3. United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

Study size

No sample size has been calculated, as this is an exploratory study which will not test a specific hypothesis. Based on a preliminary feasibility assessment, the expected number of person counts for immunoglobulins in the data sources included in this study range from 10,900 (CDW Bordeaux) to 73,600 (CPRD GOLD).

Statistical analysis

Objective 1

The prevalence of individuals with a recorded immunoglobulin prescription (expressed as the proportion of individuals with any immunoglobulin prescription in the study population) will be stratified by immunoglobulin ingredient, and route of administration, presented overall and per calendar year. Estimates will be stratified by age and sex. These analyses will be conducted using the *IncidencePrevalence* R packages based on OMOP CDM mapped data.

Objective 2

The quarterly prevalence of individuals with a prespecified immunoglobulin brands prescription will be estimated (expressed as the proportion of individuals prescribed a specific immunoglobulin brand among prevalent immunoglobulin users). These analyses will be conducted using the *IncidencePrevalence* R packages based on OMOP CDM mapped data.

Objective 3

The number of immunoglobulin prescriptions, treatment duration, and initial and cumulative dose of the index drug will be provided per prespecified immunoglobulin brand as minimum, q25 median, q75, and maximum. This analysis will be conducted using the *DrugUtilisation* R package based on OMOP CDM mapped data.

Objective 4

Characteristics of individuals initiating treatment with prespecified immunoglobulin brands during the study period will be described for each prespecified immunoglobulin brand by means of large-scale characterisation and prespecified patient-level characteristics. Categorical variables will be summarised as counts and proportions, while continuous variables will be reported as minimum, q25, median, q75, and maximum. Demographic characteristics, including age and sex, will be assessed at the date of immunoglobulin initiation (index date). Characterisation of prespecified indications for use will be assessed any time prior to 7 days after the index date, 30 days prior to 7 days after the index date, and 7 days prior to 7 days after the index date. Large-scale characterisation of comorbidities prior to immunoglobulin treatment will be assessed within 30 days prior to the index date, within 1 year prior to the index date, and any time prior to the index date. Characterisation of prespecified common infections and prespecified antibiotics treatment among prespecified immunoglobulin brand initiators will be assessed up to 30 days post-index and up to 365 days post-index. These analyses will be conducted using the *CohortCharacteristics* and *DrugUtilisation* R packages based on OMOP CDM mapped data.

A minimum cell count of 5 will be used when reporting results, with any smaller count reported as “<5” and zero counts as “0”.

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Study milestones and deliverables	Planned dates*
Final Study Protocol	19 January 2026
Creation of Analytical code	December 2025/January 2026
Execution of Analytical Code on the data	January 2026
Draft Study Report	30 January 2026
Final Study Report	To be confirmed by EMA

*Planned dates are dependent on obtaining approvals from the internal review boards of the data sources.

6. RATIONALE AND BACKGROUND

Immunoglobulins are purified products from plasma of human donors. They can be routinely administered as replacement therapy in immunodeficient patients or are used as immunomodulating doses to treat various immune-related and inflammatory diseases.[1, 2] Immunoglobulins are not only used for authorised indications, such as primary immunodeficiency disorders and Kawasaki disease, but also for unauthorised (off-label) indications.[3] Prolonged low levels of certain immunoglobulins can increase the risk of certain infections and replenishment of these immunoglobulins can reduce this risk.[4] The global demand of immunoglobulins increases every year, resulting in intermittent shortages that could affect individuals with conditions that have limited alternative treatments.[1, 3] This study aims to generate real-world evidence on the treatment and characteristics of individuals receiving immunoglobulins.

7. RESEARCH QUESTION AND OBJECTIVES

Research questions

What are the treatment and patient characteristics of individuals receiving immunoglobulins across European countries?

Research objectives

The specific objectives of this study are:

1. To estimate the overall and annual prevalence of immunoglobulin use in the general population, overall and stratified by i) type of immunoglobulin, and ii) route of administration. Estimates will be stratified by age and sex.
2. To describe the distribution and quarterly trends of prespecified immunoglobulin brands among prevalent immunoglobulin users (if available).
3. To estimate the number of immunoglobulin prescriptions, treatment duration, and dose (initial, cumulative) of immunoglobulin use during the study period.
4. To characterise patients initiating treatment with prespecified immunoglobulins in terms of i) demographics at index date, ii) indication for use, iii) comorbidities, iv) common infections post-index, and v) antibiotics post-index.

8. RESEARCH METHODS

8.1. Study design

A cohort study will be conducted using routinely collected health data from 3 data sources from 3 countries across Europe and in 3 EU member states. The study will comprise of:

- A population-level drug utilisation study which will be conducted to address *objectives 1* and *2,* assessing the prevalence of individuals with a recorded immunoglobulin prescription, stratified by type of immunoglobulin and route of administration, among the general population (**Figure 1a**) and the prevalence of prespecified immunoglobulin brands among individuals with an immunoglobulin prescription (**Figure 1b**).
- A patient-level drug utilisation study which will be conducted to address *objectives 3* and *4,* assessing treatment characteristics and clinical characteristics of individuals initiating treatment with prespecified immunoglobulin brands, including dose, treatment duration, number of prescriptions, and indication for use, comorbidities, and common infections and antibiotics prescribed (**Figure 2**).

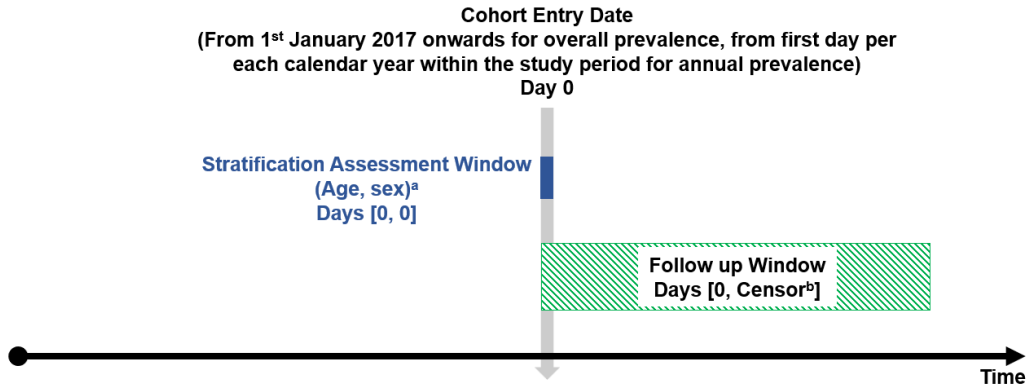


Figure 1a. Graphical depiction of the study design *objective 1*.

a. Stratification by sex or age group (i) 1 to 18 years, ii) 19 to 65 years, and iii) >65 years and older) will be done at cohort entry date.
b. Earliest of: 1) loss to follow-up, 2) death, 3) end of observation period (the latest available data), or 4) study end date 31/12/2024.

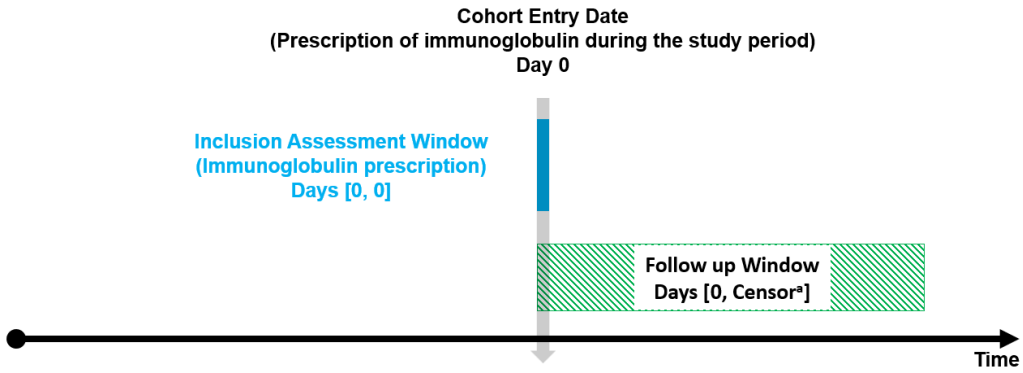


Figure 1b. Graphical depiction of the study design *objective 2*.

a. Earliest of: 1) loss to follow-up, 2) death, 3) end of observation period (the latest available data), or 4) study end date 31/12/2024.

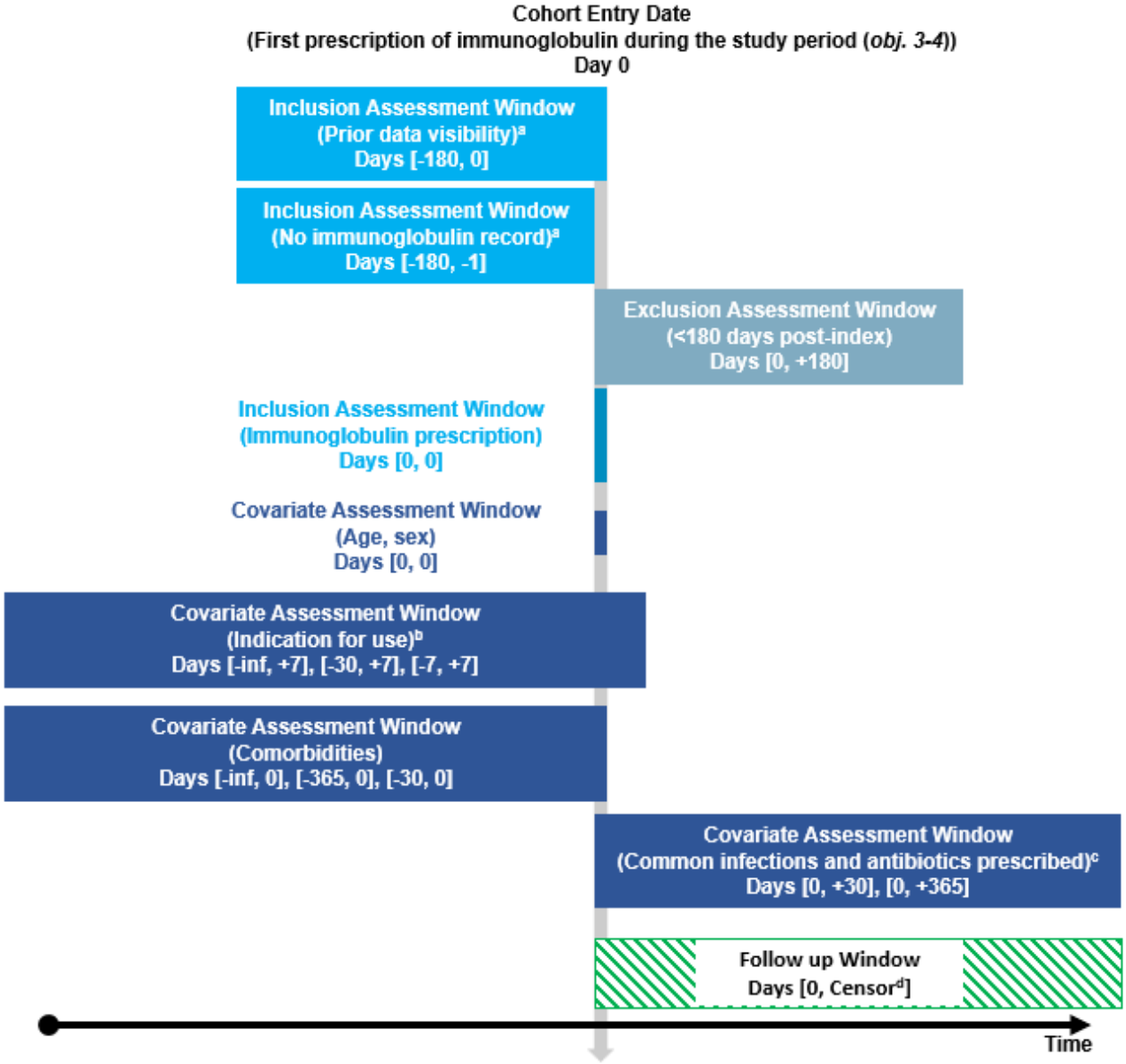


Figure 2. Graphical depiction of the study design *objectives 3–4*.

a. Criterion only applies for primary care data sources (IQVIA DA Germany and CPRD GOLD)
b. Indication for use include the following prespecified indication groups 1) primary immunodeficiency syndrome, 2) secondary immunodeficiencies, 3) neurology, 4) haematology, 5) infectious diseases, 6) solid organ transplantation, 7) internal medicine, 8) hepatology, and 9) other indications. Detailed information can be found in **Section 8.6.3.**
c. Overview of prespecified infections and antibiotics can be found in **Section 8.6.3.**
d. Earliest of: 1) loss to follow-up, 2) death, 3) end of observation period (the latest available data), or 4) study end date 31/12/2024

8.2. Follow-up

For prevalence estimations of individuals with recorded immunoglobulin prescriptions among the general study population (*objective 1*), individuals present in the data source between 1st of January 2017 and 31st of December 2024 will be included. For prevalence estimations among immunoglobulin users (*objective 2*), follow up will start on date of immunoglobulin prescription during the study period.

For patient-level drug utilisation (*objective 3*) and characterisation of individuals initiating immunoglobulin treatment (*objective 4*), follow-up of incident immunoglobulin users will start on the date of the first immunoglobulin prescription record of prespecified immunoglobulin brands during the study period. For primary care data sources, individuals are required to have 180 days data visibility prior to study inclusion and should not have a record of immunoglobulin prescription in the 180 days prior to study inclusion. For hospital care data settings, individuals are not required to have prior data availability, and no washout period will be applied prior to study inclusion. To ensure sufficient follow-up (*objectives 3–4*), only individuals with a first record of immunoglobulin prescription at least 180 days before the end of data availability in each data source will be included.

Follow-up (*objectives 1–4*) will end on the earliest of i) loss to follow-up, ii) death, iii) end of observation period (the latest available data), iv) or study end date 31/12/2024, whichever occurs first.

The code lists used to identify the start and end of follow-up determining events are presented in **Annex IV**.

8.3. Study population with inclusion and exclusion criteria

Objective 1

Inclusion criteria

- Present in the data source during the period of 01/01/2017 to 31/12/2024.

Exclusion criteria

- Not applicable for this objective.

Objective 2

Inclusion criteria

- Present in the data source during the period of 01/01/2017 to 31/12/2024.
- Drug prescription or dispensing record of prespecified immunoglobulin brands during the study period.

Exclusion criteria

- Not applicable for this objective.

The preliminary code list for immunoglobulins is provided in **ANNEX IV**.

Objectives 3–4

Inclusion criteria

- Present in the data source during the period of 01/01/2017 to 31/12/2024.
- Minimum 180 days of available history before index data. This criterion does not apply for hospital data source CDW Bordeaux.
- First drug prescription or dispensing record of prespecified immunoglobulin brand during the study period.
- No prior immunoglobulin exposure in the 180 days prior to the index date. This criterion does not apply for hospital data source CDW Bordeaux.

Exclusion criteria

- Individuals with a first immunoglobulin record <180 days prior to the end of data availability in the respective data source (to ensure sufficient follow-up).

The preliminary code list for immunoglobulins brands is provided in **ANNEX IV**.

8.4. Study setting and data sources

This study will be conducted using routinely collected data from primary and secondary care data sources in the DARWIN EU® network of data partners from 3 European countries, of 3 EU member states. All data were *a priori* mapped to the OMOP CDM.

Table 1. Data sources.

Country	Name of data source	Health care setting	Type of data	Number of active individuals	Calendar period covered by each data source	Contributing to
France	CDW Bordeaux	Hospital care	EHR	247,200	2005 – 09/2025	All objectives
Germany	IQVIA DA Germany	Outpatient General Practitioner and Specialist Care	EHR	4,484,200	1989 – 12/2024	All objectives
United Kingdom	CPRD GOLD	Outpatient General Practitioner Care	EHR	2,632,700	1987 – 05/2025	All objectives

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital; CPRD GOLD = Clinical Practice Research Datalink GOLD; EHR = electronic health records; IQVIA DA Germany = IQVIA Disease Analyzer Germany. Number of active individuals is defined as the number of individuals present in the last six months of the respective data source.

1. France: Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux)
2. Germany: IQVIA Disease Analyzer Germany (IQVIA DA Germany)
3. United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

Data sources selection

These data sources fulfil the criteria required in terms of data quality, completeness, timeliness, and representativeness for a drug utilisation and characterisation studies while covering different regions of Europe (**Annex II**).

8.5. Study period

The study period is from 01/01/2017 to 31/12/2024. The data availability of the included data sources aligns with the study period.

8.6. Variables

8.6.1. Exposure

For *objective 1,* the primary exposure is defined as a prescription or dispensing record of a prespecified immunoglobulin drug (ingredient level). For *objective 2,* prescriptions of all prespecified immunoglobulin brands of an individual during the study period will be included. For *objectives 3* and *4,* the prescription or dispensing record of prespecified immunoglobulin brands represents the first recorded prescription in the study period and individuals from primary care data sources were required to have no prior immunoglobulin use in the 180 days prior the index date.

To define treatment episodes, sequential prescriptions will be grouped into drug eras, allowing a maximum gap of 30 days between the end of one prescription and the start of the next. More details about the definition of a treatment episode are provided in **Section 8.8.3**.

The preliminary concept sets used for the identification of exposures are described in **Annex IV**. These codes will be refined during the study execution following the DARWIN EU® phenotyping standard processes, which involve the review of code lists, and the review of phenotypes after their execution in the participating data sources. Final concept sets will be defined following input from EMA.

8.6.2. Outcome

The outcomes of interest are as follows:

- Prevalence of individuals with a recorded immunoglobulin prescription among the general population, including type of immunoglobulin, route of administration (*objective 1*).
- Prevalence of individuals with a prespecified immunoglobulin brands prescription among prevalent immunoglobulin users (*objective 2*).
- Initial and cumulative dose, number of prescriptions, and treatment duration of prespecified immunoglobulin brands among treatment initiators (*objective 3*).
- Characterisation of individuals initiating treatment with prespecified immunoglobulin brands(*objective 4*).

8.6.3. Covariates, including confounders, effect modifiers, and other variables

The variables for *objective 1* are as follows:

- Calendar period
    - Year
- Route of administration:
    - Intravenous
    - Subcutaneous
    - Intramuscular
    - Other
    - Missing
- Age groups, defined at cohort entry date:
    - Overall population
    - 1 to 18 years
    - 19 to 65 years
    - >65 years and older
- Sex, defined at cohort entry date:
    - Overall
    - Male
    - Female

The variables for *objective 2* are as follows:

- Calendar period
    - Quarter of year
- Prespecified brands, including (if available):
    - Flebogamma DIF
    - Kiovig
    - Privigen
    - Octagam (5% and 10%)
    - Yimmugo
    - Ig vena
    - Intratect
    - Iqymune
    - Panzyga/Globiga
    - Gamunex
    - Hizentra
    - Hyqvia
    - Cuvitru
    - Cutaquig
    - Xembify
    - Gammagard
    - Nanogam/Optiglobin
    - Clairyg
    - Tegeline
    - Pentaglobin
    - Keycute/Naxiglo
    - Gammaplex
    - Beriglobin
    - Rhesonativ
    - Rhophylac

The variables for characterisation of immunoglobulin users (*objective 4*) are as follows:

- Demographics, at index date:
    - Sex: Female/male
    - Age
    - Age group: 1 to 18 years, 19 to 65 years, >65 years and older

- Indication for use: Prespecified conditions will be used as proxies to assess the indication for immunoglobulin use, including both authorised and non-authorised indications. The assessment windows will be any time prior to 7 days after the index date [-inf, +7], 30 days prior to 7 days after the index date [-30, +7], and 7 days prior to 7 days after the index date [-7, +7].
    - Primary immunodeficiency syndrome, including:
        - Primary immunodeficiency syndromes
    - Secondary immunodeficiencies, including:
        - Secondary immunodeficiencies
    - Neurology, including:
        - Guillain Barré syndrome (GBS)
        - Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)
        - Multifocal motor neuropathy (MMN)
        - Myasthenia gravis
        - Stiff person syndrome
        - Lambert-Eaton myasthenia syndrome
    - Haematology, including:
        - Immune thrombocytopenia (ITP)
        - Acquired von Willebrand disease
        - Foetal Neonatal Alloimmune Thrombocytopenia (FNAIT)
    - Infectious diseases, including:
        - Measles
    - Solid organ transplantation, including:
        - Transplantation
    - Internal medicine, including:
        - Kawasaki's disease
        - Inflammatory myopathy
        - (Juvenile) dermatopolymyositis
        - ANCA vasculitis (replacement therapy)
        - Systemic lupus erythematosus (SLE)
    - Hepatology, including:
        - Hepatitis A
    - Other indications, which will be assessed overall and separately for each indication, where available, including:
        - Oncology
        - Autoimmune or paraneoplastic encephalitis
        - Epilepsy

        - Progressive systemic sclerosis
        - Sjögren syndrome
        - COVID-19
        - Alzheimer

- Comorbidities: The top 10 most frequent diagnostic codes (comorbidities) will be identified through large-scale characterisation. These will be assessed 30 days prior to the index date [-30, 0], 1 year prior to the index date [-365, 0], and any time prior the index date [-inf, 0].

Common infections: Prespecified common infections among individuals initiating treatment with prespecified immunoglobulin brands will be assessed up to 30 days post-index [0, +30] and up to 365 days post-index [0, +365]. The following types of infections [4] will be assessed:

- Systemic infections, including:
    - Gram negative sepsis
    - Bacteraemia
- Bacterial infections, including:
    - Bacterial infectious disease
- Central nervous system infections, including:
    - Meningitis
- Respiratory & ear, nose, throat, ocular infections, including:
    - Otitis
    - Conjunctivitis
    - Bronchitis
    - Sinusitis
    - Respiratory tract infections
- Fungal infections, including:
    - Opportunistic mycosis
    - Invasive fungal infection
- Gastrointestinal & intra-abdominal infections, including:
    - Acute diarrhoea
    - Gastrointestinal infections
    - Peritonitis
- Urinary infections, including:
    - Urinary tract infections
- Viral infections:
    - Chronic enteroviral infections
    - Herpesvirus infections

- Antibiotic treatment: Exposure to prespecified antibiotics will be assessed up to 30 days post-index [0, +30] and up to 365 days post-index [0, +365]. The following classes of antibiotic ingredients will be assessed:
    - Tetracyclines
    - Amphenicols
    - Beta-lactam antibacterials, penicillins
    - Other beta-lactam antibacterials
    - Sulphonamides and trimethoprim
    - Macrolides, lincosamides, and streptogramins
    - Aminoglycoside antibacterials
    - Quinolone antibacterials
    - Other antibacterials

The preliminary concept sets used for the identification of covariates are described in **Annex IV**. Final concept sets will be defined following input from EMA.

8.7. Study size

No sample size has been calculated, as this is a characterisation and drug utilisation study with a descriptive design, which will not test a specific hypothesis. In addition, we will use already available data to describe treatment and characteristics of individuals receiving immunoglobulins. Thus, the sample size is driven by the availability of data for individuals with a prescription for prespecified immunoglobulin types and brands. Based on a preliminary feasibility assessment, the expected number of person counts for immunoglobulins in the data sources included in this study range from 10,900 (CDW Bordeaux) to 73,600 (CPRD GOLD).

8.8. Analysis

8.8.1. Federated network analyses

All analyses will be conducted separately for each data source and will be carried out in a federated manner, allowing analyses to be run locally without sharing individuals' data.

Before sharing the study package, test runs of the analytics will be performed on a subset of the data sources, and quality control checks will be performed. After all the tests are passed (see **Annex III. Operational and reporting considerations**), the final package will be released in a version-controlled study repository for execution against all the participating data sources.

8.8.2. Data privacy protection

The data partners will locally execute the analytics against the OMOP CDM in R Studio and review and approve the default aggregated results. They will then be made available to the Principal Investigators and study team in secure online repository of DTZ (Data Transfer Zone). All results will be locked and timestamped for reproducibility and transparency. The study results of all data sources will be checked, after which they are made available to the team, and the Study Dissemination Phase can start. All analyses will be conducted separately for each data source, and will be carried out in a federated manner, allowing analyses to be run locally without sharing patient-level data. Cell counts <5 will be suppressed when reporting results to comply with the data source's privacy protection regulations.

8.8.3. Statistical model specification and assumptions of the analytical approach considered

Objective 1

Trends of immunoglobulin use during the study period will be assessed based on OMOP CDM mapped data using the *IncidencePrevalence* R package (https://github.com/darwin-eu/IncidencePrevalence), developed by DARWIN EU®.

The prevalence of individuals with a recorded immunoglobulin prescription (expressed as the proportion of individuals with any immunoglobulin prescription in the general study population) will be presented by immunoglobulin ingredient, route of administration, and stratified by sex and age.

Prevalence will be calculated as overall and annual, which summarises the total number of individuals with recorded immunoglobulin use during a given period divided by the population at risk of receiving immunoglobulins during that period. Therefore, period prevalence will give the proportion of individuals exposed at any time during a specified interval. Binomial 95% confidence intervals will be calculated.

Objective 2

Trends of immunoglobulin use during the study period will be assessed based on OMOP CDM mapped data using the *IncidencePrevalence* R package (https://github.com/darwin-eu/IncidencePrevalence), developed by DARWIN EU®.

The quarterly prevalence of individuals with prescriptions for prespecified immunoglobulin brands will be estimated (expressed as the proportion of individuals prescribed each specific immunoglobulin brand among prevalent immunoglobulin users).

Prevalence will be calculated as quarterly period prevalence, which summarises the total number of individuals with recorded immunoglobulin brand prescription during a quarter divided by the population of prevalent immunoglobulin users during that period. Therefore, period prevalence will give the proportion of individuals exposed to a specific brand at any time during the specified interval. Binomial 95% confidence intervals will be calculated.

An illustration of the calculation of period prevalence is shown below in **Figure 3**. Between time t+2 and t+3, two of the five study participants receive immunoglobulin treatment, giving a prevalence of 40%. Meanwhile, for the period t to t+1 all five also had some observation time during the year with one of the five study participants having a recorded immunoglobulin prescription, giving a prevalence of 20%.

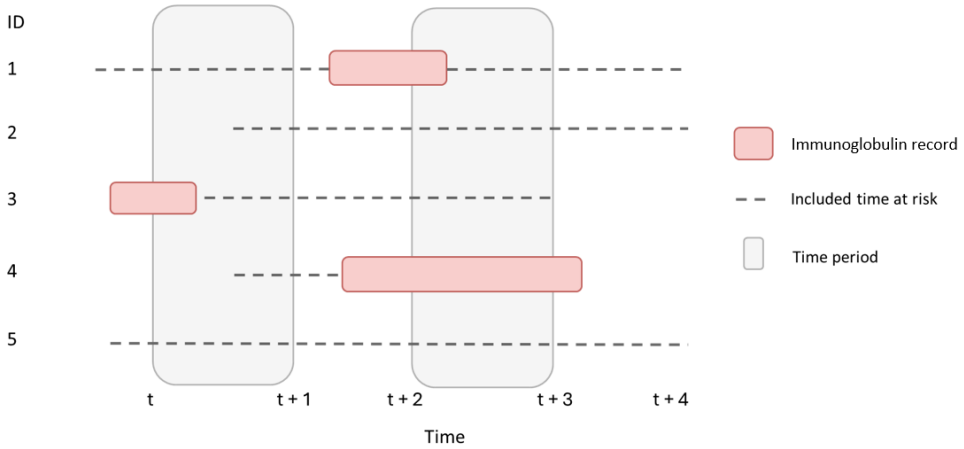


Figure 3. Prevalence example.

Objective 3

The dose, duration of use, and number of immunoglobulin prescriptions will be calculated per prespecified immunoglobulin brand based on OMOP CDM mapped data using the *DrugUtilisation* R package (https://github.com/darwin-eu/DrugUtilisation), developed by DARWIN EU®.

Drug exposure calculations

Drug eras are defined as follows: exposure starts at the date of the first prescription of prespecified immunoglobulin brand during the study period. For primary care data sources, a washout period of 180 days will be applied prior to inclusion. For each prescription, the estimated duration of use will be retrieved from the drug exposure table in the OMOP CDM, using the recorded start and end date of the exposure. Subsequent prescriptions will be combined into continuous exposed treatment 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 ≤30 days. The time between the two joined eras will be considered as exposed by the first era as shown in **Figure 4**, first row. The cumulative dose is the sum of defined daily doses (DDDs) multiplied by the number of days exposed to each dose, i.e., the total dose taken throughout the exposures considered in the time-window reported per prespecified immunoglobulin brand.

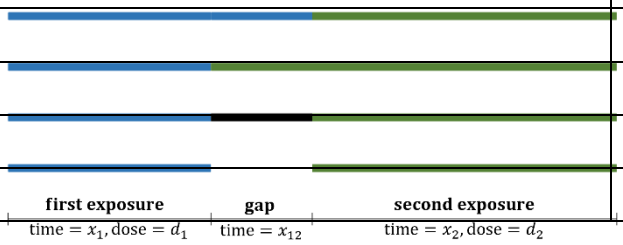
Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"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

Figure 4. Gap era joint mode.

If two exposures overlap, the overlap time will be considered exposed to the first exposure (**Figure 5**). No time will be added at the end of the combined drug era to account for the overlap. If two exposures start at the same date, the overlapping period will be considered exposed to both.

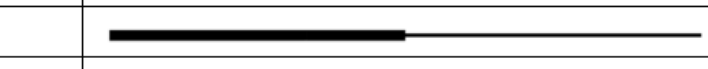
Overlap mode	Schematics	Dose overlap
"first"		d_1
"second"		d_2
"both"		$d_1 + d_2$
"maximum"		$\max(d_1, d_2)$

Figure 5. Gap era overlap mode.

The number of prescriptions, initial and cumulative dose of the index drug, as well as duration of use, will be provided per prespecified immunoglobulin brand as minimum, q25, median, q75, and maximum. For data sources where duration cannot be calculated, due to e.g., missing information on quantity or dosing, treatment duration will not be provided.

Objective 4

Characteristics of individuals will be assessed in predefined time windows around the date of the first recorded prescription of immunoglobulins (index date)during the study period. For primary care data sources, a washout period of 180 days will be applied. Characteristics will be described for each prespecified immunoglobulin brand by means of large-scale characterisation and prespecified patient-level characteristics based on OMOP CDM mapped data using the *CohortCharacteristics* (https://github.com/darwin-eu/CohortCharacteristics) and *DrugUtilisation* (https://github.com/darwin-eu/DrugUtilisation) R packages, developed by DARWIN EU®.

Characteristics of interest will be reported as counts and proportions for categorical variables and as minimum, q25, median, q75, and maximum for continuous variables. Demographic characteristics, including age and sex, will be assessed at the date of first recorded prescription of immunoglobulins (index date) during the study period. Characterisation of prespecified indications for use will be assessed any time prior to 7 days after the index date, 30 days prior to 7 days after the index date, and 7 days prior to 7 days after the index date. Large-scale characterisation of comorbidities prior to immunoglobulin treatment will be assessed 30 days prior to the index date, 1 year prior to the index date, and any time prior to the index date. Characterisation of prespecified common infections and prespecified antibiotics treatment among immunoglobulin initiators will be assessed up to 30 days post-index and up to 365 days post-index.

8.8.4. Output

Output will include the following:

A PDF report including an executive summary and the following tables and figures.

- Table 1. Mock table shell: Study attrition of individuals with a record of immunoglobulin prescription among the general study population, presented by data source (*objective 1*).

	CDW Bordeaux	IQVIA DA Germany	CPRD GOLD
Qualifying initial records			
Cohort start date between 1/1/2017 and 31/12/2024			

- Table 2. Mock table shell: Study attrition of individuals initiating immunoglobulin treatment among the general study population, presented by data source (*objectives 3–4*).

	CDW Bordeaux	IQVIA DA Germany	CPRD GOLD
Qualifying initial records			
Cohort start date between 1/1/2017 and 31/12/2024			
Immunoglobulin prescription			
Prior history requirement*	NA		
No immunoglobulin record in 180 days prior to study inclusion*	NA		
Potential 180 days of follow-up			

* = not required for hospital data sources

- Table 3. Mock table shell: Number of immunoglobulin prescriptions, treatment duration, and dose (initial, cumulative) of immunoglobulin use during the study period, per immunoglobulin brand, per data source.

Variable	Format	CDW Bordeaux	IQVIA DA Germany	CPRD GOLD
Number of subjects	N			
Number of records	N			
Immunoglobulin brand A				
Initial dose	Median [q25 – q75]			
	Mean			
	Min-max			
Cumulative dose	Median [q25 – q75]			
	Mean			
	Min-max			
Number of exposures	Median [q25 – q75]			
	Mean			
	Min-max			
Days exposed	Median [q25 – q75]			
	Mean			
	Min-max			
Immunoglobulin brand B/C/D, etc.				
Initial dose	Median [q25 – q75]			
	Mean			
	Min-max			
Cumulative dose	Median [q25 – q75]			

Variable	Format	CDW Bordeaux	IQVIA DA Germany	CPRD GOLD
	Mean			
	Min-max			
Number of exposures	Median [q25 – q75]			
	Mean			
	Min-max			
Days exposed	Median [q25 – q75]			
	Mean			
	Min-max			

- Table 4. Mock table shell: Demographic characteristics of individuals initiating immunoglobulin therapy at index date, per immunoglobulin brand, per data source.

Variable	Format	CDW Bordeaux	IQVIA DA Germany	CPRD GOLD
Immunoglobulin brand A				
Number of subjects	N			
Number of records	N			
Cohort start date*	Median			
Cohort end date*	Median			
Prior observation	Median [q25 – q75]			
Future observation	Median [q25 – q75]			
Age(years)	Median [q25 – q75]			
	Min-max			
Age group (years)				
• 1 to 18	N (%)			

Variable	Format	CDW Bordeaux	IQVIA DA Germany	CPRD GOLD
• 19 to 65	N (%)			
• >65	N (%)			
Sex				
• Male	N (%)			
• Female	N (%)			
Immunoglobulin brand B/C/D, etc.				
Number of subjects	N			
Number of records	N			
Cohort start date	Median			
Cohort end date	Median			
Prior observation	Median [q25 – q75]			
Future observation	Median [q25 – q75]			
Age (years)	Median [q25 – q75]			
	Min-max			
Age group (years)				
• 1 to 18	N (%)			
• 19 to 65	N (%)			
• >65	N (%)			
Sex				
• Male	N (%)			
• Female	N (%)			

* = Interquartile ranges for cohort start and end date can be found in the Shiny app.

- Table 5. Mock table shell: Indications of use of individuals initiating immunoglobulin therapy during the study period, per immunoglobulin brand, per data source.

	Any time prior to 7 days after index date [-inf, +7]			30 days prior to 7 days after the index date [-30, +7]			7 days prior to 7 days after the index date [-30, +7]		
	CDW Bordeaux	IQVIA DA Germany	CPRD GOLD	CDW Bordeaux	IQVIA DA Germany	CPRD GOLD	CDW Bordeaux	IQVIA DA Germany	CPRD GOLD
Indication of use	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Immunoglobulin brand A									
Primary immunodeficiency syndrome									
Secondary immunodeficiencies									
Neurology									
Haematology									
Infectious diseases									
Solid organ transplantation									
Internal medicine									
Dermatology									
Hepatology									
Other indications*									
Immunoglobulin brand B/C/D, etc.									
Primary immunodeficiency syndrome									
Secondary immunodeficiencies									

	Any time prior to 7 days after index date [-inf, +7]			30 days prior to 7 days after the index date [-30, +7]			7 days prior to 7 days after the index date [-30, +7]		
	CDW Bordeaux	IQVIA DA Germany	CPRD GOLD	CDW Bordeaux	IQVIA DA Germany	CPRD GOLD	CDW Bordeaux	IQVIA DA Germany	CPRD GOLD
Indication of use	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Neurology									
Haematology									
Infectious diseases									
Solid organ transplantation									
Internal medicine									
Dermatology									
Hepatology									
Other indications*									

* = Frequencies of 'Other indications' will be provided overall and separately for each indication, where available.

- Table 6. Mock table shell: Top 10 recorded conditions in individuals initiating immunoglobulin therapy, prior to the index date, per immunoglobulin brand, categorised by data source.

Any time prior to the index date [-inf, 0]						One year prior to the index date [-365, 0]						One month prior to the index date [-30, 0]					
CDW Bordeaux		IQVIA DA Germany		CPRD GOLD		CDW Bordeaux		IQVIA DA Germany		CPRD GOLD		CDW Bordeaux		IQVIA DA Germany		CPRD GOLD	
Condition	n (%)	Condition	n (%)	Condition	n (%)	Condition	n (%)	Condition	n (%)	Condition	n (%)	Condition	n (%)	Condition	n (%)	Condition	n (%)
Immunoglobulin brand A																	
Condition 1																	
Condition 2																	
Condition 3																	
Condition 4																	
Condition 5																	
Condition 6																	
Condition 7																	
Condition 8																	
Condition 9																	
Condition 10																	
Immunoglobulin brand B/C/D, etc.																	
Condition 1																	
Condition 2																	
Condition 3																	
Condition 4																	
Condition 5																	

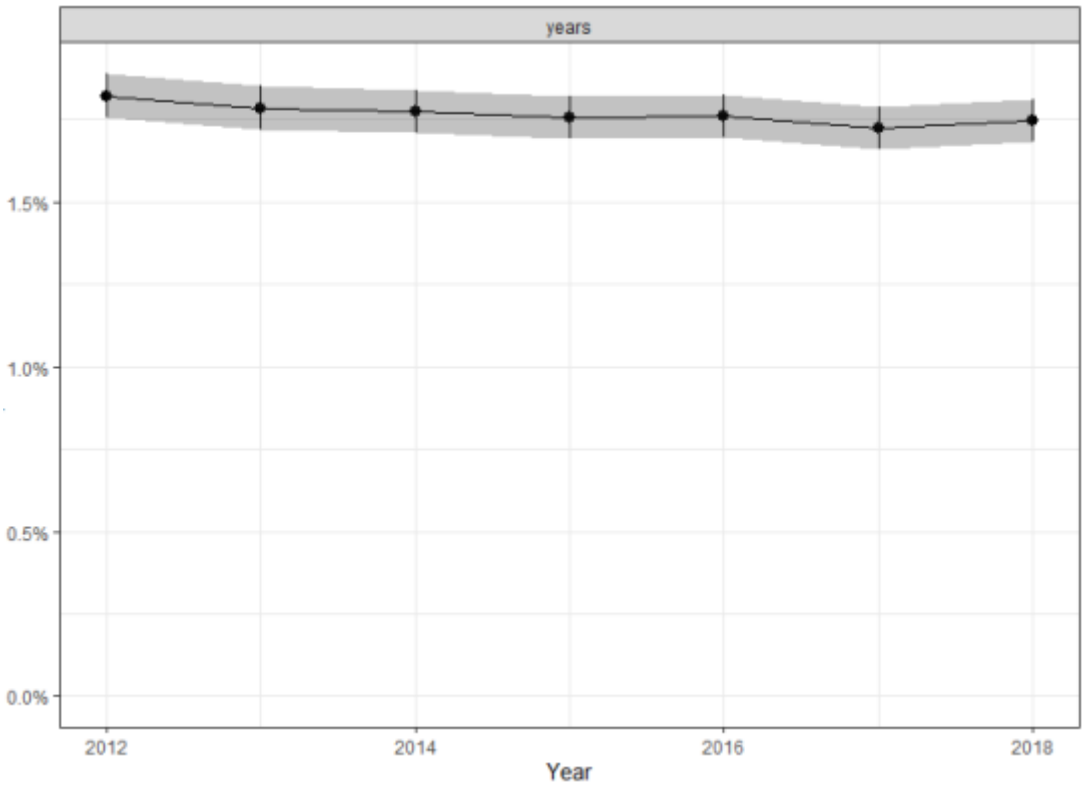
Any time prior to the index date [-inf, 0]						One year prior to the index date [-365, 0]						One month prior to the index date [-30, 0]					
CDW Bordeaux		IQVIA DA Germany		CPRD GOLD		CDW Bordeaux		IQVIA DA Germany		CPRD GOLD		CDW Bordeaux		IQVIA DA Germany		CPRD GOLD	
Condition	n (%)	Condition	n (%)	Condition	n (%)	Condition	n (%)	Condition	n (%)	Condition	n (%)	Condition	n (%)	Condition	n (%)	Condition	n (%)
Condition 6																	
Condition 7																	
Condition 8																	
Condition 9																	
Condition 10																	

- Table 7. Mock table shell: Common infections among individuals who initiated immunoglobulin therapy during the study period, provided per immunoglobulin brand, per data source.

Indication of use	CDW Bordeaux		IQVIA DA Germany		CPRD GOLD	
	[0, +30] n (%)	[0, +365] n (%)	[0, +30] n (%)	[0, +365] n (%)	[0, +30] n (%)	[0, +365] n (%)
Immunoglobulin brand A						
Pre-specified infection A						
Pre-specified infection B						
Pre-specified infection C/D/E, etc.						
Immunoglobulin brand B/C/D, etc.						
Pre-specified infection A						
Pre-specified infection B						
Pre-specified infection C/D/E, etc.						

- Table 8. Mock table shell: The frequency of antibiotics prescribed among individuals initiating immunoglobulin therapy during the study period, provided per immunoglobulin brand, per data source.

Indication of use	CDW Bordeaux		IQVIA DA Germany		CPRD GOLD	
	[0, +30] n (%)	[0, +365] n (%)	[0, +30] n (%)	[0, +365] n (%)	[0, +30] n (%)	[0, +365] n (%)
Immunoglobulin brand A						
Pre-specified antibiotic A						
Pre-specified antibiotic B						
Pre-specified antibiotic C/D/E, etc.						
Immunoglobulin brand B/C/D, etc.						
Pre-specified antibiotic A						
Pre-specified antibiotic B						
Pre-specified antibiotic C/D/E, etc.						



- Mock figure: Annual prevalence of immunoglobulin use, overall and stratified by ingredient, per data source.

In addition to the mock figure above, the following figures will also be provided:

- 'Annual prevalence of immunoglobulin use, stratified by ingredient and route of administration, per data source'
- Annual prevalence of immunoglobulin use, stratified by ingredient and sex, per data source'
- 'Annual prevalence of immunoglobulin use, stratified by ingredient and age group, per data source'
- 'Quarterly prevalence of immunoglobulin brands, per data source'

An interactive dashboard will be generated by incorporating all the results (tables and figures) included in the PDF report mentioned above.

8.9. Evidence synthesis

Results from analyses described in **Section 8.8** will be presented separately for each data source. No meta-analysis of results will be conducted.

9. STRENGTHS AND LIMITATIONS

Strengths

This study leverages several real-world data sources from three European countries, including France, Germany, and the United Kingdom, covering primary care and hospital care data sources. These data sources enable a comprehensive assessment of immunoglobulin use and patient characteristics across varied healthcare settings. Use of the OMOP CDM ensures standardised data structuring, harmonised variables, and consistent cohort definitions across sources. This facilitates reproducible analyses and enables robust characterisation of demographic and clinical profiles of individuals initiating immunoglobulin treatment and trends of immunoglobulin use during the study period.

Limitations

The study will be informed by routinely collected healthcare data, which introduces several important considerations that may influence the interpretation of the findings.

The study will include data from three European countries. As such, the results reflect only the populations captured within these data sources and may not be generalisable to other countries or healthcare systems.

Electronic health records are primarily designed for clinical purposes rather than research, and as such, may contain incomplete, inconsistent, or variably recorded information. Therefore, the documentation of comorbidities, necessary for patient-level characterisation, may vary across data sources. The actual clinical indication for prescribing immunoglobulins is not directly recorded in the data sources. Instead, proxy measures based on diagnosis codes around the time of the first treatment during the study period are used. Consequently, the estimation of potential indications may be incomplete or imprecise as this might not be recorded in all patients. To minimise incompleteness, different time windows around the immunoglobulin prescription date will be applied to assess the indication of use.

Additionally, a recorded prescription does not guarantee that the medication was dispensed or consumed, therefore assumptions of actual use have been made. Furthermore, the type of health care setting may affect the prevalence of prescriptions of specific immunoglobulin types, e.g., intravenous immunoglobulins are predominantly administered in a hospital setting and not in primary care. The general study population which will be included to estimate the prevalence of immunoglobulin use may also be affected by the type of health care setting and the definition of the observation period by each data source. Primary care data sources generally encompass a broader cohort of individuals, observed from registration until deregistration (CPRD GOLD) or from first to last recorded event (IQVIA DA Germany), while the hospital data source (CDW Bordeaux) comprises individuals requiring inpatient care which are observed from their first to last visit.

To ensure comprehensive characterisation of all incident individuals, a minimum of 180 days of prior data availability is required for primary care data sources. This criterion may reduce the study size and will not be applied for hospital-based settings, where patients typically seek care for acute or specialised conditions and might, as a result, not have a long duration of longitudinal registration, as would be expected in a primary care setting data sources. Consequently, for CDW Bordeaux, it is uncertain whether included individuals are true incident users. Moreover, only a subset of included patients from hospital-based settings may contribute to time windows prior to the index date. The prior observation requirement may also imply selection bias favouring chronic indications, i.e., data in some pathological conditions may be limited or absent.

Of note, certain brands of interest cannot be assessed in the current study due to limitations, such as market authorisation occurring after the study period or the unavailability of an RxNorm code for those specific brands.

10. REFERENCES

1. Forshee, R., et al., *CBER Surveillance Program Biologics Effectiveness and Safety (BEST) Initiative.* 2022.
2. Albin, S. and C. Cunningham-Rundles, *An update on the use of immunoglobulin for the treatment of immunodeficiency disorders.* Immunotherapy, 2014. **6**(10): p. 1113-26.
3. Riera-Arnau, J., et al., *Use of non-specific immunoglobulins in Catalonia in three third-level hospitals: a descriptive analysis of a hospital-prescribed medication registry.* Front Pharmacol, 2024. **15**: p. 1420682.
4. Furst, D.E., *Serum immunoglobulins and risk of infection: how low can you go?* Semin Arthritis Rheum, 2009. **39**(1): p. 18-29.
5. FDA. *Immune Globulin Intravenous (IGIV) and/or Immune Globulin Subcutaneous (IGSC) Lots with Increased Reports of Allergic/Hypersensitivity Reactions*. 2025 28-10-2025 [cited 2025 29-10-2025]; Available from: https://www.fda.gov/vaccines-blood-biologics/immune-globulin-intravenous-igiv-andor-immune-globulin-subcutaneous-igsc-lots-increased-reports.

11. ANNEXES

ANNEX I. Description of data sources

DATA SOURCES DESCRIPTION

France: Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux)

#	Section	Description
1	Database Identification and country	CDW Bordeaux (Clinical Data Warehouse of Bordeaux University Hospital) Nouvelle-Aquitaine, France
2	Data partner information section	CHU DE BORDEAUX - DIRECTION GENERALE Gironde / Nouvelle-Aquitaine
3	Coverage and timespan	Data collection since 2005 Extent: Regional. It covers the population of Bordeaux metropolitan area, and possibly beyond, as the health care centre for referrals and expertise for the Nouvelle Aquitaine region. The database contains data from 2005 onwards.
4	Healthcare setting / type of data	Secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care, and claims data. The database currently captures information about patient demographics, visit details, conditions, procedures, drugs, measurements, and mortality.
5	Data collection process	Outpatient electronic health records, and Inpatient hospital electronic health records, and Inpatient hospital billing systems, and Biobank. The integrated data is extracted from the hospital production information system via a real-time research database. The data is then processed and quality controlled by a team dedicated to maintaining the database. Internal evaluations were carried out to ensure consistency between the research database and the patient bedside software.
6	General representativeness	This is the 6th largest metropolitan area in France, and CHUBX is the largest hospital in the region. More than 75% of the patients administered to Bordeaux university hospital reside in the Gironde departments, with almost 50% coming directly from the Bordeaux metropolitan area. The hospital also captures additional cases from Nouvelle-Aquitaine region.
7	Data content /source coding	Diagnosis source data is coded in ICD-10 terminology. Procedures are coded in CCAM (French terminology). Laboratory measurements are coded in local terminology and partially mapped to LOINC. Drugs are coded through a local terminology and then mapped to UCD (French terminology), as well as ATC codes.
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. We use the hospital's unique identifier to generate the patient identifier in OMOP. If two identities are merged at the hospital, the merge is taken into account in the CDW. An automatic (hourly) detection of suspected duplicated identities has been implemented at the hospital since 2020, with merging of duplicated identities by a specialised team. Identities since 2015 were processed retrospectively. Thus, the rate of identity duplication in the database is low, especially since 2015.
9	Quality control (database specific)	- The integrated data comes from the hospital production information system through a real-time replicated database. Consistency evaluations between the replicated database and the production system are performed by the technical team in charge of maintaining the replicated database. - In the same way, consistency checks are performed between the replicated database and the data integrated into the i2b2 CDW. In addition, dashboards enable monitoring the data integrated into the i2B2 CDW, in particular by controlling the amount of data available over time, and its evolution, according to the various data sources. - An internal evaluation was carried out to ensure the consistency between the data integrated

#	Section	Description
		into i2b2 and the data available in the software used at the patient's bedside. In addition, many use cases were performed on the i2b2 CDW, with return to the patient chart and comparison of the data integrated into i2b2 and the data available in the care file.
10	Linkage	Death certificates (without the cause of death).
11	Vital status	The database is linked to the French death registry.
12	Limitations	CDW Bordeaux is limited to events captured in the hospital setting and thus does not include patient events not treated by the hospital (e.g. rare cancers). Patient events that are not included in CDW Bordeaux are rare disease treatments or specialist events that occur outside of CHUBX.
13	Main references	Cossin S, Diouf S,Griffier R,Le Barrois d'Orgeval P,Diallo G,Jouhet V "Linkage of Hospital Records and Death Certificates by a Search Engine and Machine Learning." JAMIA open (2021): 33709061
14	Link to HMA-EMA catalogue and database webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111112 Website: https://www.chu-bordeaux.fr/

Germany: IQVIA Disease Analyzer Germany (IQVIA DA Germany)

#	Section	Description
1	Database Identification and country	IQVIA DA Germany (IQVIA Disease Analyzer Germany) Germany
2	Data partner information section	IQVIA
3	Coverage and timespan	Data collection since 1989 Extent: Nation-wide. GP and specialists in Germany using specific patient management software.
4	Healthcare setting / type of data	Primary care – gps, and primary care specialists (e.g. paediatricians). Diagnoses, medication, and procedures from an ambulatory setting. Medications are recorded as prescriptions of marketed products.
5	Data collection process	Outpatient electronic health records. By clinicians at healthcare contact.
6	General representativeness	No specific details on general representativeness given.
7	Data content /source coding	Prescription is on product code level (German PZN), ICD10, NFC, Local lab coding.
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. There can be patients registered under different ID numbers, because there is no linkage between different GPs.
9	Quality control (database specific)	Data is quality checked on plausibility.
10	Linkage	No.
11	Vital status	Death information is derived from medical events.
12	Limitations	No database-specific limitations documented. General limitations for the data type applicable.
13	Main references	No main reference provided.

#	Section	Description
14	Link to HMA-EMA catalogue and database webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/104282 Website: https://www.iqvia.com/

United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

#	Section	Description
1	Database Identification and country	CPRD GOLD (Clinical Practice Research Datalink GOLD) United Kingdom
2	Data partner information section	University of Oxford NDORMS
3	Coverage and timespan	Data collection since 1987 Extent: Nation-wide. CPRD GOLD consists of patients in contributing practices using Vision software. Historically this covered the whole of the UK, but the number of contributing practices in the England is dropping. In January 2025 only 3 practices from England were a part of CPRD GOLD, while historical patient data were from the whole of the UK, and will continue to be so. In the future, no practices from England will be present, only practices from Scotland, Wales, and Northern Ireland.
4	Healthcare setting / type of data	Primary care – gps, and primary care specialists (e.g. paediatricians), and secondary care – specialists (ambulatory or hospital outpatient care), and hospital inpatient care. CPRD GOLD data include patient demographics, biological measurements, clinical symptoms and diagnoses, referrals to specialist/hospital and their outcome, laboratory tests/results, and prescribed medications.
5	Data collection process	Outpatient electronic health records. Data is entered by clinicians into the EHR. Data is processed by CPRD and provides data releases for research.
6	General representativeness	CPRD GOLD has been assessed and found to be broadly representative of the UK general population in terms of age, gender, and ethnicity. In CPRD GOLD in January 2025 there were 2,730,707 current acceptable patients (i.e. registered at currently contributing practices that use Vision software, excluding transferred out, deceased patients, and those flagged by CPRD as not acceptable for clinical research for data quality issues). This equals to 4.07%, based on the UK population estimates of 67,026,300 from the Office of National Statistics (mid-2023). Current patients are only from Scotland, Wales, and Northern Ireland. Historically, GOLD does contain data from England as well.
7	Data content /source coding	Gemscript, Read, dm+d
8	Data Harmonization	The data has been mapped to the OMOP CDM v5.4 and the OMOP standard vocabularies (SNOMED, RxNorm, LOINC). The format, structural and semantic conformance has been verified upon onboarding into the DARWIN EU® data network. In GOLD, a patient can be registered under different ID numbers upon changing practice or re-registration. Researchers are not able to identify these patients, as the data are anonymised. However, GOLD covers less than 5% of the current UK GP practices and it is unlikely that an individual who does change GP practice ends up in another GP practice which uses the Vision software and accepts the CPRD data collection agreement. The very small number of duplicated IDs will have different observation periods and should not have an impact on the data analyses.
9	Quality control (database specific)	CPRD GOLD only includes practices whose data quality is assessed to be up-to-standard (uts). Each practice is associated to an uts date set when the data quality standards become satisfactory, and CPRD recommend using only longitudinal data starting from this uts date. Every time CPRD collect the EHR from a practice, checks are run for the data quality standards and if they are not adequate, the EHR is not accepted. When the data quality becomes acceptable again, CPRD updates the practice uts date. CPRD also check data quality standards at the patient

#	Section	Description
		level and associate each patient to a flag, reporting if its data is acceptable for clinical research. Only patients with acceptable data quality are included in the population to be mapped to CDM.
10	Linkage	CPRD GOLD can be linked to several sources, however our Oxford OMOP CDM is only linked to the CPRD GOLD Ethnicity Record and to the CPRD Townsend Deprivation Index at Practice Level
11	Vital status	Vital status is retrieved from the GP records. Population registry (ONS) data can be requested on a study-by-study basis and linked. This data only covers England and is planned to be mapped to OMOP in the future. The cause of death is not captured.
12	Limitations	The main limitation is due to the fact that CPRD GOLD is limited to GP records, and although it contains information on referrals and discharge letters, it may not fully capture specific hospital information. Events from hospital and specialist care are not covered.
13	Main references	Sanchez-Santos MT, Axson EL,Dedman D,Delmestri A "Data Resource Profile Update: CPRD GOLD." International journal of epidemiology (2025): 40499193
14	Link to HMA-EMA catalogue and database webpage	HMA-EMA Catalogue entry: https://catalogues.ema.europa.eu/data-source/1111113 Website: https://cprd.com

ANNEX II. Fitness for use assessment

Data source justification for inclusion and key characteristics

France: Clinical Data Warehouse of Bordeaux University Hospital (CDW Bordeaux)

CDW Bordeaux will be included in this study because it is a hospital data source that provides relevant information on the use of immunoglobulins in the general population.

Based on a preliminary feasibility assessment, the expected number of person counts for immunoglobulin use in CDW Bordeaux will be 10,900.

Moreover, data availability and follow-up in CDW Bordeaux is sufficient, as data availability starts in 2005, and the date of most recent data extraction is 09/2025, which aligns with the study period. The median follow-up of the first observation period is 247 days.

There are no study specific limitations present in CDW Bordeaux.

Lastly, IRB approval for CDW Bordeaux is estimated to take 1 to 2 weeks, which makes the execution of this study feasible within the current study timelines.

Germany: IQVIA Disease Analyzer Germany (IQVIA DA Germany)

IQVIA DA Germany will be included in this study because it is a primary care data source that provides relevant information on the use of immunoglobulins in the general population.

Based on a preliminary feasibility assessment, the expected number of person counts for immunoglobulin use in IQVIA DA Germany will be 47,500.

Moreover, data availability and follow-up in IQVIA DA Germany is sufficient, as data availability starts in 1989, and the date of most recent data extraction 12/2024, which aligns with the study period. The median follow-up of the first observation period is 116 days.

There are no study specific limitations present in IQVIA DA Germany.

Lastly, IQVIA DA Germany requires no IRB approval, which makes the execution of this study feasible within the current study timelines.

United Kingdom: Clinical Practice Research Datalink GOLD (CPRD GOLD)

CPRD GOLD will be included in this study because it is a primary care data source that provides relevant information on the use of immunoglobulins in the general population.

Based on a preliminary feasibility assessment, the expected number of person counts for immunoglobulin use in CPRD GOLD will be 73,600.

Moreover, data availability and follow-up in CPRD GOLD is sufficient, as data availability starts in 1987, and the date of most recent data extraction is 05/2025, which aligns with the study period. The median follow-up of the first observation period is 2,150 days.

There are no study specific limitations present in CPRD GOLD.

Lastly, CPRD GOLD has blanket approval, which makes the execution of this study feasible within the current study timelines.

Table S1. Fitness-for-use assessment of data sources.

Design elements	Operational definition	Data elements for valid capture	Criticality of the quality of the element, including justification where relevant	Suggested extensiveness assessment	Suggested assessment of other quality dimensions	Suggested substantiation by documentation
Study population	General study population (*obj. 1)*	N/A	N/A	N/A	N/A	N/A
	Population with an immunoglobulin prescription (*obj. 2–4*)	Prescription of immunoglobulin treatment (RxNorm code)	High	100% will have an immunoglobulin prescription, the expected number of persons counts for immunoglobulins in the data sources included in this study range from 10,900 (CDW Bordeaux) to 73,600 (CPRD GOLD).	100% of prescriptions have been mapped to RxNorm	N/A
Treatment/exposure	Immunoglobulin prescription	Prescription of immunoglobulin treatment (RxNorm code)	High	N/A (to be assessed on a research question basis)	N/A	N/A
Comparator group (not relevant)	N/A	N/A	N/A	N/A	N/A	N/A
Key outcomes per objective	Immunoglobulin prescription (*obj. 1*)	Prescription of prespecified immunoglobulin treatment (RxNorm code), including, if available, route of administration	Medium	Immunoglobulin prescriptions are included in all data sources. The expected number of persons counts for immunoglobulins in the data sources included in this study range from 10,900 (CDW Bordeaux) to 73,600 (CPRD GOLD).	N/A	N/A

Design elements	Operational definition	Data elements for valid capture	Criticality of the quality of the element, including justification where relevant	Suggested extensiveness assessment	Suggested assessment of other quality dimensions	Suggested substantiation by documentation
	Immunoglobulin prescription (*obj. 2*)	Prescription of prespecified immunoglobulin brands (RxNorm code)	Medium	N/A (to be assessed on a research question basis)	N/A	N/A
	Immunoglobulin prescription (*obj. 3*)	Prescription of prespecified immunoglobulin brands (RxNorm code), including treatment duration and dose	Medium	N/A (to be assessed on a research question basis)	N/A	N/A
	Demographic and clinical characteristics (*obj. 4*)	Concept IDs for sex, age, and various clinical characteristics	Medium	N/A (to be assessed on a research question basis)	N/A	N/A
Covariates (including confounders if relevant)	N/A	N/A	N/A	N/A	N/A	N/A
Follow-up time (if relevant)	N/A	N/A	N/A	N/A	N/A	N/A

CDW Bordeaux = Clinical Data Warehouse of Bordeaux University Hospital; CPRD GOLD = Clinical Practice Research Datalink GOLD

EMA Data Quality Framework for EU medicines regulation: application to Real-World Data for more information (https://www.ema.europa.eu/system/files/documents/other/data-quality-framework-eu-medicines-regulation-application-real-world-data_en.pdf).

ANNEX III. Operational and reporting considerations

DATA MANAGEMENT

Data management

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

The analytic code for this study will be written in R and will use standardised analytics wherever possible. Each data partner will execute the study code against their data source containing patient-level data and then return the results (csv files), 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.

Data storage and protection

For this study, participants from various EU member states will process personal data from individuals that is collected in national/regional electronic health record data sources. 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 data sources 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 EU® Remote Research Environment (RRE). These output files do not contain any data that allow identification of subjects included in the study. The RRE 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.

QUALITY CONTROL

Data source quality control

When defining cohorts for indications, a systematic search of possible codes for inclusion will be identified using the *CodelistGenerator* R package (https://github.com/darwin-eu/CodelistGenerator). This package allows the user to define a search strategy and will use this to query the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. In addition, the *CohortDiagnostics* (https://github.com/OHDSI/CohortDiagnostics) and *DrugExposureDiagnostics* (https://cran.r-project.org/web/packages/DrugExposureDiagnostics/index.html) R packages will be run, if needed, to assess the use of different codes across the data sources contributing to the study and identify any codes potentially omitted in error. The *DrugExposureDiagnostics* package evaluates ingredient-specific attributes and patterns in drug exposure records.

The study code will be based on DARWIN EU® R packages: *IncidencePrevalence* to estimate the prevalence of individuals with a recorded immunoglobulin prescription and *CohortCharacteristics* and *DrugUtilisation* to characterise the drug use and describe patient characteristics. These packages will include numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R package will be made publicly available via GitHub.

PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

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

ANNEX IV. Preliminary lists with concept definitions

List of conditions concepts definition is provided in the table below:

Table S2. Preliminary list of condition definitions.

Phenotype	Concept name	Concept id (including descendants)	Exclude concept id	Vocabulary
Haematology	Immune thrombocytopenia	4103532	No	SNOMED
Haematology	Acquired von Willebrand disease	4125641	No	SNOMED
Haematology	Neonatal alloimmune thrombocytopenia	4345345	No	SNOMED
Hepatology	Viral hepatitis, type A	4223947	No	SNOMED
Infectious diseases	Measles	4030555	No	SNOMED
Infectious diseases	Exposure to Measles virus	40479413	No	SNOMED
Internal medicine	Acute febrile mucocutaneous lymph node syndrome	314381	No	SNOMED
Internal medicine	Idiopathic inflammatory myopathy	45765443	No	SNOMED
Internal medicine	Dermatomyositis	80182	No	SNOMED
Internal medicine	Antineutrophil cytoplasmic antibody positive vasculitis	42535714	No	SNOMED
Internal medicine	Systemic lupus erythematosus	257628	No	SNOMED
Neurology	Guillain-Barre syndrome	4164770	No	SNOMED
Neurology	Chronic inflammatory demyelinating polyradiculoneuropathy	381009	No	SNOMED
Neurology	Motor neuropathy with multiple conduction block	4046338	No	SNOMED
Neurology	Myasthenia gravis	76685	No	SNOMED
Neurology	Stiff-person syndrome	379008	No	SNOMED
Neurology	Eaton-Lambert syndrome	4237155	No	SNOMED
Other indications*	Malignant melanoma of skin	141232	No	SNOMED
Other indications*	Malignant neoplastic disease	443392	No	SNOMED
Other indications*	Neoplasm of hematopoietic cell type	4189640	No	SNOMED
Other indications*	Malignant neoplasm of skin	4155297	Yes	SNOMED
Other indications*	Carcinoma in situ	433435	Yes	SNOMED
Other indications*	Paraneoplastic encephalitis	4312671	No	SNOMED
Other indications*	Autoimmune encephalitis	4318558	No	SNOMED
Other indications*	Epilepsy	380378	No	SNOMED
Other indications*	Seizure disorder	4029498	No	SNOMED
Other indications*	Progressive systemic sclerosis	40485046	No	SNOMED
Other indications*	Sjogren’s syndrome	254443	No	SNOMED
Other indications*	COVID-19	37311061	No	SNOMED
Other indications*	Alzheimer's disease	378419	No	SNOMED

Phenotype	Concept name	Concept id (including descendants)	Exclude concept id	Vocabulary
Primary immunodeficiency syndrome	Primary immune deficiency disorder	4239314	No	SNOMED
Primary immunodeficiency syndrome	Congenital immunodeficiency disease	4263109	No	SNOMED
Primary immunodeficiency syndrome	Lymphocyte function antigen-1 defect	4098626	No	SNOMED
Primary immunodeficiency syndrome	Transient hypogammaglobulinemia of infancy	4230184	No	SNOMED
Secondary immunodeficiencies	Secondary immune deficiency disorder	4140977	No	SNOMED
Secondary immunodeficiencies	Adult-onset immunodeficiency	42536602	No	SNOMED
Transplantation	Solid organ transplant to recipient	4208341	No	SNOMED
Transplantation	Transplantation of bone marrow	4028623	No	SNOMED
Systemic infections	Sepsis caused by Gram negative bacteria	40493038	No	SNOMED
Systemic infections	Bacteraemia	132736	No	SNOMED
Bacterial infections	Bacterial infectious disease	432545	No	SNOMED
Central nervous system infections	Meningitis	435785	No	SNOMED
Fungal infections	Opportunistic mycosis	432248	No	SNOMED
Fungal infections	Invasive fungal infection	36717290	No	SNOMED
Gastrointestinal & intra-abdominal infections	Peritonitis	196152	No	SNOMED
Gastrointestinal & intra-abdominal infections	Gastrointestinal infection	37396146	No	SNOMED
Gastrointestinal & intra-abdominal infections	Acute diarrhea	4261727	No	SNOMED
Respiratory & ear, nose, throat, ocular infections	Sinusitis	4283893	No	SNOMED
Respiratory & ear, nose, throat, ocular infections	Respiratory tract infection	4170143	No	SNOMED
Respiratory & ear, nose, throat, ocular infections	Otitis	4183452	No	SNOMED
Respiratory & ear, nose, throat, ocular infections	Conjunctivitis	379019	No	SNOMED
Respiratory & ear, nose, throat, ocular infections	Bronchitis	256451	No	SNOMED
Urinary infections	Urinary tract infectious disease	81902	No	SNOMED
Viral infections	Herpesvirus infection	435463	No	SNOMED
Viral infections	Disease caused by Picornaviridae	4022207	No	SNOMED

* = Prespecified indications of use classified as 'Other indications' will be assessed overall and separately for each indication, where available, as specified in **section 8.6.3**.

List of medicines concepts definition is provided in the table below:

Table S3. Preliminary list of immunoglobulin and antibiotic ingredient definitions.

Substance Name	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
respiratory syncytial virus immune globulin intravenous	respiratory syncytial virus immune globulin intravenous	Immunoglobulins	J06B	19013765	Yes
immunoglobulin G	immunoglobulin G	Immunoglobulins	J06BA	19117912	Yes
freeze-dried pepsin-treated human normal immunoglobulin	freeze-dried pepsin-treated human normal immunoglobulin	Immunoglobulins	J06BA	35197905	Yes
ph4-treated acidic human normal immunoglobulin	ph4-treated acidic human normal immunoglobulin	Immunoglobulins	J06BA	35197913	Yes
ph4-treated acidic human normal immunoglobulin(for s.c. injection)	ph4-treated acidic human normal immunoglobulin(for s.c. injection)	Immunoglobulins	J06BA	35197969	Yes
polyethylene glycol-treated human normal immunoglobulin	polyethylene glycol-treated human normal immunoglobulin	Immunoglobulins	J06BA	35198039	Yes
freeze-dried ph4-treated human normal immunoglobulin	freeze-dried ph4-treated human normal immunoglobulin	Immunoglobulins	J06BA	35198103	Yes
freeze-dried sulfonated human normal immunoglobulin	freeze-dried sulfonated human normal immunoglobulin	Immunoglobulins	J06BA	35198193	Yes
freeze-dried polyethylene glycol-treated human normal immunoglobulin	freeze-dried polyethylene glycol-treated human normal immunoglobulin	Immunoglobulins	J06BA	35198206	Yes
immunoglobulin M, human	immunoglobulin M, human	Immunoglobulins	J06BA	42903696	Yes
immunoglobulin A	immunoglobulin A	Immunoglobulins	J06BA	43531966	Yes
Rho(D) immune globulin	Rho(D) immune globulin	Immunoglobulins	J06BB01	535714	Yes
tetanus immune globulin	tetanus immune globulin	Immunoglobulins	J06BB02	35604680	Yes
varicella-zoster immune globulin	varicella-zoster immune globulin	Immunoglobulins	J06BB03	543291	Yes
hepatitis B immune globulin	hepatitis B immune globulin	Immunoglobulins	J06BB04	501343	Yes
rabies immune globulin, human	rabies immune globulin, human	Immunoglobulins	J06BB05	19135830	Yes
Immunoglobulin Anti-Rubella	Immunoglobulin Anti-Rubella	Immunoglobulins	J06BB06	40798902	Yes
human vaccinia immune globulin	human vaccinia immune globulin	Immunoglobulins	J06BB07	19122168	Yes

Substance Name	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
staphylococcus epidermidis immunoserum rabbit	staphylococcus epidermidis immunoserum rabbit	Immunoglobulins	J06BB08	43013161	Yes
staphylococcus aureus immunoserum	staphylococcus aureus immunoserum	Immunoglobulins	J06BB08	43532492	Yes
cytomegalovirus immune globulin	cytomegalovirus immune globulin	Immunoglobulins	J06BB09	586491	Yes
diphtheria antitoxin	diphtheria antitoxin	Immunoglobulins	J06BB10	19031041	Yes
Hepatitis A immunoglobulin	hepatitis A immunoglobulin; systemic	Immunoglobulins	J06BB11	21601269	Yes
Immunoglobulin Anti-Tickborne Encephalitis	Immunoglobulin Anti-Tickborne Encephalitis	Immunoglobulins	J06BB12	40798903	Yes
pertussis immunoglobulin	pertussis immunoglobulin; systemic	Immunoglobulins	J06BB13	21601271	Yes
measles immunoglobulin	measles immunoglobulin; systemic	Immunoglobulins	J06BB14	21601272	Yes
Mumps immunoglobulin	mumps immunoglobulin; systemic	Immunoglobulins	J06BB15	21601273	Yes
anthrax immune globulin	anthrax immune globulin	Immunoglobulins	J06BB19	35605786	Yes
Bacillus anthracis immunoserum rabbit	Bacillus anthracis immunoserum rabbit	Immunoglobulins	J06BB19	42903978	Yes
Nebacumab	Nebacumab	Immunoglobulins	J06BC01	40798985	Yes
raxibacumab	raxibacumab	Immunoglobulins	J06BC02	43013193	Yes
bezlotoxumab	bezlotoxumab	Immunoglobulins	J06BC03	1718211	Yes
obiltoxaximab	obiltoxaximab	Immunoglobulins	J06BC04	35603994	Yes
palivizumab	palivizumab	Immunoglobulins	J06BD01	537647	Yes
MOTAVIZUMAB	MOTAVIZUMAB	Immunoglobulins	J06BD02	36851985	Yes
tixagevimab	tixagevimab	Immunoglobulins	J06BD03	702418	Yes
ansuvimab	ansuvimab	Immunoglobulins	J06BD04	739418	Yes
sotrovimab	sotrovimab	Immunoglobulins	J06BD05	1536976	Yes
REGDANVIMAB	REGDANVIMAB	Immunoglobulins	J06BD06	36858135	Yes
casirivimab	casirivimab	Immunoglobulins	J06BD07	37003288	Yes

Substance Name	Concept name	Class	ATC code	Ingredient Concept ID	Include descendants
nirsevimab	nirsevimab	Immunoglobulins	J06BD08	746155	Yes
Sipavibart	Sipavibart	Immunoglobulins	J06BD09	1253346	Yes
Tetracyclines	Tetracyclines	Antibiotics	J01A	21602797	Yes
Amphenicols	Amphenicols	Antibiotics	J01B	21602813	Yes
Beta-lactam antibacterials, penicillins	Beta-lactam antibacterials, penicillins	Antibiotics	J01C	21602818	Yes
Other beta-lactam antibacterials	Other beta-lactam antibacterials	Antibiotics	J01D	21602868	Yes
Sulfonamides and trimethoprim	Sulfonamides and trimethoprim	Antibiotics	J01E	21602929	Yes
Macrolides, lincosamides and streptogramins	Macrolides, lincosamides and streptogramins	Antibiotics	J01F	21602968	Yes
Aminoglycoside antibacterials	Aminoglycoside antibacterials	Antibiotics	J01G	21602990	Yes
Quinolone antibacterials	Quinolone antibacterials	Antibiotics	J01M	21603006	Yes
Other antibacterials	Other antibacterials	Antibiotics	J01X	21603041	Yes

List of immunoglobulins brands concepts definition is provided in the table below:

Table S4. Preliminary list of immunoglobulin brand definitions.

Brand Name	Concept name	Concept ID	Include descendants
Flebogamma DIF	Immunoglobulin G Injectable Solution [Flebogamma DIF]	35745366	Yes
Flebogamma DIF	Immunoglobulin G Injection [Flebogamma DIF]	21085351	Yes
Flebogamma DIF	Immunoglobulin G Prefilled Syringe [Flebogamma DIF]	36893531	Yes
Kiovig	Immunoglobulin G Injectable Solution [Kiovig]	41018997	Yes
Kiovig	Immunoglobulin G Prefilled Syringe [Kiovig]	36887597	Yes
Kiovig	Immunoglobulin G Injection [Kiovig]	21124428	Yes
Privigen	immunoglobulin G Injection [Privigen]	40220571	Yes
Privigen	Immunoglobulin G Injectable Solution [Privigen]	40726095	Yes
Privigen	Immunoglobulin G Intravenous Solution [Privigen]	36783517	Yes
Privigen	Immunoglobulin G Prefilled Syringe [Privigen]	36886637	Yes
Octagam (5% and 10%)	immunoglobulin G Injection [Octagam]	40220559	Yes
Octagam (5% and 10%)	Immunoglobulin G Injectable Solution [Octagam]	40726091	Yes
Octagam (5% and 10%)	Immunoglobulin G Prefilled Syringe [Octagam]	36889584	Yes

Brand Name	Concept name	Concept ID	Include descendants
Octagam (5% and 10%)	Immunoglobulin G Intravenous Solution [Octagam]	36783515	Yes
Yimmugo	immunoglobulin G Injection [Yimmugo]	1465644	Yes
Yimmugo	immunoglobulin G Injectable Solution [Yimmugo]	845238	Yes
Ig vena	Immunoglobulin G Injectable Solution [Ig Vena]	43659776	Yes
Intratect	Immunoglobulin G Injectable Solution [Intratect]	43785444	Yes
Intratect	Immunoglobulin G Prefilled Syringe [Intratect]	35757897	Yes
Intratect	Immunoglobulin G Injection [Intratect]	21134327	Yes
Iqymune	Immunoglobulin G Injection [Iqymune]	40726086	Yes
Iqymune	Immunoglobulin G Injectable Solution [Iqymune]	41018998	Yes
Panzyga/Globiga	immunoglobulin G Injection [Panzyga]	35201515	Yes
Panzyga/Globiga	Immunoglobulin G Injectable Solution [Panzyga]	36813729	Yes
Panzyga/Globiga	Immunoglobulin G Prefilled Syringe [Panzyga]	35412031	Yes
Panzyga/Globiga	Immunoglobulin G Injectable Solution [Panzyga]	40726088	Yes
Gamunex	immunoglobulin G Injection [Gamunex]	40220604	Yes
Gamunex	Immunoglobulin G Injectable Solution [Gamunex]	40726093	Yes
Gamunex	Immunoglobulin G Intravenous Solution [Gamunex]	36783516	Yes
Gamunex	Immunoglobulin G Prefilled Syringe [Gamunex]	35762066	Yes
Hizentra	Immunoglobulin G Injectable Solution [Hizentra]	40726090	Yes
Hizentra	immunoglobulin G Injection [Hizentra]	40220468	Yes
Hizentra	immunoglobulin G Prefilled Syringe [Hizentra]	37498237	Yes
Hizentra	ph4-treated acidic human normal immunoglobulin(for s.c.injection) Injectable Solution [Hizentra]	35152334	Yes
Hyqvia	Immunoglobulin G Injection [HyQvia]	35407336	Yes
Hyqvia	Immunoglobulin G Injectable Solution [HyQvia]	40988033	Yes
Hyqvia	Immunoglobulin G Prefilled Syringe [HyQvia]	35411221	Yes
Cuvitru	immunoglobulin G Injection [Cuvitru]	1718181	Yes
Cuvitru	Immunoglobulin G Injectable Solution [Cuvitru]	40726096	Yes
Cutaquig	immunoglobulin G Injection [Cutaquig]	789805	Yes
Cutaquig	immunoglobulin G Injectable Solution [Cutaquig]	36929633	Yes
Xembify	immunoglobulin G Injection [Xembify]	1361585	Yes
Xembify	immunoglobulin G Injectable Solution [Xembify]	845239	Yes
Gammagard	Immunoglobulin G Injectable Suspension [Gammagard]	41207103	Yes
Gammagard	immunoglobulin G Injection [Gammagard]	40220624	Yes
Gammagard	Immunoglobulin G Prefilled Syringe [Gammagard]	36891553	Yes
Gammagard	Immunoglobulin G Injectable Solution [Gammagard]	35749536	Yes
Gammagard	Immunoglobulin G Injectable Solution [Gammagard]	40726094	Yes

Brand Name	Concept name	Concept ID	Include descendants
Clairyg	Immunoglobulin G Injection [CLAIRYG]	35408919	Yes
Clairyg	Immunoglobulin G Injectable Solution [CLAIRYG]	43034816	Yes
Clairyg	Immunoglobulin G Prefilled Syringe [CLAIRYG]	43149994	Yes
Tegeline	Immunoglobulin G Injectable Solution [TEGELINE]	43034817	Yes
Tegeline	Immunoglobulin G Injection [TEGELINE]	35406781	Yes
Tegeline	Immunoglobulin G Prefilled Syringe [TEGELINE]	43172126	Yes
Pentaglobin	Immunoglobulin G Injectable Solution [Pentaglobin]	40721840	Yes
Pentaglobin	Immunoglobulin G Oral Solution [Pentaglobin]	43694274	Yes
Pentaglobin	human immunoglobulin Injectable Solution [Pentaglobin]	41207106	Yes
Pentaglobin	immunoglobulin M, human Injectable Solution [Pentaglobin]	42929914	Yes
Gammaplex	immunoglobulin G Injection [Gammaplex]	40220565	Yes
Gammaplex	Immunoglobulin G Injectable Solution [Gammaplex]	40726089	Yes
Nanogam/Optiglobin	Immunoglobulin G Injection [Nanogam]	36269625	Yes
Nanogam/Optiglobin	Immunoglobulin G Injectable Solution [Nanogam]	783868	Yes
Beriglobin	Immunoglobulin G Injectable Solution [Beriglobin]	43713448	Yes
Beriglobin	Immunoglobulin G Prefilled Syringe [Beriglobin]	41050285	Yes
Rhesonativ	Immunoglobulin G Injectable Solution [Rhesonativ]	40894536	Yes
Rhesonativ	Rho(D) Immune Globulin Injectable Solution [Rhesonativ]	43692085	Yes
Rhophylac	Immunoglobulin G Prefilled Syringe [Rhophylac]	41112997	Yes
Rhophylac	Rho(D) Immune Globulin Injectable Solution [Rhophylac]	35774715	Yes
Rhophylac	Rho(D) immune globulin Prefilled Syringe [Rhophylac]	40241802	Yes
Rhophylac	Rho(D) Immune Globulin Injection [Rhophylac]	43258523	Yes
Rhophylac	Rho(D) Immune Globulin Injectable Solution [Rhophylac 300]	43781959	Yes
Rhophylac	Rho(D) Immune Globulin Injectable Solution [Rhophylac 200]	43817962	Yes

ANNEX V. ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 4)

Study title: DARWIN EU® - Assessment of immunoglobulin use in clinical practice

EU PAS Register® number: EUPAS1000000823
Study reference number (if applicable): P4-C1-020

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]	☒	☐	☐	
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☒	5
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
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:

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

[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**
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.4
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
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	8.5
	4.2.2 Age and sex	☒	☐	☐	8.6
	4.2.3 Country of origin	☒	☐	☐	8.4
	4.2.4 Disease/indication	☒	☐	☐	8.6
	4.2.5 Duration of follow-up	☒	☐	☐	8.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.3

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.6.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	8.8
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)	☒	☐	☐	Annex I

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	Annex I
	9.1.3 Covariates and other characteristics?	☒	☐	☐	Annex I
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)	☒	☐	☐	Annex I
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	Annex I
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	Annex I
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Annex I
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	Annex I
	9.3.3 Covariates and other characteristics?	☒	☐	☐	Annex I
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

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

Comments:

Section 11: Data management and quality control		**Yes**	**No**	**N/A**	**Section Number**
11.1	Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	Annex III
11.2	Are methods of quality assurance described?	☒	☐	☐	Annex III
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?	☒	☐	☐	9
	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)	☒	☐	☐	Annex II

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?	☒	☐	☐	Annex II
13.2	Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	Annex II
13.3	Have data protection requirements been described?	☒	☐	☐	Annex II

Comments:

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

Comments:

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

Comments:

Name of the main author of the protocol: Ellen Gerritsen

Date: 21/11/2025

Signature: 

ANNEX VI. Glossary

Additional definitions are available in the EMA Glossary of terms https://www.ema.europa.eu/en/about-us/glossaries.

Aggregated Data

Data collected and combined from multiple sources to generate summary information, typically anonymised.

Benefit-Risk Assessment

Evaluation of the positive therapeutic effects of a medicine compared to its risks (e.g., side effects).

Common Data Model (CDM)

A standardized data structure that enables data from multiple sources to be harmonized, making analysis consistent and reproducible. DARWIN EU® utilises the OMOP CDM maintained by the OHDSI community.

Complex Studies (C3)

Studies requiring the development or customisation of specific study designs, protocols, and Statistical Analysis Plans (SAPs), with extensive collection or extraction of data. Examples include etiological studies measuring the strength and determinants of an association between an exposure and the occurrence of a health outcome in a defined population considering sources of bias, potential confounding factors, and effect modifiers.

Coordination Centre (CC)

The central hub responsible for managing and overseeing the activities within DARWIN EU®. It is based at Erasmus University Medical Centre in Rotterdam, the Netherlands.

Data Access

The process of obtaining permission to use specific datasets for regulatory or scientific studies.

Data Quality Framework

A set of standards and procedures to ensure accuracy, completeness, timeliness, and consistency of data used in DARWIN EU®.

Data Source

A data source or repository of structured health-related data, such as electronic health records (EHRs), insurance claims, or registries.

DARWIN EU®

The European Medicines Agency's (EMA) federated network of real-world data sources designed to generate evidence to support regulatory decision-making.

EMA (European Medicines Agency)

The regulatory body responsible for the evaluation and supervision of medicinal products in the EU, overseeing DARWIN EU®.

Evidence Generation

The process of analysing real-world data to produce scientific information that can inform healthcare or regulatory decisions.

Federated Network

A data infrastructure where data remain at their original location but can be analysed in a harmonised way across multiple partners using a common model and tools.

GDPR (General Data Protection Regulation)

The EU regulation governing the protection of personal data and privacy, crucial to how DARWIN EU® handles health data.

Health Technology Assessment (HTA)

A systematic evaluation of properties and impacts of health technology, often using DARWIN EU® data to support assessments.

Metadata

Descriptive information about a data source (e.g., its content, quality, and structure), essential for identifying relevant data sources in DARWIN EU® studies.

Off-the-Shelf Studies (OTS)

Studies for which a standard protocol per study/analysis type and standardised analytics may be developed and applied or adapted, typically relating to a descriptive research question. This includes studies on disease epidemiology, for example, the estimation of the prevalence or incidence of health outcomes in defined time periods and population groups, or drug utilisation studies at the population or patient level.

OHDSI (Observational Health Data Sciences and Informatics)

An open-science collaborative community that develops tools and standards (including the OMOP CDM) to enable large-scale analytics of observational health data. OHDSI provides the technical and scientific foundation for DARWIN EU®'s analytical ecosystem.

Patient-Level Data

Data related to individuals, de-identified, used for longitudinal or detailed analyses.

OMOP (Observational Medical Outcomes Partnership)

A common data model (CDM) that standardises the structure and content of observational healthcare data, enabling systematic analysis across disparate datasets. DARWIN EU® uses the OMOP CDM to ensure interoperability and consistency in real-world evidence generation.

Real-World Data (RWD)

Data relating to individual health status or healthcare delivery that is collected from routine clinical practice rather than from randomised controlled trials.

Real-World Evidence (RWE)

Clinical evidence derived from the analysis of RWD, used to inform decisions by regulators, payers, or clinicians.

Regulatory Decision-Making

The process by which authorities like EMA assess data to authorise, monitor, or modify the use of medicines in the EU.

Routine Repeated Studies (RR)

Studies that are either Off-the-Shelf or Complex studies repeated on a regular basis, following the same protocol and study code, but with updated data and/or different data partners.

Study Protocol

A detailed plan describing how a specific real-world study will be conducted, including objectives, design, data sources, and analyses.

Very Complex Studies (C4)

Studies which cannot rely only on electronic health care data sources, or which would require complex methodological work, for example, due to the occurrence of events that cannot be defined by existing diagnosis codes, including events that do not yet have a diagnosis code, where it may be necessary to combine a diagnosis code with other data such as results of laboratory investigations. These studies might require the collection of data prospectively, or the inclusion of new (not previously onboarded) data sources.