Study Protocol

P4-C1-002

DARWIN EU® - Descriptive study of tetanus immunoglobulin use and tetanus-prone wounds in Europe

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28/07/2025

Version 2.0

Public

CONTENTS

Study title	DARWIN EU® - Descriptive study of tetanus immunoglobulin use and tetanus-prone wounds in Europe
Protocol version identifier	V2.0
Date of last version of protocol	28/07/2025
EUPAS number	EUPAS1000000685
Active substance	• Tetanus antitoxin, WHO ATC code J06AA02 • Tetanus immunoglobulin, WHO ATC code J06BB02
Medicinal product	Not applicable
Research question and objectives	Research question What is the incidence and prevalence of tetanus immunoglobulins use and tetanus-prone wounds over time across Europe? Study objectives 1. To estimate incidence, prevalence, and treatment rate of tetanus immunoglobulins use in the general population, overall and stratified by calendar year. 2. To estimate incidence rate and prevalence of tetanus-prone wounds in the general population, overall and stratified by calendar year and type of wound.
Country(ies) of study	Spain, United Kingdom, Germany, Netherlands, Croatia
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LIST OF ABBREVIATIONS

Acronyms/term	Description
AEMPS	Spanish Agency of Medicines and Medical Devices
ATC	Anatomical Therapeutic Chemical classification system
BIFAP	Base de datos para la Investigación Farmacoepidemiológica en el Ámbito Público
CDM	Common Data Model
CM	Clinical Modification
CPRD GOLD	Clinical Practice Research Datalink GOLD
DARWIN EU®	Data Analysis and Real World Interrogation Network
DRE	Digital Research Environment
DOI	Declaration of interests
DQD	Data Quality Dashboard
DRE	Digital Research Environment
DUS	Drug Utilisation Study
ED	Emergency Department
EEA	European Economic Area
EHR	Electronic Health Records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EUDA	European Union Drug Agency
GP	General Practitioner
GDPR	General Data Protection Regulation
ICD	International Classification of Diseases
ICU	Intensive Care Unit
ID	Index date
IMASIS	Institut Municipal Assistència Sanitària Information System
InGef RDB	InGef Research Database
IP	Inpatient
IPCI	Integrated Primary Care Information
MA	Marketing Authorisation
NA	Not applicable
NAJS	Croatian National Public Health Information System
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OP	Outpatient
OT	Other

PAS	Post-Authorization Studies
PCP	Primary care physicians
RCT	Randomised Controlled Trial
SD	Standard deviation
SHI	Statutory Health Insurance provider
SNOMED	Systematized Nomenclature of Medicine
SNS	Spanish National Health Service
TIG	Tetanus immunoglobulin
WHO	World Health Organisation

1. TITLE

DARWIN EU® - Descriptive study of tetanus immunoglobulin use and tetanus-prone wounds in Europe

2. DESCRIPTION OF THE STUDY TEAM

Study team role	Names	Organisation
Principal Investigator	Ellen Gerritsen Dina Vojinovic	IQVIA
Data Scientist	Akram Mendez Isabella Kaczmarczyk	IQVIA
Study Manager	Natasha Yefimenko	Erasmus MC
Data Partner*	**Names**	**Organisation**
BIFAP	Ana LIorente-Garcia Miguel Angel Macia Martinez	Agencia Española de Medicamentos y Productos Sanitarios
CPRD GOLD	Hezekiah Omulo Mandickel Kamtengeni	University of Oxford
IMASIS	Juan Manuel Ramírez-Anguita Angela Leis Miguel-Angel Mayer	Consorci Mar Parc de Salut Barcelona
InGef RDB	Annika Vivirito Josephine Jacob Raeleesha Norris Alexander Harms	InGef - Institut für angewandte Gesundheitsforschung Berlin GmbH
IPCI	Katia Verhamme Marcel de Wilde Mees Mosseveld	Erasmus University Medical Center
NAJS	Ivan Pristaš Marko Čavlina Antea Jezidžić Jakov Vuković Anamaria Jurčević Karlo Pintarić	Croatian Institute for Public Health

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

3. ABSTRACT

Title

DARWIN EU® – Descriptive study of tetanus immunoglobulin use and tetanus-prone wounds in Europe

Rationale and background

Tetanus is a rare but serious neurological condition caused by a neurotoxin from *Clostridium tetani,* typically introduced through contaminated wounds. Although vaccine-preventable, tetanus remains a public health concern due to the irreversible nature of the toxin once it enters neurons. Post-exposure prophylaxis, including wound care, tetanus immunoglobulin (TIG), and a booster vaccination, is critical for individuals with tetanus-prone injuries, depending on immunisation status. In 2022, 53 cases were reported in the European Union (EU), underscoring the importance of timely and appropriate clinical intervention. This study aims to generate real-world evidence on TIG prescribing patterns and the epidemiology of tetanus-prone wounds across Europe to support regulatory decision-making and inform clinical practice.

Research question and objectives

Research question

What is the incidence and prevalence of tetanus immunoglobulins use and tetanus-prone wounds over time across Europe?

Study objectives

1. To estimate incidence, prevalence, and treatment rate of tetanus immunoglobulins use in the general population, overall and stratified by calendar year.
2. To estimate incidence rate and prevalence of tetanus-prone wounds in the general population, overall and stratified by calendar year and type of wound.

Methods

Study design

This retrospective cohort study at population level aims to describe the incidence, prevalence, and treatment rate of tetanus immunoglobulin use (*objective 1*), and the incidence and prevalence of tetanus-prone wounds (*objective 2*).

Study period

1st of January 2017 to 31st of December 2023 (or latest available data).

Population

Population-level drug utilisation analyses of TIG *(objective 1*) and population-level descriptive epidemiology of tetanus-prone wounds (*objective 2*) will include all individuals registered in the respective database between 1st of January 2017 and 31st of December 2023 (or latest date available). To estimate incidence rates, individuals must have at least 1 year of data visibility prior to becoming eligible for study inclusion. However, no such requirement will be applied for prevalence analyses and treatment rate. Children aged <1 year of age will be excluded. For the hospital databases included in the prevalence analysis and treatment rate, the study population will be defined by the hospital's catchment area.

Variables

Drugs of interest:

- Tetanus antitoxin, WHO ATC code J06AA02
- Tetanus immunoglobulin, WHO ATC code J06BB02

Condition of interest:

- Tetanus-prone wounds

Data source

1. Base de datos para la Investigación Farmacoepidemiológica en el Ámbito Público (BIFAP), Spain
2. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
3. Institut Municipal Assistència Sanitària Information System (IMASIS), Spain
4. InGef Research Database (InGef RDB), Germany
5. Integrated Primary Care Information (IPCI), Netherlands
6. Croatian National Public Health Information System (NAJS), Croatia

Sample size

No sample size has been calculated, as this is a descriptive study.

Statistical analysis

Population-level utilisation of TIG (objective 1): Overall and annual incidence rates (expressed as number of new users of TIG per 1,000 person-years) and overall and annual period prevalence (expressed as proportion of individuals with TIG records in the study population) will be estimated. In addition, the overall and annual treatment rate (expressed as proportion of total number of TIG records in the study population) will be estimated. IMASIS will only be included to estimate prevalence and treatment rate of TIG use, as the denominator for this data source will be based on the catchment area of the hospital. The statistical analyses will be performed based on OMOP CDM mapped data using "*IncidencePrevalence*" R package. The results will be reported per database.

Population-level descriptive epidemiology of tetanus-prone wounds (objective 2): Overall and annual incidence rates (expressed as number of individuals newly diagnosed with tetanus-prone wounds per 1,000 person-years) and overall and annual period prevalence (expressed as proportion of individuals with tetanus-prone wounds in the study population) will be estimated. IMASIS will only be included to estimate the prevalence of tetanus-prone wounds, as the denominator for this data source will be based on the catchment area of the hospital. The statistical analysis will be performed based on OMOP CDM mapped data using the "*IncidencePrevalence*" R package. The results will be reported per database. If the observed counts are sufficient, results will also be stratified per type of wound.

Meta-analyses by healthcare setting: Where applicable, meta-analysis will be conducted to pool incidence or prevalence estimates by healthcare setting (primary care, hospital care, registry), using the data from ≥2 databases per healthcare setting.

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

4. AMENDMENTS AND UPDATES

None.

5. MILESTONES

Study milestones and deliverables	Planned dates*
Final Study Protocol	17th July 2025
Creation of Analytical code	July/August 2025
Execution of Analytical Code on the data	September 2025
Draft Study Report	24th October 2025
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

Tetanus is a life-threatening neurological disorder (1). In 2022, there were 53 reported tetanus cases in the European Union (2). It is caused by a neurotoxin produced by *Clostridium tetani*, a spore forming bacterium commonly found in soil and animal faeces. Infections occur when spores enter the body via wounds, burns and bites, following injecting drug use, or during surgical procedures. Depending on the type of wound, the symptoms typically appear within a few days to several weeks after infection. Once in the body, the neurotoxin produced by the spores affects the nervous system, leading to muscle spasms and rigidity (3). Despite being vaccine-preventable (4), tetanus remains a public health concern due to the inability of antitoxin treatments to neutralise the toxin once it has entered neurons. Therefore, timely clinical management is essential (5). For individuals presenting with tetanus-prone wounds, post-exposure prophylaxis may include thorough wound cleansing, surgical debridement, and administration of tetanus immunoglobulin (TIG), depending on the individual's immunisation history. A reinforcing dose of a tetanus-containing vaccine may also be indicated (5, 6).

Understanding the real-world use of TIG and the occurrence of tetanus-prone wounds is essential for informing public health decisions and guiding appropriate clinical management strategies. This study aims to provide epidemiological evidence on the incidence and prevalence of TIG use and tetanus-prone wounds across Europe.

7. RESEARCH QUESTION AND OBJECTIVES

Research question

What is the incidence and prevalence of tetanus immunoglobulins use and tetanus-prone wounds over time across Europe?

Study objectives

1. To estimate incidence, prevalence, and treatment rate of tetanus immunoglobulins use in the general population, overall and stratified by calendar year.
2. To estimate incidence rate and prevalence of tetanus-prone wounds in the general population, overall and stratified by calendar year and type of wound.

Description of the proposed study objectives is shown in **Table 1**.

Table 1. Primary and secondary research questions and objective.

A. Study objective 1.

Objective:	To estimate incidence, prevalence, and treatment rate of tetanus immunoglobulins use in the general population, overall and stratified by calendar year.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	All individuals registered in the respective database between 1st of January 2017 and 31st of December 2023 (or latest date available). For estimation of incidence rates, individuals must have at least 1 year of data visibility prior to becoming eligible for study inclusion. However, no such requirement will be applied for prevalence and treatment rate analyses. Children aged <1 year of age will be excluded.
Exposure:	Not applicable
Comparator:	None
Outcome:	Tetanus immunoglobulins (TIG)
Time *(when follow up begins and ends):*	Follow-up, i.e. when an individual enters the denominator population, will start when study participants fulfil inclusion criteria. For incidence analyses, follow-up will start on the respective date of the latest of the following: 1) study start date (1st of January 2017) or 2) date at which individual has 1 year of prior history. For prevalence analyses, follow-up will start on the study start date (1st of January 2017). End of follow-up is defined as the earliest of the following: 1) end of study period (31st of December 2023), 2) end of data availability, 3) loss to follow up or 4) death, whichever came first. For estimation of incidence rates of outcome of interest, the first occurrence of the outcome of interest after follow-up will also be included as a censoring criterion.
Setting:	Primary care, registry, claims, inpatient and outpatient specialist care setting using data from 6 data sources: BIFAP (Spain), CPRD GOLD (UK), IMASIS (Spain), InGef RDB (Germany), IPCI (Netherlands), and NAJS (Croatia). IMASIS will only be included to estimate prevalence and treatment rate of TIG use.
Main measure of effect:	Number of new/incident records of TIG overall and stratified by database. Overall and annual incidence rates of TIG use (expressed as number of new users of TIG per 1,000 person-years), stratified by database. Overall and annual period prevalence of TIG use (expressed as proportion of individuals with a TIG record in the study population), stratified by database. Overall and annual treatment rate of TIG (expressed as proportion of total number of TIG records in the study population), stratified by database.

B. Study objective 2.

Objective:	To estimate incidence rate and prevalence of tetanus-prone wounds in the general population, overall and stratified by calendar year and type of wound.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	All individuals registered in the respective databases between 1st of January 2017 and 31st of December 2023 (or latest data available). For estimation of incidence rates, eligible individuals must have at least 1 year of data visibility prior to becoming eligible for study inclusion. However, no such requirement will be applied for prevalence analyses. Children <1 year of age will be excluded.

Exposure:	Not applicable
Comparator:	None
Outcome:	Tetanus-prone wounds
Time *(when follow up begins and ends):*	Follow-up, i.e. when an individual enters the denominator population, will start when study participants fulfil inclusion criteria. For incidence analyses, follow-up will start on the respective date of the latest of the following: 1) study start date (1st of January 2017) or 2) date at which individual has 1 year of prior history. For prevalence analyses, follow-up will start on the study start date (1st of January 2017). End of follow-up is defined as the earliest of the following: 1) end of study period (31st of December 2023), 2) end of data availability, 3) loss to follow up or 4) death, whichever came first. For estimation of incidence rates of outcome of interest, the first occurrence of the outcome of interest after follow-up will also be included as a censoring criterion.
Setting:	Primary care, registry, claims, inpatient and outpatient specialist care setting using data from 6 data sources: BIFAP (Spain), CPRD GOLD (UK), IMASIS (Spain), InGef RDB (Germany), IPCI (Netherlands), and NAJS (Croatia). IMASIS will only be included to estimate prevalence of tetanus-prone wounds.
Main measure of effect:	Number of new/incident tetanus-prone wounds overall and stratified by database and type of wound. Overall and annual incidence rates (expressed as number of individuals newly diagnosed with tetanus-prone wounds per 1,000 person-years), stratified by database and, if possible, type of wound. Overall and annual period prevalence of number of individuals diagnosed with tetanus-prone wounds (expressed as proportion of individuals with a tetanus-prone wound diagnosis in the study population), stratified by database and, if possible, type of wound.

8. RESEARCH METHODS

8.1 Study type and study design

A cohort study will be conducted using routinely collected health data from 6 data sources. The study will comprise a population-level cohort study (Population-level drug utilisation of TIG (*objective 1*) and a population-level descriptive epidemiology of tetanus-prone wounds (*objective 2*) among the general population).

8.2 Study setting and data sources

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

1. Base de datos para la Investigación Farmacoepidemiológica en el Ámbito Público (BIFAP), Spain
2. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom
3. Institut Municipal Assistència Sanitària Information System (IMASIS), Spain
4. InGef Research Database (InGef RDB), Germany
5. Integrated Primary Care Information (IPCI), Netherlands
6. Croatian National Public Health Information System (NAJS), Croatia

For this study, we have selected 6 data sources that were considered fit for purpose from the databases available in the DARWIN EU® Database Catalogue. The selection process was based on several key criteria. First of all, the number of records for TIG and for tetanus-prone wounds was assessed for each data source. Secondly, the geographical distribution of the data sources was considered to ensure a diverse and representative sample. Additionally, we selected databases which cover the relevant setting for the particular outcomes of interest (primary care, registry, claims, inpatient hospital care and outpatient hospital or specialist care setting). The experience gained from databases that had previously participated in similar DARWIN EU® studies was considered, leveraging their proven reliability and data quality.

Information on data source(s) planned to be used with a justification for their choice in terms of ability to capture the relevant data is described in **Table 2**.

When it came to assessing the reliability of data sources, the data partners were asked to describe their internal data quality process on the source data as part of the DARWIN EU® onboarding procedure. To further ensure data quality, we utilised the Achilles tool, which systematically characterises the data and presents it in a dashboard format that is inspected. The generated data characteristics such as age distribution, condition prevalence per year, data density, and measurement value distribution were compared against expectations for the data. Additionally, the data quality dashboard (DQD) provided more objective checks on plausibility consistently across the data sources. In terms of relevance, more general-purpose diagnostic tools, "*CohortDiagnostics"* (https://github.com/darwin-eu-dev/CohortDiagnostics) and "*DrugExposureDiagnostics"* (https://darwin-eu.github.io/DrugExposureDiagnostics/), were developed. The "*CohortDiagnostic"* R package evaluated phenotype algorithms for OMOP CDM datasets, offering a standard set of analytics for understanding patient capture including data generation. It provided additional insights into cohort characteristics, record counts and index event misclassification. The "*DrugExposureDiagnostics"* R package assessed ingredient specific diagnostics for drug exposure records. Furthermore, timeliness was guarded by extracting the release dates for each dataset in the network and monitoring when data were out-of-date with the expected refresh cycle (typically quarterly or half-yearly). In addition, it was important to have clear understanding of the time period covered by each released database, as this can vary across different domains. To facilitate this, the "*CdmOnboarding"* (and Achilles) packages contained a 'data density' plot. This plot displayed the number of records per OMOP domain on a monthly basis. This allowed getting insights when data collection started, when new sources of data were added, and until when data was included.

Table ***2***. Description of the selected data sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data	Number of active subjects	Data lock for the last update
Spain	BIFAP	Database covers a healthcare setting where prescriptions for TIG and diagnosis of tetanus-prone wounds may be recorded	Primary care, hospital inpatient care	EHR, claims, registries	16.9 million	27/12/2024
United Kingdom	CPRD GOLD	Database covers a healthcare setting where prescriptions for TIG and diagnosis of tetanus-prone wounds may be recorded	Primary care, hospital outpatient and inpatient care	EHR	2.83 million	15/03/2025
Spain	IMASIS	Database covers a healthcare setting where prescriptions for TIG and diagnosis of tetanus-prone wounds may be recorded	Outpatient and inpatient hospital care	EHR	0.10 million	04/03/2025
Germany	InGef RDB	Database covers a healthcare setting where prescriptions for TIG and diagnosis of tetanus-prone wounds may be recorded	Pharmacists, primary care, outpatient specialist care and inpatient hospital care	Claims	7.76 million	18/04/2025
Netherlands	IPCI	Database covers a healthcare setting where prescriptions for TIG and diagnosis of tetanus-prone wounds may be recorded	Primary care	EHR	1.33 million	16/04/2025
Croatia	NAJS	Database covers a healthcare setting where prescriptions for TIG and diagnosis of tetanus-prone wounds may be recorded	Primary care, outpatient specialist care and inpatient hospital care	EHR and registries	4.3 million	08/02/2025

BIFAP = Base de datos para la Investigación Farmacoepidemiológica en el Ámbito Público; CPRD GOLD = Clinical Practice Research Datalink GOLD; EHR = Electronic Health Record; IMASIS = Institut Municipal Assistència Sanitària Information System; InGef RBD = InGef Research Database; IPCI = Integrated Primary Care Information; NAJS = Croatian National Public Health Information System; TIG = tetanus immunoglobulin.

Base de datos para la Investigación Farmacoepidemiológica en el Ámbito Público (BIFAP), Spain

BIFAP (http://www.bifap.org/index_EN.html) is a longitudinal population-based data source of medical patient records of the Spanish National Health Service (SNS) from 9 participating Regions throughout Spain out of the 17 Spanish Regions. Population currently included represents 36% of the total Spanish population. Spain has a SNS that provides universal access to health services through the Regional Healthcare Services. Primary care physicians (PCPs), both general practitioners and paediatricians, have a central role. They act as gatekeepers of the system and also exchange information with other levels of care to ensure the continuity of care. Most (98.9%) of the population is registered with a PCP and, in addition, most drug prescriptions are written at the primary care level. BIFAP includes a collection of databases linked at individual patient level. The main one is the Primary care Database given the central role of PCPs in the SNS. Linked, there are additional important structural databases like the medicines dispensed at community pharmacies and the patients' hospital diagnosis at discharge. 7 out of the 9 regions have linkage to hospital data. However, hospital data is available for different time periods for each region. From 2014 onwards, linkage to hospital data is available for >68% of patients. Linkage to SARS-CoV-2 diagnostics test and COVID-19 vaccination registries are also included. Additional databases are also linked for a subset of patients (hospital pharmacy, cause of death registry). BIFAP program is a non-profit program financed by the Spanish Agency of Medicines and Medical Devices (AEMPS), a government agency belonging to the Ministry of Health in collaboration with the regional health authorities.

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

The Clinical Practice Research Datalink (CPRD) GOLD is a database of anonymised electronic health records (EHR) from General Practitioner (GP) clinics in the UK that use the Vision® software system for their management.(7) The source population encompasses 98% of the UK, registered with GPs responsible for non-emergency care and referrals. Participating GPs provide CPRD EHR for all registered patients who did not specifically request to opt out of data sharing. Covering 4.6% of the current UK population, GOLD includes 4.9% of contributing GP practices, providing comprehensive information within its defined source population. GOLD contains data from all four UK constituent countries, and the current regional distribution of its GP practices is 5.7% in England, 55.6% in Scotland, 28.4% in Wales, and 10.2% in Northern Ireland (May 2022).

GOLD data include patient's demographic, biological measurements, clinical symptoms and diagnoses, referrals to specialist/hospital and their outcome, laboratory tests/results, and prescribed medications. GPs receive information about patient contacts with secondary care, but this information must be manually entered into the patient record and therefore, may be incomplete. GOLD has been assessed and found broadly representative of the UK general population in terms of age, gender, and ethnicity.(7) GOLD has been widely used internationally for observational research to produce nearly 3,000 peer-reviewed publications, making GOLD the most influential UK clinical database so far.(8-10)

In terms of quality checks, the integrity, structure, and format of the data is reviewed. Collection-level validation ensures integrity by checking that data received from practices contain only expected data files and ensures that all data elements are of the correct type, length, and format. Duplicate records are identified and removed. Transformation-level validation checks for referential integrity between records ensure that there are no orphan records included in the database (for example, that all event records link to a patient), while research-quality-level validation covers the actual content of the data. CPRD provides a patient-level data quality metric in the form of a binary 'acceptability' flag. This is based on recording and internal consistency of key variables including date of birth, practice registration date and transfer out date.

Institut Municipal Assistència Sanitària Information System (IMASIS), Spain

The Institut Municipal Assistència Sanitària Information System (IMASIS) is the Electronic Health Record (EHR) system of Parc de Salut Mar Barcelona which is a complete healthcare services organisation.

Currently, this information system includes and shares the clinical information of two general hospitals (Hospital del Mar and Hospital de l'Esperança), one mental health care centre (Centre Dr. Emili Mira) and one social-healthcare centre (Centre Fòrum) including emergency room settings, which are offering specific and different services in the Barcelona city area (Spain). At present, IMASIS includes clinical information from around 1 million patients with at least one diagnosis and who have used the services of this healthcare system since 1990 and from different settings such as admissions, outpatients, emergency room and major ambulatory surgery. The diagnoses are coded using The International Classification of Diseases ICD-9-CM and ICD-10-CM. The average follow-up period per patient in years is 6.37 (SD±6.82).

InGef Research Database (InGef RDB), Germany

The InGef database comprises anonymized longitudinal claims data of about 10 million individuals across more than 50 statutory health insurance providers (SHIs) throughout Germany. Data are longitudinally linked over a period of currently ten years. Patients can be traced across health care sectors. All patient-level and provider-level data in the InGef research database are anonymised to comply with German data protection regulations and German federal law. German SHI claims data available in the InGef database includes information on demographics (year of birth, gender, death date if applicable, region of residence on administrative district level); hospitalizations; outpatient services (diagnoses, treatments; specialities of physicians); dispensing of drugs; dispensing of remedies and aids; and sick leave and sickness allowance times. In addition, costs or cost estimates from SHI perspective are available for all important cost elements. All diagnoses in Germany are coded using the International Classification of Diseases, version 10 in the German Modification (ICD-10-GM). The persistence (membership over time) is rather high in the InGef database: During a time period of 5 years (2009 to 2013), 70.6% of insurance members survived and remained insured with the same SHI without any gap in their observational time. Persons leaving one of the participating SHIs and entering another participating SHI, can be linked during yearly database consistency updates and are thus not lost over time. The InGef database is dynamic in nature, i.e. claims data are updated in an ongoing process and new SHIs may join or leave the database. By law, only the last 10 years of data are allowed to be used. At every new release this window shifts, dropping older data and adding new data.

Integrated Primary Care Information (IPCI), Netherlands

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

National Public Health Information System (NAJS), Croatia

The National Public Health Information System (Nacionalni javnozdravstveni informacijski sustav - NAJS) is an organised system of information services by the Croatian Institute of Public Health. This database was established in 1998, with nationwide coverage, representing approximately 5.4 million inhabitants. Settings covered include public primary, secondary/outpatient, and inpatient care. Data is retrieved primarily from EHR and holds information on demographics, inpatient and outpatient visits, conditions and procedures,

drugs (outpatient and inpatient prescriptions), measurements, and inpatient and outpatient dates of death. NAJS provides linkage between medical and public health data collected and stored in health registries and other health data collections, including cancer registry, mortality, work injuries, occupational diseases, communicable and non-communicable diseases, health events, disabilities, psychosis and suicide, diabetes, drug abuse and others. The CDM population comprises all publicly insured persons residing in Croatia starting in 2015. NAJS will provide data from 2017 onwards only, as prior data might include information on duplicated patients.

8.3 Study period

The study period will be from 1st of January 2017 until the earliest of 31st of December 2023 (please see **Table 2** for more details on the last update for each database).

8.4 Follow-up

Follow-up will start when study participants fulfil inclusion criteria. For incidence estimations, individuals must have available data records between 1st of January 2017 and 31st of December 2023, and at least 1 year of data visibility prior to becoming eligible for study inclusion. For prevalence and treatment rate estimations, individuals with available data records between 1st of January 2017 and 31st of December 2023 will be included. End of follow-up will be defined as earliest of 1) end of study period (31st of December 2023), 2) end of data availability, 3) loss to follow-up, or 4) death, whichever comes first. For estimation of incidence rates of outcomes of interest, the first occurrence of the outcome of interest after follow-up will also be included as a censoring criterion.

The operational definition of the index date and other primary time anchors are presented by means of **Table 3**.

Table ***3***. Operational definition of time 0 (index date) and other primary time anchors.

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care Setting [1]	Code Type[2]	Diagnosis position	Incident with respect to…	Measurement characteristics/validation	Source of algorithm
All participants from the respective data source eligible for the study – Incident use of TIG	Study entry date	Singly entry	Incident	[-365, -1]	IP, OP, OT	RxNorm	n/a	Prior use of TIG	n/a	n/a
All participants from the respective data source eligible for the study – Prevalent use of TIG	Study entry date	Single entry	Prevalent	n/a	IP, OP, OT	RxNorm	n/a	n/a	n/a	n/a
All participants from the respective data source eligible for the study – Treatment rate of TIG	Study entry date	Multiple entries	Prevalent	n/a	IP, OP, OT	RxNorm	n/a	n/a	n/a	n/a
All participants from the respective data source eligible for the study – Incident diagnosis of tetanus prone wounds	Study entry date	Single entry	Incident	[-180, -1]	IP, OP, OT	SNOMED	n/a	Prior diagnosis of tetanus-prone wounds	n/a	n/a
All participants from the respective data source eligible for the study – Prevalent diagnosis of tetanus prone wounds	Study entry date	Single entry	Prevalent	n/a	IP, OP, OT	SNOMED	n/a	n/a	n/a	n/a

TIG = tetanus immunoglobulin; [1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable.

Incidence, prevalence, and treatment rate all require an appropriate denominator population. For prevalence and treatment rate, individuals enter the denominator population on the respective date of the latest of the following: 1) study start date or 2) start of observation period. An example of entry and exit into the denominator population for incidence calculations is shown in **Figure 1**. In this example, person ID 1 has already sufficient prior history before the study start date, and the observation period ends after the study end date, so they will contribute during the complete study period. Person ID 2 and 4 enter the study only when they have sufficient prior history. Person ID 3 leaves when exiting the database (the end of observation period). Lastly, person ID 5 has two observation periods in the database. The first period contributes time from study start until end of observation period, the second starts contributing time again once sufficient prior history is reached and exits at study end date.

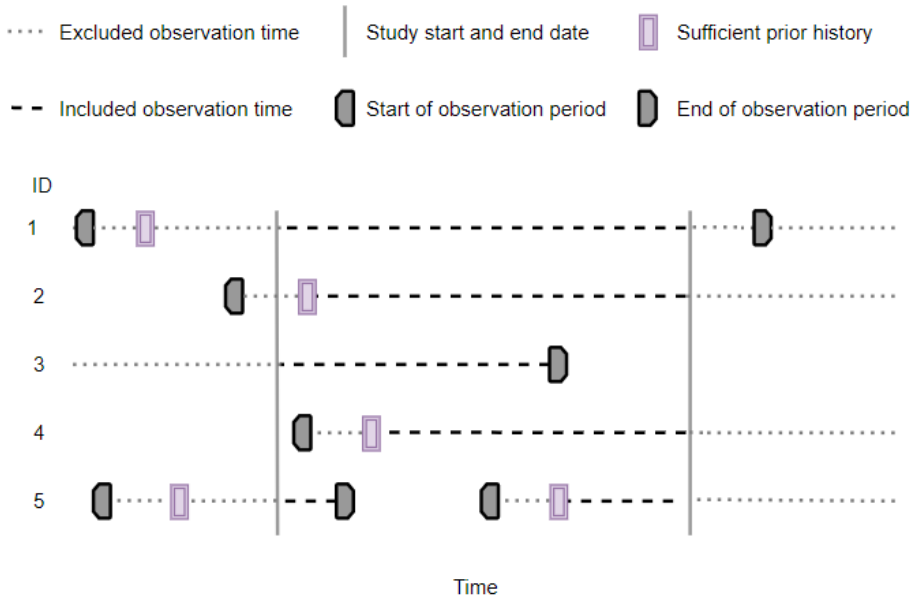

Figure 1. Included observation time for the denominator population of incidence calculations.

8.5 Study population with inclusion and exclusion criteria

The study population will include all individuals registered in the data source between the 1st of January 2017 and 31st of December 2023. For incidence calculations, individuals need to have at least 1 year of data visibility prior to becoming eligible for study inclusion. Additionally, for incidence calculations of TIG use, individuals should not have a record of TIG in the 365 days prior to study inclusion. For incidence calculations of tetanus-prone wounds, individuals should not have a diagnosis of tetanus-prone wounds in the 180 days prior to study inclusion. For prevalence and treatment rate calculations, no prior data visibility is required.

The operational definitions of inclusion criteria are presented by means of **Table 4.**

Table *4*. Operational definitions of inclusion criteria.

Criterion	Details	Order of application*	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Observational period in the data source during the period 01/01/2017-31/12/2023 (or the latest date available)	All individuals present in the data source in the period 2017-2023 (or the latest date available)	n/a	n/a	IP, OP, OT	n/a	n/a	All participants from the respective data source eligible for the study	n/a	n/a
Prior database history required for incidence calculations	Study participants will be required to have 365 days of prior history observed before contributing observation time for incidence calculations	Prior	[-365, 0]	IP, OP, OT	n/a	n/a	All participants from the respective data source eligible for the study	n/a	n/a
Washout period TIG required for incidence calculations	Study participants are required to have no record of TIG in the 365 days prior to contributing observation time for incidence calculations	After	[-365, -1]	IP, OP, OT	RxNorm	n/a	All participants from the respective data source eligible for the study initiating treatment with TIG	n/a	n/a
Washout period tetanus-prone wound required for incidence calculations	Study participants are required to have no record of tetanus-prone wounds in the 180 days prior to contributing observation time for incidence calculations	After	[-180, -1]	IP, OP, OT	SNOMED	n/a	All participants from the respective data source eligible for the study diagnosed with tetanus-prone wound	n/a	n/a

TIG = tetanus immunoglobulin; [1] IP = inpatient, OP = outpatient, ED = emergency department, OT = other, n/a = not applicable. [2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter). *Order of application specifies whether the eligibility criterion is applied before or after selection of the study entry date. For example, selecting “before” means that all possible study entry dates are identified, and then one or more is chosen. For instance, selecting 'after' means that the first possible study entry date is chosen, followed by the application of the inclusion and/or exclusion criteria. If the patient does not meet the criterion, then the patient drops out.

8.6 Variables

8.6.1 Exposure

Not applicable.

8.6.2 Outcomes

The outcome for *objective 1* is as follows:

- Use of TIG, defined as a recorded RxNorm prescription or SNOMED procedure code of TIG, among individuals meeting the inclusion criteria during the study period.

The outcome for *objective 2* is as follows:

- Occurrence of tetanus-prone wounds among individuals meeting the inclusion criteria during the study period, defined based on any of the following:
  - A SNOMED code for a tetanus-prone wound
  - A SNOMED code for a tetanus-prone wound in combination with a RxNorm prescription of systemic antibiotics (either IV or oral broad-spectrum) within ±7 days
  - A SNOMED code for a tetanus-prone wound in combination with a SNOMED code for pre-specified procedures within ±3 days

The preliminary concept sets used for the identification of the outcomes of interest are described in **Annex I**. The final code lists will be determined following input from EMA. The operational definition of the outcomes is presented in the **Table 5**.

8.6.3 Other covariates, including confounders, effect modifiers and other variables

Covariate for stratification in population-level utilisation of TIG will include:

- Calendar year

Covariates for stratification in population-level descriptive epidemiology of tetanus-prone wounds will include:

- Calendar year
- Type of wound: Overall, open fractures, bite wounds, penetrating wounds, wounds with foreign bodies, wounds with pyogenic infections, wound with excessive tissue damage, dirty wounds, replanted avulsed tooths, drug injections, burns, contusion, deep stab wounds, unknown

The operational definition of the covariates is described in **Table 6**. The preliminary list of concepts for the type of wounds is provided in **Annex I**.

Table ***5***. Operational definitions of outcome.

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations	Measurement characteristics/ validation	Source of algorithm
TIG – first incidence record during study period	Preliminary code lists provided in **Annex I**	Yes	Count	[-365, -1]	IP, OP, OT	RxNorm	n/a	All individuals present in data source during study period	n/a	n/a
TIG – prevalence and treatment rate	Preliminary code lists provided in **Annex I**	Yes	Count	n/a	IP, OP, OT	RxNorm	n/a	All individuals present in data source during study period	n/a	n/a
Tetanus-prone wounds –first incidence diagnosis during study period	Preliminary code lists provided in **Annex I**	Yes	Count	[-180, -1]	IP, OP, OT	SNOMED	n/a	All individuals present in data source during study period	n/a	n/a
Tetanus-prone wounds – prevalence and treatment rate	Preliminary code lists provided in **Annex I**	Yes	Count	n/a	IP, OP, OT	SNOMED	n/a	All individuals present in data source during study period	n/a	n/a

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

Table ***6***. Operational definitions of covariates.

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations	Measurement characteristics/ validation	Source for algorithm
Calendar year	Results will be stratified per calendar year	Categorical	0	IP, OP, OT	n/a	n/a	All study populations	n/a	n/a
Type of wound	Preliminary code lists provided in **Annex I**	Categorical	0	IP, OP, OT	SNOMED	n/a	All participants from the respective data source eligible for the study diagnosed with tetanus-prone wound	n/a	n/a

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

8.7 Study size

No formal sample size calculation was conducted for this descriptive study, as the objective is to describe the incidence, prevalence, and treatment rate of TIG records and tetanus-prone wounds among the general population, irrespective of sample size. Based on a preliminary feasibility assessment, the expected number of TIG person counts differs across data sources and ranges from 1,500 in IMASIS to 64,800 in NAJS. The expected number of person counts for tetanus-prone wounds varies by wound type.

8.8 Analysis

The type of analysis by study type is fixed, as can be observed in Table **7**.

Table ***7***. Description of study types and type of analysis.

Study type	Type of analysis
Population Level DUS	• Number of TIG records • Population-based incidence rates of TIG • Population-based prevalence of TIG prescriptions
Population-level descriptive epidemiology	• Number of tetanus-prone wounds • Incidence rates of tetanus-prone wounds • Prevalence of tetanus-prone wounds

8.8.1 Federated network analysis

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

The data partners locally execute the analytics against the OMOP CDM in R Studio, then review and approve the by default aggregated results before returning them to the Coordination Centre. Sometimes multiple execution iterations are performed, and additional fine tuning of the code base is needed. A service desk is available during the study execution for support.

8.8.2 Patient privacy protection

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

8.8.3 Statistical model specification and assumptions of the analytical approach considered

R-packages

The incidence, prevalence, and treatment rate of TIG records, and the incidence and prevalence of tetanus-prone wounds among the general population will be calculated based on OMOP CDM mapped data using the R package "*IncidencePrevalence*" R package, developed by DARWIN EU® (https://github.com/darwin-eu/IncidencePrevalence).

Number of TIG records and tetanus-prone wounds

The overall number of new TIG prescriptions and of new tetanus-prone wounds will be provided.

Incidence calculations of TIG use and tetanus-prone wounds

Overall and annual incidence rates of TIG use will be calculated as the number of new users of TIG per 1,000 person-years of the population at risk of getting exposed during the overall period and per calendar year. In addition, overall and annual incidence rates of tetanus-prone wounds will be calculated as the number of newly diagnosed individuals per 1,000 person-years of the population at risk of getting exposed during the overall period and per calendar year. For each patient, at least 1 year of data visibility will be required prior to an outcome of interest. For incidence calculations of TIG use, individuals should not have a TIG record in the year prior to study inclusion. For incidence calculations of tetanus-prone wounds, individuals should not have a tetanus-prone wound diagnosis in the 180 days prior to study inclusion. Those study participants who enter the denominator population will then contribute time-at-risk up to start of their new outcome of interest during the study period. Only the first prescription and wound diagnosis of a participant during the study period will contribute to the incidence rate, with participants' time contributions censored as soon as they experience the outcome of interest. Participants without the outcome of interest will contribute time-at-risk as described above. Time-at-risk of subjects who die will be censored at the time of death. Similarly, time-at-risk of subjects who are lost to follow-up will be censored at the time of loss to follow-up (last contact). Subjects with data until the end of the study period without experiencing the outcome of interest will be administratively censored at the end of the study period. Incidence rates will be given together with 95% Poisson confidence intervals.

An illustration of the calculation of incidence of selected pre-specified medication of interest is shown below in **Figure 2**. Patient ID 1 and 4 contribute time-at-risk up to their first event during the study period. Patient ID 2 and 5 are not seen to have the outcome of interest and so contribute time-at-risk but no incident outcomes. Meanwhile, patient ID 3 first contributes time-at-risk starting at the day when the washout period of a previous exposure, before study start, has ended, and ending when the next exposure of the outcome of interest is starting. Repeated events will not be taken into consideration, which means that time-at-risk after experiencing the outcome of interest during the study period will be excluded.

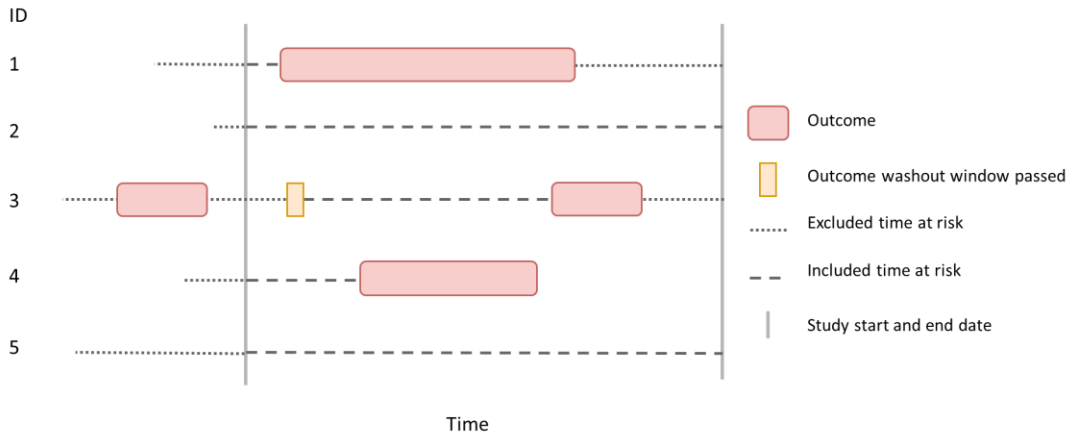

Figure 2. Incidence example

In the current study, the denominator counts for the hospital-based IMASIS database are derived from the hospital's catchment area, rather than from a well-defined population with known person-time-at-risk. Consequently, the person-time-at-risk of TIG use or tetanus-prone wounds diagnosis is unknown: for this reason IMASIS will be excluded from the incidence calculations.

Prevalence calculations of TIG use and tetanus-prone wounds

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

An illustration of the calculation of period prevalence is shown below in **Figure 3**. Between time t+2 and t+3, two of the five study participants experience the outcome of interest, giving a prevalence of 40%. Meanwhile, for the period t to t+1 all five also have some observation time during the year with one of the five study participants experiencing the outcome of interest, giving a prevalence of 20%.

The catchment area of hospital database IMASIS will be used as the denominator of this data source.

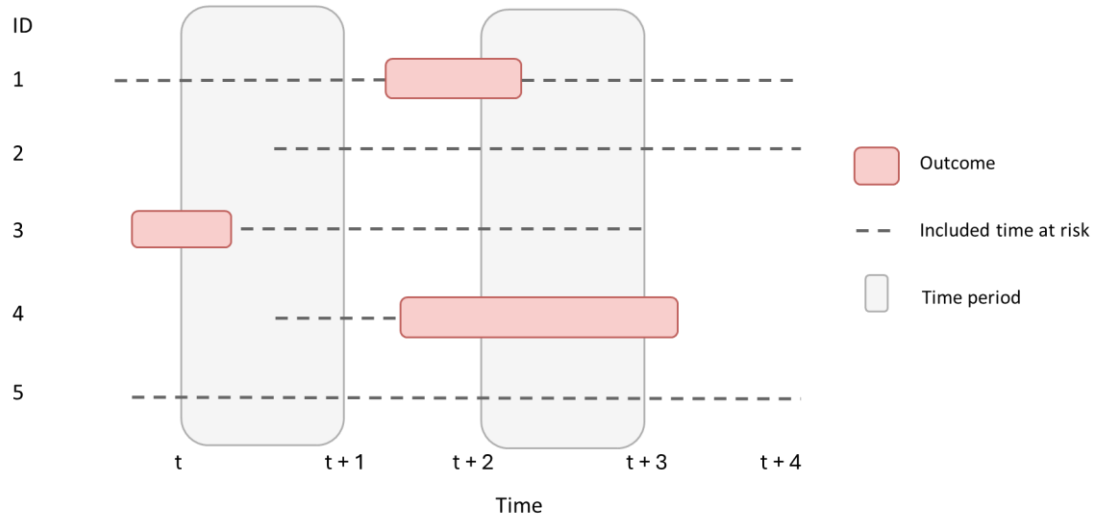

Figure 3. Prevalence example

Treatment rate calculations of TIG

Treatment rate will be calculated as overall and annual treatment rate, which summarises the total number of TIG records during a given period divided by the population at risk of getting exposed to TIG during that period. Multiple TIG records are allowed per individual. Therefore, treatment rate provides the proportion of all exposures during a specified interval.

The catchment area of hospital database IMASIS will be used as the denominator of this data source. An illustration of the calculation of treatment rate is shown below in **Figure 4**. Between time t+2 and t+3, there are two records of the outcome of interest among the five study participants who are at risk of the exposure, giving a treatment rate of 40%. Meanwhile, for the period t to t+1 there are three records of the outcome of interest among the five study participants who all have some observation time during the year, giving a treatment rate of 60%.

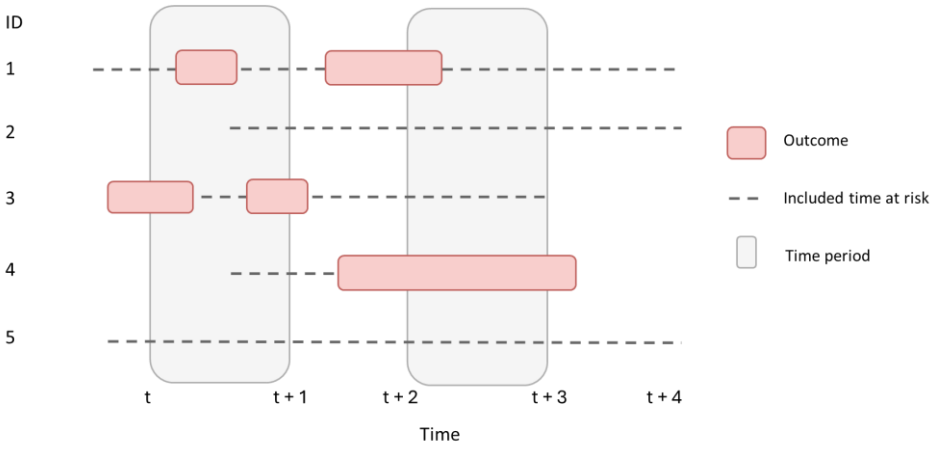

Figure 4. Treatment rate example

8.8.4 Methods to deal with missing data

For the drug utilisation studies we assume that the absence of a prescription record means that the person does not receive the respective drug. For indications, we assume that the missingness of a record of the respective condition means that the condition is not the indication for the drug prescription.

8.8.5 Sensitivity analysis

Not applicable.

8.9 Evidence synthesis

Results from analyses described in section 8.8 Analysis will be presented separately for each database. Additionally, a random-effect meta-analysis of pooling incidence or prevalence estimates of ≥2 databases per healthcare setting will be performed.

9. DATA MANAGEMENT

9.1 Data management

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

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

9.2 Data storage and protection

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

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

10. QUALITY CONTROL

General database quality control

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

Study specific quality control

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

The study code will be based on the "*IncidencePrevalence*" R package. This package will include numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R package will be made publicly available via GitHub.

11. LIMITATIONS OF THE RESEARCH METHODS

The study will be informed by routinely collected healthcare data, and it is important to consider several factors that may influence the interpretation of the results.

General limitations:

Data sources/setting: this study utilises data from six data sources: BIFAP, CPRD GOLD, IMASIS, InGef RDB, IPCI, and NAJS. The results derived from these databases may not be representative of prescriptions and diagnosis in other countries or databases. Variations in results are expected across different countries and healthcare settings. Additionally, discrepancies may arise due to differences in how observation periods are handled across data sources. For instance, some databases use the last interaction with the healthcare system to define the end of the observation period. As a result, infrequent users may have shorter follow-up periods, decreasing the time-at-risk (i.e., the denominator) for incidence rate calculations. This could lead to an overestimation of incidence rates in the final months of the study period, as users are fully captured by the end of the study. Furthermore, the healthcare setting might impact the incidence, prevalence, and treatment rate of tetanus-prone wound types. For instance, more serious wounds are

expected to be treated in a hospital setting, while less deep wounds can be treated in primary care. Therefore, non-hospital data sources could potentially not capture serious tetanus-prone wounds.

Drug prescriptions: a recorded prescription does not necessarily indicate that the patient actually took the drug. Therefore, assumptions of actual use are made.

Study-specific limitations:

Catchment area hospital database: in the current study, the denominator counts of the hospital based IMASIS database are based on the catchment area of the hospital. As a result, the person-time-at-risk of TIG use or tetanus-prone wounds diagnosis is unknown, meaning that the incidence cannot be calculated for this database. Consequently, data from IMASIS is only used to calculate prevalence in this study.

Phenotype of tetanus-prone wounds: there is no diagnostic code available for tetanus-prone wounds, and guidelines state that individual risk assessment is required for each wound. ICD or SNOMED codes often lack the granularity needed to distinguish tetanus-prone wounds from non-tetanus prone wounds. For example, general wound codes may not specify characteristics, such as contamination with soil or faeces, depth or tissue devitalization, or mechanism (e.g., crush, puncture, laceration). Additionally, there is a lack of unstructured data, which may contain essential information to classify wounds as tetanus prone. Without these, wound classification relies entirely on structured codes, limiting clinical nuance. This can lead to misclassification and under-identification of clinically relevant cases. Consequently, the incidence and prevalence of tetanus-prone wounds will likely be an underestimation of the actual incidence and prevalence.

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

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

13. GOVERNANCE BOARD ASPECTS

Some of the data sources require approval from their respective IRB board, except for data sources with a blanket approval which will not require any further specific approvals to undertake this study.

14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

14.1 Study report

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

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

15. REFERENCES

1. Seki M, Sugiyama M, Maeda T, Kasai F. Challenges in Rehabilitation of a Tetanus Patient With Severe Complications. Cureus. 2024;16(12):e76494.

2. ECDC. Tetanus. Annual epidemiological report for 2022. Stockholm; 2024.

3. Bleck TP. Tetanus: Pathophysiology, management, and prophylaxis. Disease-a-Month. 1991;37(9):551-603.

4. George EK, De Jesus O, Tobin EH, Vivekanandan R. Tetanus (Clostridium tetani Infection). StatPearls [Internet]: StatPearls Publishing; 2024.

5. Organization WH. The immunological basis for immunization series: module 3: tetanus. update 2018 ed. Geneva: World Health Organization; 2018.

6. Collins S, White J, Ramsay M, Amirthalingam G. The importance of tetanus risk assessment during wound management. IDCases. 2015;2(1):3-5.

7. Herrett E, Gallagher AM, Bhaskaran K, Forbes H, Mathur R, van Staa T, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). Int J Epidemiol. 2015;44(3):827-36.

8. Carey IM, Nirmalananthan N, Harris T, DeWilde S, Chaudhry UAR, Limb E, et al. Prevalence of co-morbidity and history of recent infection in patients with neuromuscular disease: A cross-sectional analysis of United Kingdom primary care data. PLoS One. 2023;18(3):e0282513.

9. Wigglesworth S, Neligan A, Dickson JM, Pullen A, Yelland E, Anjuman T, et al. The incidence and prevalence of epilepsy in the United Kingdom 2013-2018: A retrospective cohort study of UK primary care data. Seizure. 2023;105:37-42.

10. Fahmi A, Wong D, Walker L, Buchan I, Pirmohamed M, Sharma A, et al. Combinations of medicines in patients with polypharmacy aged 65-100 in primary care: Large variability in risks of adverse drug related and emergency hospital admissions. PLoS One. 2023;18(2):e0281466.

16. ANNEXES

Annex I: List of preliminary concept definitions

Preliminary list of concept definition for TIG

Concept id	Concept Code	Concept Name	Exclude	Descendants
35604680	1727875	tetanus immune globulin	-	Yes
4298489	384702009	Anti-tetanus immunoglobulin injection	-	Yes
36713286	572261000119106	Administration of human tetanus immune globulin	-	Yes

Preliminary list of concept definition for tetanus-prone wounds

Concept id	Concept Code	Concept Name	Exclude	Descendants
441737	125667009	Contusion	-	Yes
442013	125666000	Burn	-	Yes
4003509	109672001	Replanted avulsed tooth	-	Yes
4022680	226034001	Injecting drug user	-	Yes
4030849	238382001	Wound abscess	-	Yes
4046789	134222005	Penetrating wound	-	Yes
4053838	125670008	Foreign body	-	Yes
4096471	262557004	Deep wound	-	Yes
4096472	262560006	Penetrating wound	-	Yes
4096474	262565001	Deep avulsion wound	-	Yes
4141909	3404009	Bite wound	-	Yes
4151842	283682007	Bite - wound	-	Yes
4178756	52329006	Fracture, open	-	Yes
4183970	298010008	Wound dirty	-	Yes
4211967	57495003	Deep wound	-	Yes
4246696	397182009	Open crush injury	-	Yes
4264281	397181002	Open fracture	-	Yes
4297984	76844004	Local infection of wound	-	Yes
36715557	721267000	Pyogenic infection of skin and subcutaneous tissues caused by bacterium	-	Yes
42689793	1068391000000100	Injury whilst gardening	-	Yes
42689805	1068541000000100	Injury whilst working on farm	-	Yes
44806474	801711000000105	O/E - wound necrotic	-	Yes
4114305	299971005	Insect sting	Yes	Yes
4173025	276433004	Insect bite - wound	Yes	Yes

Preliminary list of concept definition for systemic antibiotics

Concept id	Concept Code	Concept Name	Exclude*	Descendants
46221507	1603834	avibactam	-	Yes
46274210	1040004	ceftaroline fosamil	-	Yes
45892599	1597609	ceftolozane	-	Yes
45774861	1539239	dalbavancin	-	Yes
45892419	1596450	gentamicin	-	Yes
45776147	1547611	oritavancin	-	Yes
45775686	1540825	tedizolid	-	Yes
43009082	OMOP4700508	cefbuperazone sodium	-	Yes
43009044	OMOP4700470	cefcapene pivoxil hydrochloride hydrate	-	Yes
43008993	OMOP4700419	cefminox sodium	-	Yes
43009045	OMOP4700471	cefpiramide sodium	-	Yes
43009083	OMOP4700509	cefroxadine	-	Yes
43008994	OMOP4700420	ceftezole sodium	-	Yes
43009087	OMOP4700513	flomoxef sodium	-	Yes
43009022	OMOP4700448	isepamicin sulfate	-	Yes
43009067	OMOP4700493	ribostamycin sulfate	-	Yes
43009009	OMOP4700435	sultamicillin	-	Yes
40798709	OMOP2721059	Cefacetrile	-	Yes
40798700	OMOP2721060	Cefazedone	-	Yes
40798704	OMOP2721061	Cefmenoxime	-	Yes
40798981	OMOP2721332	Nifurtoinol	-	Yes
40799027	OMOP2721386	Piromidic Acid	-	Yes
40799118	OMOP2721468	Sulfametoxydiazine	-	Yes
40799120	OMOP2721470	Sulfaperin	-	Yes
40799121	OMOP2721471	Sulfaphenazole	-	Yes
40166675	473837	telavancin	-	Yes
37498010	2265702	cefiderocol	-	Yes
37496518	2198944	lefamulin	-	Yes
36878831	OMOP1007304	nadifloxacin	-	Yes
35884386	OMOP5031290	Rufloxacin	-	Yes
35198192	OMOP4819557	aspoxicillin hydrate	-	Yes
35198093	OMOP4819458	biapenem	-	Yes
35197989	OMOP4819354	carumonam sodium	-	Yes
35197975	OMOP4819340	cefozopran hydrochloride	-	Yes
35198137	OMOP4819502	cefteram pivoxil	-	Yes
35200469	2055906	eravacycline	-	Yes

35198107	OMOP4819472	faropenem sodium hydrate	-	Yes
35197938	OMOP4819303	garenoxacin mesilate hydrate	-	Yes
35200953	2059269	omadacycline	-	Yes
35198003	OMOP4819368	pazufloxacin mesilate	-	Yes
35197897	OMOP4819262	prulifloxacin	-	Yes
35198144	OMOP4819509	rokitamycin	-	Yes
35200881	2059018	sarecycline	-	Yes
35198165	OMOP4819530	sitafloxacin hydrate	-	Yes
35198145	OMOP4819510	tebipenem pivoxil	-	Yes
19123877	626	amdinocillin	-	Yes
19088223	627	amdinocillin pivoxil	-	Yes
19101402	26397	arbekacin	-	Yes
19086759	2236	cephalothin	-	Yes
19086790	2238	cephapirin	-	Yes
19095043	2408	chlortetracycline	-	Yes
19123240	6084	josamycin	-	Yes
19092353	6513	lymecycline	-	Yes
19126622	7069	moxalactam	-	Yes
19129642	7798	oxolinic acid	-	Yes
19088795	33277	phenethicillin	-	Yes
19125201	66958	pristinamycin	-	Yes
19096054	34649	propicillin	-	Yes
19136024	9462	rolitetracycline	-	Yes
19136044	9806	sisomicin	-	Yes
19136210	10114	streptozocin	-	Yes
19136423	10175	sulfalene	-	Yes
19136426	10176	sulfamerazine	-	Yes
19136429	10178	sulfamethazine	-	Yes
19136481	10183	sulfamoxole	-	Yes
19136493	10188	sulfapyridine	-	Yes
19100438	37775	temocillin	-	Yes
19137362	10463	thiamphenicol	-	Yes
19102105	39823	xibornol	-	Yes
19018516	18609	azidocillin	-	Yes
19015123	1266	azlocillin	-	Yes
19018742	19727	brodimoprim	-	Yes
19070174	2178	cefamandole	-	Yes
19070680	2179	cefatrizine	-	Yes

19028241	20482	cefetamet	-	Yes
19072255	2182	cefmetazole	-	Yes
19028286	20485	cefodizime	-	Yes
19072857	2183	cefonicid	-	Yes
19028288	20486	ceforanide	-	Yes
19051271	2188	cefotiam	-	Yes
19001904	27130	cefpirome	-	Yes
19051345	2190	cefsulodin	-	Yes
19052683	2233	cephaloridine	-	Yes
19047240	21264	clofoctol	-	Yes
19047265	21272	clomocycline	-	Yes
19023508	3328	dibekacin	-	Yes
19050750	42322	fleroxacin	-	Yes
19054936	4448	floxacillin	-	Yes
19064329	25112	flumequine	-	Yes
19010400	113608	fusidate	-	Yes
19069006	26797	hetacillin	-	Yes
19008870	29256	mandelic acid	-	Yes
19003644	6812	methacycline	-	Yes
19072054	29629	methampicillin	-	Yes
19007701	6927	mezlocillin	-	Yes
19072122	30005	midecamycin	-	Yes
19009138	6985	miocamycin	-	Yes
19017585	7337	netilmicin	-	Yes
19015464	31901	nitroxoline	-	Yes
19023254	7629	oleandomycin	-	Yes
19024197	7701	ornidazole	-	Yes
19027679	7960	pefloxacin	-	Yes
19010564	113831	pipemidate	-	Yes
19047071	8372	pivampicillin	-	Yes
19036545	35797	rosoxacin	-	Yes
19063874	9478	roxithromycin	-	Yes
19000817	10168	sulbenicillin	-	Yes
19000818	10172	sulfadimethoxine	-	Yes
19000820	10181	sulfamethoxypyridazine	-	Yes
19040624	37328	sulfametrole	-	Yes
19002077	10322	talampicillin	-	Yes
19078399	57021	teicoplanin	-	Yes

19041153	37771	temafloxacin	-	Yes
19006043	10864	troleandomycin	-	Yes
1790868	641	amikacin	-	Yes
1768849	2176	cefaclor	-	Yes
1769535	2177	cefadroxil	-	Yes
1771162	2180	cefazolin	-	Yes
1796458	25037	cefdinir	-	Yes
1748975	20481	cefepime	-	Yes
1796435	25033	cefixime	-	Yes
1773402	2184	cefoperazone	-	Yes
1774470	2186	cefotaxime	-	Yes
1774932	2187	cefotetan	-	Yes
1775741	2189	cefoxitin	-	Yes
1749008	20489	cefpodoxime	-	Yes
1776684	2191	ceftazidime	-	Yes
1749083	20492	ceftibuten	-	Yes
1777254	2192	ceftizoxime	-	Yes
1777806	2193	ceftriaxone	-	Yes
1778162	2194	cefuroxime	-	Yes
1786621	2231	cephalexin	-	Yes
1786842	2239	cephradine	-	Yes
1797513	2551	ciprofloxacin	-	Yes
1750500	21212	clarithromycin	-	Yes
1759842	48203	clavulanate	-	Yes
1800835	2625	cloxacillin	-	Yes
1786617	22299	daptomycin	-	Yes
1790024	23437	dirithromycin	-	Yes
1789276	228476	gatifloxacin	-	Yes
1778262	5690	imipenem	-	Yes
1784749	6099	kanamycin	-	Yes
1790692	6398	lincomycin	-	Yes
1789515	229367	quinupristin	-	Yes

Preliminary list of concept definition for pre-specified procedures

Concept ID	Concept Code	Concept Name	Exclude	Descendants
607469	1153457002	Care of open wound	-	Yes
607654	1155760007	Care of malignant wound	-	Yes
4057680	19697009	Debridement and suture	-	Yes
4075360	225148005	Surgical debridement of wound	-	Yes
4075361	225149002	Debridement of wound with topical agent	-	Yes
4101851	27930000	Debridement of open fracture	-	Yes
4120998	302437009	Operation on skin wound	-	Yes
4248822	40872008	Excisional debridement of burn	-	Yes
4311933	85875009	Debridement of wound of skin	-	Yes
40486961	446247009	Debridement of wound of upper limb	-	Yes

Preliminary list of concept definition for wound type

Concept id	Concept Code	Concept Name	Exclude	Descendants
4183970	298010008	Wound dirty	-	Yes
4003509	109672001	Replanted avulsed tooth	-	Yes
36715557	721267000	Pyogenic infection of skin and subcutaneous tissues caused by bacterium	-	Yes
4096472	262560006	Penetrating wound	-	Yes
4264281	397181002	Open fracture	-	Yes
4022680	226034001	Injecting drug user	-	Yes
4053838	125670008	Foreign body	-	Yes
4095262	262568004	Deep stab wound	-	Yes
441737	125667009	Contusion	-	Yes
442013	125666000	Burn	-	Yes
4151842	283682007	Bite - wound	-	Yes

Annex II: ENCePP checklist for study protocols

Study title:
DARWIN EU® - Descriptive study of tetanus immunoglobulin use and tetanus-prone wounds in Europe

EU PAS Register® number: EUPAS1000000685
Study reference number (if applicable): P4-C1-002

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

Comments:

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

Comments:

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

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

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	8.2, 8.5
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	8.3
	4.2.2 Age and sex	☒	☐	☐	8.6
	4.2.3 Country of origin	☒	☐	☐	8.2
	4.2.4 Disease/indication	☒	☐	☐	8.6
	4.2.5 Duration of follow-up	☒	☐	☐	8.4
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	8.5

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	8.6
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☐	☐	☒	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.3 Is exposure categorized according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g., dose, duration)	☐	☐	☒	
5.5 Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

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

Comments:

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

Comments:

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

Comments:

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

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.8
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	8.7

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.3 Are descriptive analyses included?	☒	☐	☐	8.8
10.4 Are stratified analyses included?	☒	☐	☐	8.8
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.2
11.2 Are methods of quality assurance described?	☒	☐	☐	10
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?	☒	☐	☐	
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	11
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.2

Comments:

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

Comments:

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

Comments:

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

Comments:

Name of the main author of the protocol: Dina Vojinovic

Date: 25th June 2025

Signature: