Study Protocol C1-003

20/12/2022

Version 2.2

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DOCUMENT HISTORY

Version	Date	Description
V1.0	03/11/2022	**Final submission to EMA**
V2.0	22/11/2022	**Second version following comments from EMA**
V2.1	30/11/2022	**Update to Study Team members**
V2.2	20/12/2022	**Remove feasibility counts**

Study Title	DARWIN EU® - DUS of Antibiotics in the 'Watch' category of the WHO AWaRe classification of antibiotics for evaluation and monitoring of use.
Protocol version identifier	V2
Date of last version of protocol	20th December 2022
EU PAS register number	To be completed once registration

Active substance

Antibiotic	Class	ATC code
Arbekacin	Aminoglycosides	J01GB12
Aspoxicillin	Penicillins	J01CA19
Azithromycin	Macrolides	J01FA10
Azlocillin	Penicillins	J01CA09
Bekanamycin	Aminoglycosides	J01GB13
Biapenem	Carbapenems	J01DH05
Carbenicillin	Penicillins	J01CA03
Carindacillin	Penicillins	J01CA05
Cefaclor	Second-generation cephalosporins	J01DC04
Cefamandole	Second-generation cephalosporins	J01DC03
Cefbuperazone	Second-generation cephalosporins	J01DC13
Cefcapene-pivoxil	Third-generation cephalosporins	J01DD17
Cefdinir	Third-generation cephalosporins	J01DD15
Cefditoren-pivoxil	Third-generation cephalosporins	J01DD16
Cefepime	Fourth-generation cephalosporins	J01DE01
Cefetamet-pivoxil	Third-generation cephalosporins	J01DD10
Cefixime	Third-generation cephalosporins	J01DD08
Cefmenoxime	Third-generation cephalosporins	J01DD05
Cefmetazole	Second-generation cephalosporins	J01DC09

	Cefminox	Second-generation cephalosporins	J01DC12
	Cefodizime	Third-generation cephalosporins	J01DD09
	Cefonicid	Second-generation cephalosporins	J01DC06
	Cefoperazone	Third-generation cephalosporins	J01DD12
	Ceforanide	Second-generation cephalosporins	J01DC11
	Cefoselis	Fourth-generation cephalosporins	to be assigned
	Cefotaxime	Third-generation cephalosporins	J01DD01
	Cefotetan	Second-generation cephalosporins	J01DC05
	Cefotiam	Second-generation cephalosporins	J01DC07
	Cefoxitin	Second-generation cephalosporins	J01DC01
	Cefozopran	Fourth-generation cephalosporins	J01DE03
	Cefpiramide	Third-generation cephalosporins	J01DD11
	Cefpirome	Fourth-generation cephalosporins	J01DE02
	Cefpodoxime-proxetil	Third-generation cephalosporins	J01DD13
	Cefprozil	Second-generation cephalosporins	J01DC10
	Cefsulodin	Third-generation cephalosporins	J01DD03
	Ceftazidime	Third-generation cephalosporins	J01DD02
	Cefteram-pivoxil	Third-generation cephalosporins	J01DD18
	Ceftibuten	Third-generation cephalosporins	J01DD14
	Ceftizoxime	Third-generation cephalosporins	J01DD07
	Ceftriaxone	Third-generation cephalosporins	J01DD04
	Cefuroxime	Second-generation cephalosporins	J01DC02
	Chlortetracycline	Tetracyclines	J01AA03
	Cinoxacin	Quinolones	J01MB06
	Ciprofloxacin	Fluoroquinolones	J01MA02
	Clarithromycin	Macrolides	J01FA09
	Clofoctol	Phenol derivatives	J01XX03
	Clomocycline	Tetracyclines	J01AA11

	Delafloxacin	Fluoroquinolones	J01MA23
	Demeclocycline	Tetracyclines	J01AA01
	Dibekacin	Aminoglycosides	J01GB09
	Dirithromycin	Macrolides	J01FA13
	Doripenem	Carbapenems	J01DH04
	Enoxacin	Fluoroquinolones	J01MA04
	Ertapenem	Carbapenems	J01DH03
	Erythromycin	Macrolides	J01FA01
	Fidaxomicin	Macrolides	A07AA12
	Fleroxacin	Fluoroquinolones	J01MA08
	Flomoxef	Second-generation cephalosporins	J01DC14
	Flumequine	Quinolones	J01MB07
	Flurithromycin	Macrolides	J01FA14
	Fosfomycin_oral	Phosphonics	J01XX01
	Fusidic-acid	Steroid antibacterials	J01XC01
	Garenoxacin	Fluoroquinolones	J01MA19
	Gatifloxacin	Fluoroquinolones	J01MA16
	Gemifloxacin	Fluoroquinolones	J01MA15
	Grepafloxacin	Fluoroquinolones	J01MA11
	Imipenem/cilastatin	Carbapenems	J01DH51
	Isepamicin	Aminoglycosides	J01GB11
	Josamycin	Macrolides	J01FA07
	Kanamycin_IV	Aminoglycosides	J01GB04
	Kanamycin_oral	Aminoglycosides	A07AA08
	Lascufloxacin	Fluoroquinolones	J01MA25
	Latamoxef	Third-generation cephalosporins	J01DD06
	Levofloxacin	Fluoroquinolones	J01MA12
	Levonadifloxacin	Fluoroquinolones	J01MA24

	Lincomycin	Lincosamides	J01FF02
	Lomefloxacin	Fluoroquinolones	J01MA07
	Loracarbef	Second-generation cephalosporins	J01DC08
	Lymecycline	Tetracyclines	J01AA04
	Meropenem	Carbapenems	J01DH02
	Metacycline	Tetracyclines	J01AA05
	Mezlocillin	Penicillins	J01CA10
	Micronomicin	Aminoglycosides	to be assigned
	Midecamycin	Macrolides	J01FA03
	Minocycline_oral	Tetracyclines	J01AA08
	Miocamycin	Macrolides	J01FA11
	Moxifloxacin	Fluoroquinolones	J01MA14
	Nemonoxacin	Quinolones	J01MB08
	Neomycin_IV	Aminoglycosides	J01GB05
	Neomycin_oral	Aminoglycosides	A07AA01
	Netilmicin	Aminoglycosides	J01GB07
	Norfloxacin	Fluoroquinolones	J01MA06
	Ofloxacin	Fluoroquinolones	J01MA01
	Oleandomycin	Macrolides	J01FA05
	Oxolinic-acid	Quinolones	J01MB05
	Oxytetracycline	Tetracyclines	J01AA06
	Panipenem	Carbapenems	J01DH55
	Pazufloxacin	Fluoroquinolones	J01MA18
	Pefloxacin	Fluoroquinolones	J01MA03
	Penimepicycline	Tetracyclines	J01AA10
	Pheneticillin	Penicillins	J01CE05
	Pipemidic-acid	Quinolones	J01MB04
	Piperacillin	Penicillins	J01CA12

	Piperacillin/tazobactam	Beta-lactam/beta-lactamase-inhibitor_anti-pseudomonal	J01CR05
	Piromidic-acid	Quinolones	J01MB03
	Pristinamycin	Streptogramins	J01FG01
	Prulifloxacin	Fluoroquinolones	J01MA17
	Ribostamycin	Aminoglycosides	J01GB10
	Rifabutin	Rifamycins	J04AB04
	Rifampicin	Rifamycins	J04AB02
	Rifamycin_IV	Rifamycins	J04AB03
	Rifamycin_oral	Rifamycins	A07AA13
	Rifaximin	Rifamycins	A07AA11
	Rokitamycin	Macrolides	J01FA12
	Rolitetracycline	Tetracyclines	J01AA09
	Rosoxacin	Quinolones	J01MB01
	Roxithromycin	Macrolides	J01FA06
	Rufloxacin	Fluoroquinolones	J01MA10
	Sarecycline	Tetracyclines	J01AA14
	Sisomicin	Aminoglycosides	J01GB08
	Sitafloxacin	Fluoroquinolones	J01MA21
	Solithromycin	Macrolides	J01FA16
	Sparfloxacin	Fluoroquinolones	J01MA09
	Spiramycin	Macrolides	J01FA02
	Streptoduocin	Aminoglycosides	J01GA02
	Streptomycin_IV	Aminoglycosides	J01GA01
	Streptomycin_oral	Aminoglycosides	A07AA04
	Sulbenicillin	Penicillins	J01CA16
	Tazobactam	Beta-lactamase-inhibitors	J01CG02
	Tebipenem	Carbapenems	J01DH06

	Teicoplanin	Glycopeptides	J01XA02
	Telithromycin	Macrolides	J01FA15
	Temafloxacin	Fluoroquinolones	J01MA05
	Temocillin	Penicillins	J01CA17
	Ticarcillin	Penicillins	J01CA13
	Tobramycin	Aminoglycosides	J01GB01
	Tosufloxacin	Fluoroquinolones	J01MA22
	Troleandomycin	Macrolides	J01FA08
	Trovafloxacin	Fluoroquinolones	J01MA13
	Vancomycin_IV	Glycopeptides	J01XA01
	Vancomycin_oral	Glycopeptides	A07AA09
Medicinal product	N/A		
Research question and objectives	This study aims to characterise the incidence of prescription of the 141 antibiotics in the 'Watch' list, including indication and treatment duration, for the period 2012-2021, stratified by year and country.		
Country(-ies) of study	The Netherlands, France, Spain, Germany and the UK.		
Author	Katia Verhamme Maria de Ridder		

LIST OF ABBREVIATIONS

Acronyms/terms	Description
CDM	Common Data Model
CHUBX	Bordeaux University Hospital
CPRD GOLD	Clinical Practice Research Datalink GOLD
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real World Interrogation Network
DUS	Drug Utilization Study
EHR	Electronic Health Records
EMA	European Medicines Agency
GP	General Practitioner
IMASIS	Institut Municipal Assistència Sanitària Information System
IPCI	Integrated Primary Care Information Project
OMOP	Observational Medical Outcomes Partnership
PCT	Primary Care Teams
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària

1. TITLE

DARWIN EU® Drug Utilisation Study on Antibiotics in the 'Watch' category of the WHO AWaRe classification of antibiotics for evaluation and monitoring of use.

2. MARKETING AUTHORISATION HOLDER

N/A

3. RESPONSIBLE PARTIES – STUDY TEAM

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

Table 1: Description of Study Team

Study team Role	Names	Organisation
Study Project Manager/Principal Investigator	Katia Verhamme Maria de Ridder	Erasmus MC
Data Scientist	Marti Catala Sabate	University of Oxford
Epidemiologist	Annika Jodicke	University of Oxford
Statistician	Maria de Ridder	Erasmus MC
Data Manager	Mees Mosseveld	Erasmus MC
Data Partner*	**Names**	**Organisation**
Local Study Coordinator/Data Analyst	Antonella Delmestri Hezekiah Omulo Mees Mosseveld Hanne van Ballegooijen Miguel-Angel Mayer Vianney Jouhet Romain Griffier Talita Duarte Salles	University of Oxford – CPRD data Erasmus MC – IPCI data IQVIA LPD/IQVIA Germany PSMAR – IMASIS data CHUBX IDIAPJGol – SIDIAP data

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

4. ABSTRACT (STAND ALONE SUMMARY OF THE STUDY PROTOCOL)

Title

DARWIN EU® Drug Utilisation Study on Antibiotics in the 'Watch' category of the WHO AWaRe classification of antibiotics for evaluation and monitoring of use.

Rationale and Background

The WHO 2021 AWaRe classification (who.int) of antibiotics for evaluation and monitoring of use classifies 258 antibiotics into 3 categories (Access/Watch/Reserve) according to their impact on antimicrobial resistance.

The Watch list includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine and/or antibiotics that are at relatively high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of stewardship programs and monitoring.

This study will improve our understanding of the use of antibiotics in the Watch category in routine health care delivery , including indication, treatment duration and trends over time. The results will contribute to the EU efforts to monitor use of antibiotics as part of the global fight against antimicrobial resistance.

Research question and Objectives

The objectives of this study are

(i) To investigate the incidence and prevalence of use of antibiotics (from the WHO Watch list) stratified by calendar year, age, sex and country/database during the study period 2012-2021.

(ii) To explore duration of antibiotic use as well as indication for antibiotic prescribing/dispensing.

Research Methods

Study design

- Population level cohort study (Objective 1, Population-level drug utilisation study on antibiotics)
- New drug user cohort study (Objective 2, Patient-level drug utilisation analysis with regard to duration and indication of antibiotic use)

Population

Population-level utilisation of antibiotics: All individuals present in the database in the period between 01/01/2012 and 31/12/2021 will be included in the analysis after 365 days of database history. For this population, incidence of use of antibiotics will be explored.

Patient-level antibiotic utilisation: All new users of antibiotics after not using the antibiotic of interest for 30 days in the period between 01/01/2012 and 31/12/2021, with at least 365 days of visibility prior to the date of their first antibiotic prescription.

Variables

Drug of interest: All antibiotics from the WHO Watch list (see also section 9.3.1 – exposure)

Data sources

1. Integrated Primary Care Information Project (IPCI), The Netherlands
2. Bordeaux University Hospital France
3. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
4. Parc Salut Mar Barcelona, Hospital del Mar (IMIM) (hospital database), Spain
5. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
6. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom

Sample size

No sample size has been calculated.

Data analyses

Population-level antibiotic use: Annual period prevalence of antibiotic use and annual incidence rates per 100,000 person years, as described in section 9.7.5.1 – Population-level drug utilisation study.

Patient-level antibiotic use: Large-scale patient-level characterisation will be conducted. Index date will be the date of the first prescription of the specific antibiotic for each person. Frequency of indication at index date will be assessed. Cumulative treatment duration will be estimated and the minimum, p25, median, p75, and maximum will be provided. See for further description section 9.7.5.2 – Patient level drug utilisation study.

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

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
Version 2.0	22/11/2022	All	Update	Update following EMA's assessment
Version 2.1	30/11/2022	3	Updated	Added new Local Study Coordinator/Data Analyst
Version 2.2	20/12/2022	Sample size	Updated	Removed feasibility count

6. MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE
Draft Study Protocol	3rd November 2022
Final Study Protocol	22nd November 2022
Creation of Analytical code	December 2022
Execution of Analytical Code on the data	December 2022
Interim Study Report (if applicable)	Not applicable
Draft Study Report	15th January 2022
Final Study Report	

7. RATIONALE AND BACKGROUND

Bacterial infections are a major cause of morbidity and mortality worldwide.[1] Antibiotics have been hugely successful in improving health outcomes, and alongside improvements in nutrition, clean water, sanitation, and vaccination provision, have aided in the global reduction of under-5 mortality from 216 deaths per 1,000 livebirths in 1950 to 39 deaths per 1,000 livebirths in 2017, and an increase in male life expectancy from 48 years to 71 years within the same time period. [2, 3]

Antibiotics play a crucial role in the treatment of infections caused by bacteria but one of the greatest concerns is the risk of resistance evoked through the inappropriate use of antibiotics with regard to indication and duration of use. [4] To improve the appropriate use of antibiotics, Antibiotic Steward Ship programs have been installed with the aim to monitor the use of antibiotcs and ensure that guidelines on the use of antibiotics are strictly adhered to. [5]

The AWaRe Classification of antibiotics was developed in 2017 by the WHO Expert Committee on Selection and Use of Essential Medicines as a tool to support antibiotic stewardship efforts at local, national and global levels, Antibiotics are classified into three groups, Access, Watch and Reserve, taking into account the impact of different antibiotics and antibiotic classes on antimicrobial resistance, to emphasize the importance of their appropriate use. [6] The 2021 update of the AWaRe classification includes an additional 78 antibiotics not previously classified, bringing the total to 258.

The Watch list includes antibiotic classes that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine and/or antibiotics that are at relatively high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of stewardship programs and monitoring. Selected Watch group antibiotics are recommended as essential first or second choice empiric treatment options for a limited number of specific infectious syndromes and are listed as individual medicines on the WHO Model Lists of Essential

It is a useful tool for monitoring antibiotic consumption, defining targets and monitoring the effects of stewardship policies that aim to optimize antibiotic use and curb antimicrobial resistance. The WHO 13th General Programme of Work 2019–2023 includes a country-level target of at least 60% of total antibiotic consumption being Access group antibiotics.

This study will improve our understanding of the use of antibiotics in the Watch category in routine health care delivery, including indication, treatment duration and trends over time. The results will contribute to the EU efforts to monitor use of antibiotics as part of the global fight against antimicrobial resistance.

8. RESEARCH QUESTION AND OBJECTIVES

Table 2: Primary and secondary research questions and objective

A. **Primary research question and objective**

Objective:	To investigate the incidence and prevalence of use of antibiotics (from the WHO Watch list) stratified by calendar year, age, sex and country/database during the study period 2012-2021
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	The study cohort will comprise all individuals present in the database in the period 2012-2021, with at least 365 days of data availability before the day they become eligible for study inclusion. Additional eligibility criteria will be applied for the calculation of incidence rates where observation time of the respective use of the antibiotic of interest is excluded during use and 30 days afterwards.
Exposure:	Antibiotics from the WHO Watch list.
Comparator:	None
Outcome:	None
Time *(when follow up begins and ends):*	Follow-up will start on a pre-specified calendar time point e.g., 1st of January for each calendar year between 2012-2021 for the calculation of annual incidence/prevalence rates. End of follow-up will be defined as the earliest of loss to follow-up, end of data availability, death, or end of study period (31st December 2021)
Setting:	Inpatient and outpatient setting using data from the following datasources: IPCI (Nl), CHUBX (France), SIDIAP (Spain), IMASIS (Spain), IQVIA DA (Germany) and CPRD GOLD (UK)
Main measure of effect:	Incidence and prevalence of antibiotic use

B. **Secondary research question and objective**

Objective:	To characterize antibiotic use in terms of duration and indication of use.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	The study cohort will comprise all individuals present in the database in the period 2012-2021 (or the latest available), with at least 365 days of data availability before the day they become eligible for study inclusion and who had received at least one prescription and/or dispensing of one of the antibiotics of interest after not using the specific antibiotic for 30 days during the study period.
Exposure:	Antibiotics from the WHO Watch list.
Comparator:	None
Outcome:	None
Time *(when follow up begins and ends):*	Follow-up will start on a pre-specified calendar time point e.g., 1st of January for each calendar year between 2012-2021 for the calculation of annual incidence/prevalence rates. End of follow-up will be defined as the earliest of loss to follow-up, end of data availability or death, or end of study period (31st December 2021)
Setting:	Inpatient and outpatient setting using data from the following datasources: IPCI (NI), CHUBX (France), SIDIAP (Spain), IMASIS (Spain), IQVIA DA (Germany) and CPRD GOLD (UK)
Main measure of effect:	Proportion of patients with one of the defined indications of use at time of antibiotic prescribing/dispensing Duration of antibiotic use (expressed as minimum, p25, median, p75, and maximum)

9. RESEARCH METHODS

9.1 Study Design

Retrospective cohort studies will be conducted using routinely-collected health data from 6 databases. The study will comprise two consecutive parts:

1. A population-based cohort study will be conducted to address objective 1, assessing the prevalence and incidence of the respective antibiotics of interest (by individual antibiotic and by antibiotic class).
2. A new drug user cohort will be used to address objective 2; to characterise patient-level antibiotic utilisation in terms of indication of use and duration of use.

9.2 Study Setting

9.2.1 Study population

The study cohort will comprise all individuals present in the database during the study period (2012-2021) and with at least 365 days of data availability before the day they become eligible for study inclusion. This requirement of at least 365 days of data history will not hold for children < 1 year.

Additional eligibility criteria will be applied for the calculation of incidence rates where the observation time of users of the antibiotic of interest is excluded during use and 30 days afterwards.

9.2.2 Study period and follow-up

The study period will be from the 1st of January 2012 until the earliest of 31st December 2021 or the respective latest date of datalock of the respective databases. Follow-up will start from the date they have reached at least 365 days of data availability (except for children < 1 year during the study period where follow-up starts at time of registration in the database).

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 patients from the database eligible for the study – Analysis of Prevalent Use	Patient present in the database during the study period (2012-2021) and with at least 1 year of valid database history (except for children < 1 year during study period	Patients can be considered multiple times with regard to prevalence of antibiotic use	Prevalent	None	IP and OP	Nap	Nap	Nap	Nap	Nap
All patients from the database eligible for the study – Analysis of Incident use.	Patient present in the database during the study period (2012-2021) and with at least 1 year of valid database history (except for children < 1 year during study period	Multiple	Incident	[-30, -1]	IP and OP	Nap	Nap	specific antibiotic	Nap	Nap

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

Both incidence and prevalence require an appropriate denominator population and their contributed observation time to first be identified. Study participants in the denominator population will begin contributing person time on the respective date of the latest of the following: 1) study start date (1st January 2012), 2) date at which they have a year of prior history recorded (except for children <=1 years during the study period). Participants will stop contributing person time at the earliest date of the following: 1) study end date (31st December 2021) or 2) end of available data in each of the data sources or 3) date at which the observation period of the specific person ends.

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

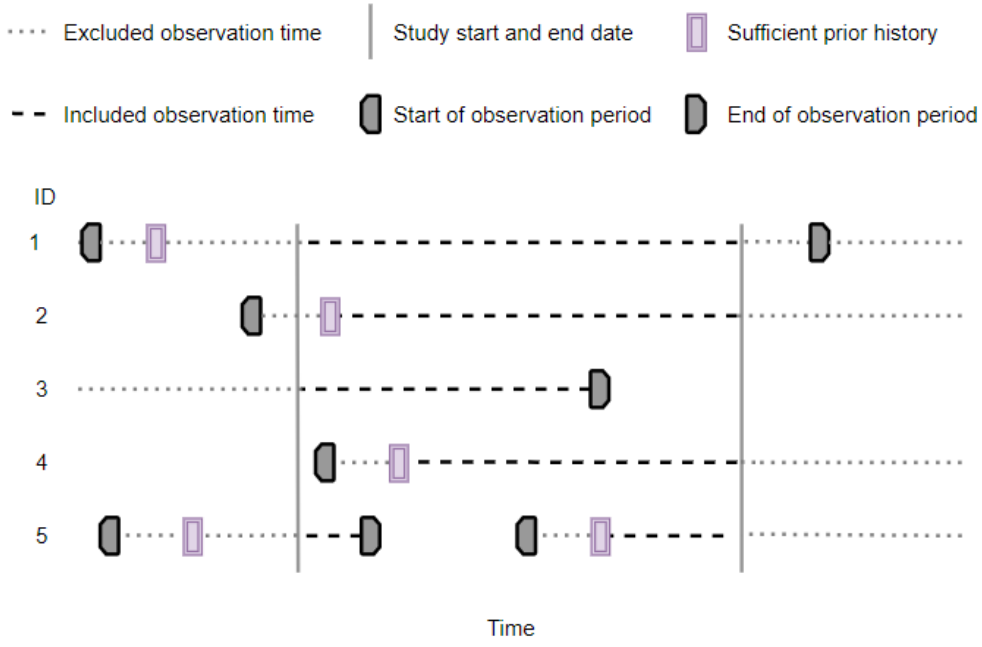

Figure 1: Included observation time for the denominator population

9.2.3 In- and exclusion criteria

9.2.3.1 Population-level Utilisation of antibiotics

The study cohort will comprise all individual present in the period 2012-2021 (or the latest available), with at least 365 days of data availability before the day they become eligible for study inclusion except for children < 1 year during the study period where this requirement does not hold.

Additional eligibility criteria will be applied for the calculation of incidence rates: The observation time of users of the antibiotic of interest is excluded during use and 30 days afterwards.

9.2.3.2 Patient-level Utilisation of antibiotics

All new users of antibiotics, after 30 days of no use of the specific antibiotic, in the period between 01/01/2012 and 31/12/2021 (or latest date available), with at least 365 days of visibility (except for children <1 year during the study period) prior to the date of their first antibiotic prescription.

Table 4: Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application*	Assessment window	Care Settings	Code Type	Diagnosis position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Observation period in the database during the period 2012-2021 (or the latest available)	See under inclusion criterion	After	N/A	Primary care and combination of primary and secondary care for IQVIA Germany and secondary care CHUBX and IMASIS	N/A	N/A	All individuals within the selected databases	N/A	N/A
Prior database history of 1 year	Study participants will be required to have a year of prior history observed before contributing observation time	After	1 year	Primary care and combination of primary and secondary care for IQVIA Germany and secondary care CHUBX and IMASIS	N/A	N/A	All individuals within the selected databases	N/A	N/A

9.3 Variables

9.3.1 Exposure

For this study, the exposure of interest is use (during study period) of antibiotics from the "Watch" category of The WHO 2021 AWaRe classification (who.int) of antibiotics. This Watch category represents antibiotics that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine and/or antibiotics that are at relatively high risk of selection of bacterial resistance.

The calculation of duration of the exposures is described in section 9.7.3- drug exposure calculations.

This list of antibiotics (with respective ATC code) is described in Table 5.

Table 5: Exposure of interest

Antibiotic	Class	ATC code
Arbekacin	Aminoglycosides	J01GB12
Aspoxicillin	Penicillins	J01CA19
Azithromycin	Macrolides	J01FA10
Azlocillin	Penicillins	J01CA09
Bekanamycin	Aminoglycosides	J01GB13
Biapenem	Carbapenems	J01DH05
Carbenicillin	Penicillins	J01CA03
Carindacillin	Penicillins	J01CA05
Cefaclor	Second-generation cephalosporins	J01DC04
Cefamandole	Second-generation cephalosporins	J01DC03
Cefbuperazone	Second-generation cephalosporins	J01DC13
Cefcapene-pivoxil	Third-generation cephalosporins	J01DD17
Cefdinir	Third-generation cephalosporins	J01DD15
Cefditoren-pivoxil	Third-generation cephalosporins	J01DD16
Cefepime	Fourth-generation cephalosporins	J01DE01
Cefetamet-pivoxil	Third-generation cephalosporins	J01DD10
Cefixime	Third-generation cephalosporins	J01DD08
Cefmenoxime	Third-generation cephalosporins	J01DD05
Cefmetazole	Second-generation cephalosporins	J01DC09
Cefminox	Second-generation cephalosporins	J01DC12
Cefodizime	Third-generation cephalosporins	J01DD09
Cefonicid	Second-generation cephalosporins	J01DC06
Cefoperazone	Third-generation-cephalosporins	J01DD12
Ceforanide	Second-generation cephalosporins	J01DC11
Cefoselis	Fourth-generation cephalosporins	to be assigned
Cefotaxime	Third-generation cephalosporins	J01DD01
Cefotetan	Second-generation cephalosporins	J01DC05
Cefotiam	Second-generation cephalosporins	J01DC07
Cefoxitin	Second-generation cephalosporins	J01DC01

Antibiotic	Class	ATC code
Cefozopran	Fourth-generation cephalosporins	J01DE03
Cefpiramide	Third-generation cephalosporins	J01DD11
Cefpirome	Fourth-generation cephalosporins	J01DE02
Cefpodoxime-proxetil	Third-generation cephalosporins	J01DD13
Cefprozil	Second-generation cephalosporins	J01DC10
Cefsulodin	Third-generation cephalosporins	J01DD03
Ceftazidime	Third-generation cephalosporins	J01DD02
Cefteram-pivoxil	Third-generation cephalosporins	J01DD18
Ceftibuten	Third-generation cephalosporins	J01DD14
Ceftizoxime	Third-generation cephalosporins	J01DD07
Ceftriaxone	Third-generation cephalosporins	J01DD04
Cefuroxime	Second-generation cephalosporins	J01DC02
Chlortetracycline	Tetracyclines	J01AA03
Cinoxacin	Quinolones	J01MB06
Ciprofloxacin	Fluoroquinolones	J01MA02
Clarithromycin	Macrolides	J01FA09
Clofoctol	Phenol derivatives	J01XX03
Clomocycline	Tetracyclines	J01AA11
Delafloxacin	Fluoroquinolones	J01MA23
Demeclocycline	Tetracyclines	J01AA01
Dibekacin	Aminoglycosides	J01GB09
Dirithromycin	Macrolides	J01FA13
Doripenem	Carbapenems	J01DH04
Enoxacin	Fluoroquinolones	J01MA04
Ertapenem	Carbapenems	J01DH03
Erythromycin	Macrolides	J01FA01
Fidaxomicin	Macrolides	A07AA12
Fleroxacin	Fluoroquinolones	J01MA08
Flomoxef	Second-generation cephalosporins	J01DC14
Flumequine	Quinolones	J01MB07
Flurithromycin	Macrolides	J01FA14
Fosfomycin_oral	Phosphonics	J01XX01
Fusidic-acid	Steroid antibacterials	J01XC01
Garenoxacin	Fluoroquinolones	J01MA19
Gatifloxacin	Fluoroquinolones	J01MA16
Gemifloxacin	Fluoroquinolones	J01MA15
Grepafloxacin	Fluoroquinolones	J01MA11
Imipenem/cilastatin	Carbapenems	J01DH51
Isepamicin	Aminoglycosides	J01GB11
Josamycin	Macrolides	J01FA07
Kanamycin_IV	Aminoglycosides	J01GB04
Kanamycin_oral	Aminoglycosides	A07AA08

Antibiotic	Class	ATC code
Lascufloxacin	Fluoroquinolones	J01MA25
Latamoxef	Third-generation cephalosporins	J01DD06
Levofloxacin	Fluoroquinolones	J01MA12
Levonadifloxacin	Fluoroquinolones	J01MA24
Lincomycin	Lincosamides	J01FF02
Lomefloxacin	Fluoroquinolones	J01MA07
Loracarbef	Second-generation cephalosporins	J01DC08
Lymecycline	Tetracyclines	J01AA04
Meropenem	Carbapenems	J01DH02
Metacycline	Tetracyclines	J01AA05
Mezlocillin	Penicillins	J01CA10
Micronomicin	Aminoglycosides	to be assigned
Midecamycin	Macrolides	J01FA03
Minocycline_oral	Tetracyclines	J01AA08
Miocamycin	Macrolides	J01FA11
Moxifloxacin	Fluoroquinolones	J01MA14
Nemonoxacin	Quinolones	J01MB08
Neomycin_IV	Aminoglycosides	J01GB05
Neomycin_oral	Aminoglycosides	A07AA01
Netilmicin	Aminoglycosides	J01GB07
Norfloxacin	Fluoroquinolones	J01MA06
Ofloxacin	Fluoroquinolones	J01MA01
Oleandomycin	Macrolides	J01FA05
Oxolinic-acid	Quinolones	J01MB05
Oxytetracycline	Tetracyclines	J01AA06
Panipenem	Carbapenems	J01DH55
Pazufloxacin	Fluoroquinolones	J01MA18
Pefloxacin	Fluoroquinolones	J01MA03
Penimepicycline	Tetracyclines	J01AA10
Pheneticillin	Penicillins	J01CE05
Pipemidic-acid	Quinolones	J01MB04
Piperacillin	Penicillins	J01CA12
Piperacillin/tazobactam	Beta-lactam/beta-lactamase-inhibitor_anti-pseudomonal	J01CR05
Piromidic-acid	Quinolones	J01MB03
Pristinamycin	Streptogramins	J01FG01
Prulifloxacin	Fluoroquinolones	J01MA17
Ribostamycin	Aminoglycosides	J01GB10
Rifabutin	Rifamycins	J04AB04
Rifampicin	Rifamycins	J04AB02
Rifamycin_IV	Rifamycins	J04AB03
Rifamycin_oral	Rifamycins	A07AA13

Antibiotic	Class	ATC code
Rifaximin	Rifamycins	A07AA11
Rokitamycin	Macrolides	J01FA12
Rolitetracycline	Tetracyclines	J01AA09
Rosoxacin	Quinolones	J01MB01
Roxithromycin	Macrolides	J01FA06
Rufloxacin	Fluoroquinolones	J01MA10
Sarecycline	Tetracyclines	J01AA14
Sisomicin	Aminoglycosides	J01GB08
Sitafloxacin	Fluoroquinolones	J01MA21
Solithromycin	Macrolides	J01FA16
Sparfloxacin	Fluoroquinolones	J01MA09
Spiramycin	Macrolides	J01FA02
Streptoduocin	Aminoglycosides	J01GA02
Streptomycin_IV	Aminoglycosides	J01GA01
Streptomycin_oral	Aminoglycosides	A07AA04
Sulbenicillin	Penicillins	J01CA16
Tazobactam	Beta-lactamase-inhibitors	J01CG02
Tebipenem	Carbapenems	J01DH06
Teicoplanin	Glycopeptides	J01XA02
Telithromycin	Macrolides	J01FA15
Temafloxacin	Fluoroquinolones	J01MA05
Temocillin	Penicillins	J01CA17
Ticarcillin	Penicillins	J01CA13
Tobramycin	Aminoglycosides	J01GB01
Tosufloxacin	Fluoroquinolones	J01MA22
Troleandomycin	Macrolides	J01FA08
Trovafloxacin	Fluoroquinolones	J01MA13
Vancomycin_IV	Glycopeptides	J01XA01
Vancomycin_oral	Glycopeptides	A07AA09

Details of exposure are described in Table 6.

Table 6: Exposure details

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting	Code Type	Diagnosis position	Applied to study populations :	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
Antibiotics from the "Watch" category of The WHO 2021 AWaRe classification	Preliminary code lists provided in Appendix 1	[-30, -1]	Calendar year	Primary and secondary care	RxNorm	N/A	All individuals present in the database during the study period	Previous antibiotic use (of the antibiotic of interest)	N/A	N/A

9.3.2 Outcomes

N/A

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

9.3.3.1 Covariates for stratification in population-level drug utilisation study:

- Age: 5-year age bands will be used: 0-1, 2-11, 12-17, 18-24, 25-29 etc. 85+
- Calendar year
- Sex

9.3.3.2 Covariates for patient-level drug utilisation study:

- Age: 5-year age bands will be used: 0-1, 2-11, 12-17, 18-24, 25-29 etc. 85+
- Route of administration: oral or parenteral.
- Sex

- The following conditions will be of interest (i.e., indication of use):
    - Bloodstream Infection
    - Bone and Joint Infection
    - Cardiovascular System Infection
    - Catheter-related Infection
    - Central Nervous System Infection
    - Eye, Ear, Nose, Throat or Mouth Infection
    - Gastrointestinal System Infection
    - Genito-Urinary Tract Infection
    - Lower Respiratory Tract Infection other than pneumonia
    - Pneumonia
    - Reproductive Tract Infection
    - Skin and Soft Tissue Infection
    - Surgical Site Infection
    - Other Infection
- Top 10 of co-morbidities from large-scale patient characterisation

The operational definition of the covariates is described in the table below. Index date is the start of the first prescription during the study period:

Table 7: Operational Definitions of Covariates

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type[2]	Diagnosis Position[3]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Indication of Use	Check for conditions of interest related to use of antibiotics	Counts	At index date and as sensitivity analyses in windows around index date: [-7, 7] and [-30, 7]	Primary and secondary care	SNOMED	N/A	Persons with new use during the study period	N/A	N/A
Comorbidity	Large-scale patient-level characterisation with regard to underlying comorbidity	Counts	At index date (ID), for 30 to 1 day before ID,	Primary care and secondary care	SNOMED	N/A	Persons with new use during the study period	N/A	N/A
Route of administration	Oral or parenteral	Count	At index date	Primary and secondary care	RxNorm	N/A	All new users	N/A	N/A

9.4 Data sources

This study will be conducted using routinely collected data from 6 databases in 5 European countries (4 EU countries and United Kingdom). All databases were previously mapped to the OMOP CDM .

1. Integrated Primary Care Information Project (IPCI), The Netherlands
2. Bordeaux University Hospital France
3. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
4. Parc Salut Mar Barcelona, Hospital del Mar (IMIM) (hospital database), Spain
5. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany
6. Clinical Practice Research Datalink GOLD (CPRD GOLD), United Kingdom

Information on the data source(s) with a justification for their choice in terms of ability to capture the relevant data is described in a **Table 8**.

Table 8: Description of data sources

Country	Name of Database	Justification for Inclusion	Health Care setting (e.g., primary care, specialist care, hospital care)	Type of Data (EHR, claims, registries)	Number of active subjects	Feasibility count of disease (if relevant)	Data lock for the last update
NL	IPCI	Covers primary care setting where antibiotic prescriptions are used	Primary care	EHR	1.39 million	N/A	1/1/2022
FR	CHUBX	Covers secondary care setting where antibiotic prescriptions are used	Secondary care (in and outpatients)	EHR	2.13 million	N/A	1/1/2022
ES	SIDIAP	Covers primary care setting where antibiotic prescriptions are used	Primary care	EHR	5.8 million	N/A	31st March 2022
ES	IMASIS	Covers secondary care setting where antibiotic prescriptions are used	Secondary care (in and outpatients)	EHR	0.6 million	N/A	9/7/2022
DE	IQVIA DA Germany	Database covers primary care setting where antibiotic prescriptions are issued.	Primary care and outpatient specialist care	EHR	8.5 million	N/A	30th June 2022
UK	CPRD GOLD	Database covers primary care setting where antibiotic prescriptions are issued.	Primary care	EHR	3 million	N/A	1st July 2022

NL = The Netherlands, FR= France, ES = Spain, DE = Germany, UK = United Kingdom, IPCI = Integrated Primary Care Information Project; CHUBX= Bordeaux University Hospital, SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària, IMASIS= Institut Municipal Assistencia Sanitaria Information System, DA = Disease Analyzer, CPRD GOLD = Clinical Practice Research Datalink GOLD, EHR = Electronic Heath record. Exposure is based on prescription data

Integrated Primary Care Information Project (IPCI), The Netherlands (Erasmus)

IPCI is collected from electronic health records (EHR) of patients registered with their general practitioners (GPs) throughout the Netherlands.[7] The selection of 374 GP practices is representative of the entire country. The database contains records from 2.8 million patients out of a Dutch population of 17M starting in 1996[7]. The median follow-up is 4.7 years. The observation period for a patient is determined by the date of registration at the GP and the date of leave/death. The observation period start date is refined by many quality indicators, e.g. exclusion of peaks of conditions when registering at the GP. All data before the observation period is kept as history data. Drugs are captured as prescription records with product, quantity, dosing directions, strength and indication. Drugs not prescribed in the GP setting might be underreported. Indications are available as diagnoses by the GPs and, indirectly, from secondary care providers but the latter might not be complete. Approval needs to be obtained for each study from the Governance Board[7]. IPCI will be onboarded as Data Partner for DARWIN EU® in 2022.

Bordeaux University Hospital (CHUBX), France

The clinical data warehouse of the Bordeaux University Hospital comprises electronic health records on more than 2 million patients with data collection starting in 2005. The hospital complex is made up of three main sites and comprises a total of 3,041 beds (2021 figures). The database currently holds information about the person (demographics), visits (inpatient and outpatient), conditions and procedures (billing codes), drugs (outpatient prescriptions and inpatient orders and administrations), measurements (laboratory tests and vital signs) and dates of death (in or out-hospital death).[8]

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

SIDIAP is collected from EHR records of patients receiving primary care delivered through Primary Care Teams (PCT), consisting of GPs, nurses and non-clinical staff[9]. The Catalan Health Institute manages 286 out of 370 such PCT with a coverage of 5.6M patients, out of 7.8M people in the Catalan population (74%). The database started to collect data in 2006. The mean follow-up is 10 years. The observation period for a patient can be the start of the database (2006), or when a person is assigned to a Catalan Health Institute primary care centre. Date of exit can be when a person is transferred-out to a primary care centre that does not pertain to the Catalan Health Institute, or date of death, or date of end of follow-up in the database. Drug information is available from prescriptions and from dispensing records in pharmacies. Drugs not prescribed in the GP setting might be underreported; and disease diagnoses made at specialist care settings are not included. Studies using SIDIAP data require previous approval by both a Scientific and an Ethics Committee. SIDIAP will be onboarded as Data Partner for DARWIN EU® in 2022.

Institut Municipal Assistencia Sanitaria Information System (IMASIS), Spain

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

Disease Analyser (DA) Germany, Germany (IQVIA)

DA Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings[11]. Data coverage includes more than 34M distinct person records out

of at total population of 80M (42.5%) in the country and collected from 2,734 providers. Patient visiting more than one provider are not cross identified for data protection reasons and therefore recorded as separate in the system. Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates. Germany has no mandatory GP system and patient have free choice of specialist. As a result, data are collected from visits to 28.8% General, 13.4% Orthopaedic Surgery, 11.8% Otolaryngology, 11.2% Dermatology, 7.7% Obstetrics/Gynaecology, 6.2% various Neurology and Psychiatry 7.0% Paediatric, 4.6% Urology, 3.7% Cardiology, 3.5% Gastroenterology, 1.5% Pulmonary and 0.7% Rheumatology practices. Drugs are recorded as prescriptions of marketed products. No registration or approval is required for drug utilisation studies.

Clinical Practice Research Datalink GOLD, United Kingdom (University of Oxford)

The Clinical Practice Research Datalink (CPRD) is a governmental, not-for-profit research service, jointly funded by the National Institute for Health and Care Research and the Medicines and Healthcare products Regulatory Agency, a part of the Department of Health, United Kingdom (UK) (https://cprd.com). CPRD GOLD[12] comprises computerized records of all clinical and referral events in primary care in addition to comprehensive demographic information and medication prescription data in a sample of UK patients (predominantly from Scotland (52% of practices) and Wales (28% of practices). The prescription records include information on the type of product, date of prescription, strength, dosage, quantity, and route of administration. Data from contributing practices are collected and processed into research databases. Quality checks on patient and practice level are applied during the initial processing. Data are available for 20 million patients, including 3.2 million currently registered patients.

Access to CPRD GOLD data requires approval via the Research Data Governance Process. CPRD GOLD will be onboarded as Data Partner for DARWIN EU® in 2022.

9.5 Study size

No sample size has been calculated. Prevalence and Incidence of antibiotic use among the study population will be estimated as part of Objective 1.

9.6 Data Management

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

9.7 Data Analysis

This section describes the details of the analysis approach and rationale for the choice of analysis, with reference to the D1.3.8.3 Complete Catalogue of Data Analysis which describes the type of analysis in function of the study type.

The analysis will include calculation of population based incidence rates and prevalence, as described in section 9.7.5.1 – Population-level drug utilisation study, characterisation of patient-level features for

antibiotic users, frequency and percentages of indications, and descriptive statistics of treatment duration of antibiotics, as described in section 9.7.5.2 – Patient level drug utilisation study.

9.7.1 Federated Network Analyses

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

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

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

9.7.2 Patient privacy protection

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

9.7.3 Statistical model specification and assumptions of the analytical approach considered

R-packages

We will use the R package "DrugUtilizationCharacteristics" for the patient-level drug utilisation analyses including patient-level characterisation, and "IncidencePrevalence" package for the population-level estimation of drug utilisation.

Drug exposure calculations

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

Two drug eras will be merged into one continuous drug era if the distance in days between end of the first era and start of the second era is ≤ 7 days. The time between the two joined eras will be considered as exposed by the first era as shown in **Figure 2**, first row. Note: dose is not considered for this study.

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 2: Gap era joint mode

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

New user cohorts

New users will be selected based on their first prescription of the respective drug of interest after the start of the study and/or in a pre-defined time window. For each patient, at least 365 days of data visibility will be required prior to that prescription. New users will be required to not have been exposed to the drug of interest for at least 30 days prior the current prescription. If the start date of a prescription does not fulfil the exposure washout criteria of 30 days of no use, the whole exposure is eliminated.

9.7.4 Methods to derive parameters of interest

Calendar time

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

Age

Age at index date will be calculated using January 1st of the year of birth as proxy for the actual birthday. The following age groups will be used for stratification: 0-1, 2-11, 12-17, 18-24, 25-29 etc. 85+

Sex

Results will be presented stratified by sex

Indication

Indication will be determined based on recordings of pre-defined conditions (see 9.3.3 – other variables), at the date of the first prescription of the respective drug (index date)[primary definition] or during assessment windows [sensitivity analyses]. If none of the specific indications was recorded on index date or during the assessment window, but there was a record for any other conditions, the person will be considered having an "other" indication.

Characterisation of patient-level features

Large-scale patient-level characterisation will be conducted. Co-variates will be extracted for the following time intervals: Concepts in the "condition" domain will be assessed for 30 to 1 day before index date, and at index date. The top-10 for both time windows will be presented.

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

9.7.5.1 Population-level drug utilisation study

Prevalence and incidence calculations will be conducted separately for each antibiotic of interest as well as by antibiotic class.

Prevalence calculations

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

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

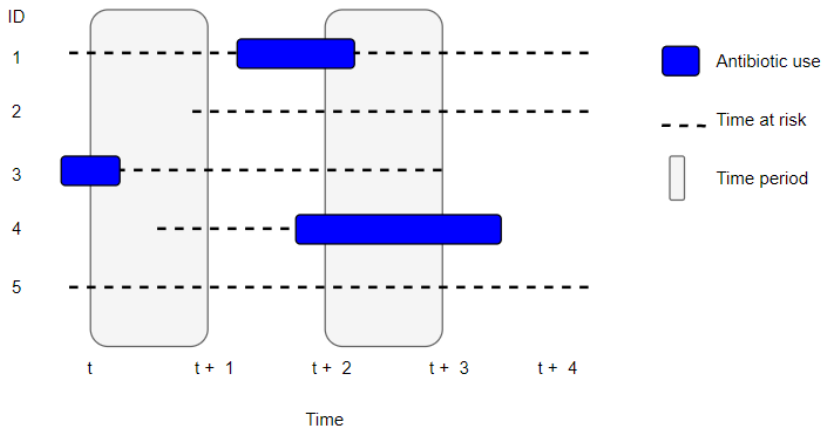

Figure 3: Period prevalence example for antibiotic use

Incidence calculations

Annual incidence rates of the antibiotics of interest will be calculated as the of number of **new users** after 30 days of no use per 100,000 person-years of the population at risk of getting exposed during the period for each calendar year. Any study participants with use of the medication of interest prior to the date at which they would have otherwise satisfied the criteria to enter the denominator population (as described above) will be excluded. Those study participants who enter the denominator population will then contribute time at risk up to their first prescription during the study period. Or if they do not have

a drug exposure, they will contribute time at risk up as described above in section 9.2.2 (study period and end of follow-up). Incidence rates will be given together with 95% Poisson confidence intervals.

An illustration of the calculation of incidence of antibiotic use is shown below in **Figure 4**. Patient ID 1 and 4 contribute time at risk up to the point at which they become incident users of antibiotics. Patient ID 2 and 5 are not seen to use antibiotics 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 antibiotic is starting. A second period of time at risk again starts after the washout period. For person ID 4, only the first and third exposures of antibiotics count as incident use, while the second exposure starts within the washout period of the first exposure. The time between start of the first exposure until the washout period after the second exposure is not considered as time at risk.

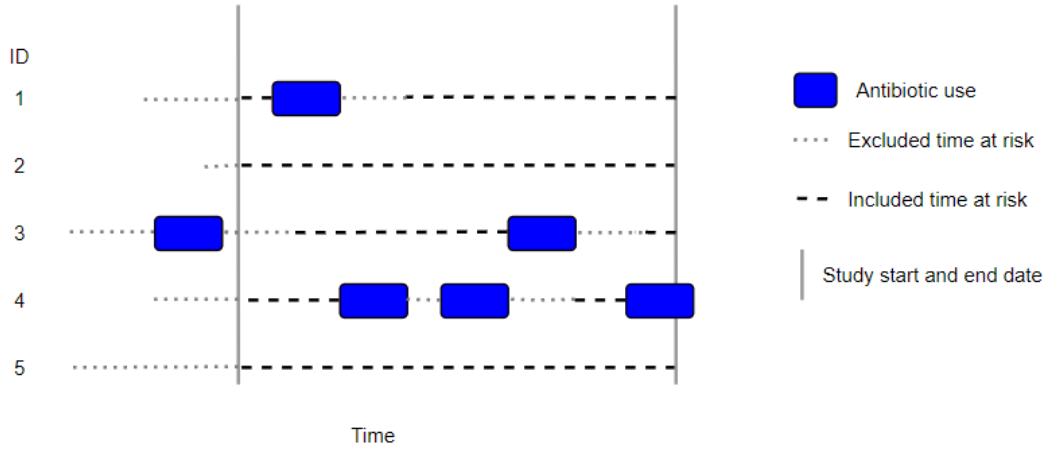

Figure 4: Incidence example for antibiotic use

9.7.5.2 Patient-level drug utilisation study

New drug user patient-level characteristics on/before index date

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

Indication

The number of persons (N, %) with a record of the respective indication of interest will be provided. If a person has a record of more than one specific indication, that person will be included in both specific indication groups.

Treatment duration

Treatment duration will be calculated as the cumulative duration of the all exposure era of the antibiotic of interest during the study period from the first incident prescription onwards. Treatment duration will be summarized providing the minimum, p25, median, p75, and maximum treatment duration. For databases,

where duration cannot be calculated due to e.g. missing information on quantity or dosing, treatment duration will not be provided.

9.7.6 Description of sensitivity analyses.

Table 9 describes the sensitivity analysis with regard to exploration of the indication of use.

Table 9: Sensitivity analyses – rationale, strengths and limitations

	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
Window to assess indication of use	Indication of use will be explored in a period of 7 days +/- the index date and in a period from 30 days before until 7 days after index date	As indication of use might not always be recorded on the date of prescription of the antibiotic of interest	Proportion of patients with an indication of use might increase.	Potential misclassification of indication of use if the disease code registered in the week before or after the index date has nothing to do with prescription of the antibiotic of interest

9.8 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 drug cohorts, non-systemic products will be excluded from the list of included codes summarised on the ingredient level. A pharmacist will review the codes of the antibiotics of interest.
When defining cohorts for indications, 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, the CohortDiagnostics R package

(https://github.com/OHDSI/CohortDiagnostics) will be run if needed to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error.
The study code will be based on two R packages currently being developed to (1) estimate Incidence and Prevalence and (2) characterise drug utilisation using the OMOP common data model. These packages will include numerous automated unit tests to ensure the validity of the codes, alongside software peer review and user testing. The R package will be made publicly available via GitHub.

9.9 Limitation of the research methods

The study will be informed by routinely collected health care data and so data quality issues must be considered. In particular, a recording of a prescription or dispensation does not mean that the patient actually took the drug. In addition, assumptions around the duration of drug use will be unavoidable. For databases, where duration cannot be calculated due to e.g. missing information on quantity or dosing, treatment duration will not be provided.

In addition, the recording of events used for patient characterisation and identification of the (potential) indication may vary across databases and recording of indication may be incomplete.

9.10 Evidence synthesis

Results from analyses described in Section 9.7 will be presented separately for each database and no pooling of results will be conducted.

10. PROTECTION OF HUMAN SUBJECTS

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

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

The output files are stored in the DARWIN Remote Research Environment. These output files do not contain any data that allow identification of subjects included in the study. The RRE implements further security measures in order to ensure a high level of stored data protection to comply with the local implementation of the General Data Protection Regulation (GDPR) (EU) 679/20161 in the various member states.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

In agreement with the new guideline on good pharmacovigilance practice (EMA/873138/2011), there will be no requirement for expedited reporting of adverse drug reactions as only secondary data will be used in this study.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 Study Report

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.

13. REFERENCES

1. Browne AJ, Chipeta MG, Haines-Woodhouse G, Kumaran EPA, Hamadani BHK, Zaraa S, Henry NJ, Deshpande A, Reiner RC, Jr., Day NPJ, Lopez AD, Dunachie S, Moore CE, Stergachis A, Hay SI, Dolecek C. Global antibiotic consumption and usage in humans, 2000-18: a spatial modelling study. Lancet Planet Health. 2021;5(12):e893-e904.

2. Collaborators GBDM. Global, regional, and national age-sex-specific mortality and life expectancy, 1950-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1684-735.

3. Burstein R, Henry NJ, Collison ML, Marczak LB, Sligar A, Watson S, Marquez N, Abbasalizad-Farhangi M, Abbasi M, Abd-Allah F, Abdoli A, Abdollahi M, Abdollahpour I, Abdulkader RS, Abrigo MRM, Acharya D, Adebayo OM, Adekanmbi V, Adham D, Afshari M, Aghaali M, Ahmadi K, Ahmadi M, Ahmadpour E, Ahmed R, Akal CG, Akinyemi JO, Alahdab F, Alam N, Alamene GM, Alene KA, Alijanzadeh M, Alinia C, Alipour V, Aljunid SM, Almalki MJ, Al-Mekhlafi HM, Altirkawi K, Alvis-Guzman N, Amegah AK, Amini S, Amit AML, Anbari Z, Androudi S, Anjomshoa M, Ansari F, Antonio CAT, Arabloo J, Arefi Z, Aremu O, Armoon B, Arora A, Artaman A, Asadi A, Asadi-Aliabadi M, Ashraf-Ganjouei A, Assadi R, Ataeinia B, Atre SR, Quintanilla BPA, Ayanore MA, Azari S, Babaee E, Babazadeh A, Badawi A, Bagheri S, Bagherzadeh M, Baheiraei N, Balouchi A, Barac A, Bassat Q, Baune BT, Bayati M, Bedi N, Beghi E, Behzadifar M, Behzadifar M, Belay YB, Bell B, Bell ML, Berbada DA, Bernstein RS, Bhattacharjee NV, Bhattarai S, Bhutta ZA, Bijani A, Bohlouli S, Breitborde NJK, Britton G, Browne AJ, Nagaraja SB, Busse R, Butt ZA, Car J, Cardenas R, Castaneda-Orjuela CA, Cerin E, Chanie WF, Chatterjee P, Chu DT, Cooper C, Costa VM, Dalal K, Dandona L, Dandona R, Daoud F, Daryani A, Das Gupta R, Davis I, Davis Weaver N, Davitoiu DV, De Neve JW, Demeke FM, Demoz GT, Deribe K, Desai R, Deshpande A, Desyibelew HD, Dey S, Dharmaratne SD, Dhimal M, Diaz D, Doshmangir L, Duraes AR, Dwyer-Lindgren L, Earl L, Ebrahimi R, Ebrahimpour S, Effiong A, Eftekhari A, Ehsani-Chimeh E, El Sayed I, El Sayed Zaki M, El Tantawi M, El-Khatib Z, Emamian MH, Enany S, Eskandarieh S, Eyawo O, Ezalarab M, Faramarzi M, Fareed M, Faridnia R, Faro A, Fazaeli AA, Fazlzadeh M, Fentahun N, Fereshtehnejad SM, Fernandes JC, Filip I, Fischer F, Foigt NA, Foroutan M, Francis JM, Fukumoto T, Fullman N, Gallus S, Gebre DG, Gebrehiwot TT, Gebremeskel GG, Gessner BD, Geta B, Gething PW, Ghadimi R, Ghadiri K, Ghajarzadeh M, Ghashghaee A, Gill PS, Gill TK, Golding N, Gomes NGM, Gona PN, Gopalani SV, Gorini G, Goulart BNG, Graetz N, Greaves F, Green MS, Guo Y, Haj-Mirzaian A, Haj-Mirzaian A, Hall BJ, Hamidi S, Haririan H, Haro JM, Hasankhani M, Hasanpoor E, Hasanzadeh A, Hassankhani H, Hassen HY, Hegazy MI, Hendrie D, Heydarpour F, Hird TR, Hoang CL, Hollerich G, Rad EH, Hoseini-Ghahfarokhi M, Hossain N, Hosseini M, Hosseinzadeh M, Hostiuc M, Hostiuc S, Househ M, Hsairi M, Ilesanmi OS, Imani-Nasab MH, Iqbal U, Irvani SSN, Islam N, Islam SMS, Jurisson M, Balalami NJ, Jalali A, Javidnia J, Jayatilleke AU, Jenabi E, Ji JS, Jobanputra YB, Johnson K, Jonas JB, Shushtari ZJ, Jozwiak JJ, Kabir A, Kahsay A, Kalani H, Kalhor R, Karami M, Karki S, Kasaeian A, Kassebaum NJ, Keiyoro PN, Kemp GR, Khabiri R, Khader YS, Khafaie MA, Khan EA, Khan J, Khan MS, Khang YH, Khatab K, Khater A, Khater MM, Khatony A, Khazaei M, Khazaei S, Khazaei-Pool M, Khubchandani J, Kianipour N, Kim YJ, Kimokoti RW, Kinyoki DK, Kisa A, Kisa S, Kolola T, Kosen S, Koul PA, Koyanagi A, Kraemer MUG, Krishan K, Krohn KJ, Kugbey N, Kumar GA, Kumar M, Kumar P, Kuupiel D, Lacey B, Lad SD, Lami FH, Larsson AO, Lee PH, Leili M, Levine AJ, Li S, Lim LL, Listl S, Longbottom J, Lopez JCF, Lorkowski S, Magdeldin S, Abd El Razek HM, Abd El Razek MM, Majeed A, Maleki A, Malekzadeh R, Malta DC, Mamun AA, Manafi N, Manda AL, Mansourian M, Martins-Melo FR, Masaka A, Massenburg BB, Maulik PK, Mayala BK, Mazidi M, McKee M, Mehrotra R, Mehta KM, Meles GG, Mendoza W, Menezes RG, Meretoja A, Meretoja TJ, Mestrovic T, Miller

TR, Miller-Petrie MK, Mills EJ, Milne GJ, Mini GK, Mir SM, Mirjalali H, Mirrakhimov EM, Mohamadi E, Mohammad DK, Darwesh AM, Mezerji NMG, Mohammed AS, Mohammed S, Mokdad AH, Molokhia M, Monasta L, Moodley Y, Moosazadeh M, Moradi G, Moradi M, Moradi Y, Moradi-Lakeh M, Moradinazar M, Moraga P, Morawska L, Mosapour A, Mousavi SM, Mueller UO, Muluneh AG, Mustafa G, Nabavizadeh B, Naderi M, Nagarajan AJ, Nahvijou A, Najafi F, Nangia V, Ndwandwe DE, Neamati N, Negoi I, Negoi RI, Ngunjiri JW, Thi Nguyen HL, Nguyen LH, Nguyen SH, Nielsen KR, Ningrum DNA, Nirayo YL, Nixon MR, Nnaji CA, Nojomi M, Noroozi M, Nosratnejad S, Noubiap JJ, Motlagh SN, Ofori-Asenso R, Ogbo FA, Oladimeji KE, Olagunju AT, Olfatifar M, Olum S, Olusanya BO, Oluwasanu MM, Onwujekwe OE, Oren E, Ortega-Altamirano DDV, Ortiz A, Osarenotor O, Osei FB, Osgood-Zimmerman AE, Otstavnov SS, Owolabi MO, P AM, Pagheh AS, Pakhale S, Panda-Jonas S, Pandey A, Park EK, Parsian H, Pashaei T, Patel SK, Pepito VCF, Pereira A, Perkins S, Pickering BV, Pilgrim T, Pirestani M, Piroozi B, Pirsaheb M, Plana-Ripoll O, Pourjafar H, Puri P, Qorbani M, Quintana H, Rabiee M, Rabiee N, Radfar A, Rafiei A, Rahim F, Rahimi Z, Rahimi-Movaghar V, Rahimzadeh S, Rajati F, Raju SB, Ramezankhani A, Ranabhat CL, Rasella D, Rashedi V, Rawal L, Reiner RC, Jr., Renzaho AMN, Rezaei S, Rezapour A, Riahi SM, Ribeiro AI, Roever L, Roro EM, Roser M, Roshandel G, Roshani D, Rostami A, Rubagotti E, Rubino S, Sabour S, Sadat N, Sadeghi E, Saeedi R, Safari Y, Safari-Faramani R, Safdarian M, Sahebkar A, Salahshoor MR, Salam N, Salamati P, Salehi F, Zahabi SS, Salimi Y, Salimzadeh H, Salomon JA, Sambala EZ, Samy AM, Santric Milicevic MM, Jose BPS, Saraswathy SYI, Sarmiento-Suarez R, Sartorius B, Sathian B, Saxena S, Sbarra AN, Schaeffer LE, Schwebel DC, Sepanlou SG, Seyedmousavi S, Shaahmadi F, Shaikh MA, Shams-Beyranvand M, Shamshirian A, Shamsizadeh M, Sharafi K, Sharif M, Sharif-Alhoseini M, Sharifi H, Sharma J, Sharma R, Sheikh A, Shields C, Shigematsu M, Shiri R, Shiue I, Shuval K, Siddiqi TJ, Silva JP, Singh JA, Sinha DN, Sisay MM, Sisay S, Sliwa K, Smith DL, Somayaji R, Soofi M, Soriano JB, Sreeramareddy CT, Sudaryanto A, Sufiyan MB, Sykes BL, Sylaja PN, Tabares-Seisdedos R, Tabb KM, Tabuchi T, Taveira N, Temsah MH, Terkawi AS, Tessema ZT, Thankappan KR, Thirunavukkarasu S, To QG, Tovani-Palone MR, Tran BX, Tran KB, Ullah I, Usman MS, Uthman OA, Vahedian-Azimi A, Valdez PR, van Boven JFM, Vasankari TJ, Vasseghian Y, Veisani Y, Venketasubramanian N, Violante FS, Vladimirov SK, Vlassov V, Vos T, Vu GT, Vujcic IS, Waheed Y, Wakefield J, Wang H, Wang Y, Wang YP, Ward JL, Weintraub RG, Weldegwergs KG, Weldesamuel GT, Westerman R, Wiysonge CS, Wondafrash DZ, Woyczynski L, Wu AM, Xu G, Yadegar A, Yamada T, Yazdi-Feyzabadi V, Yilgwan CS, Yip P, Yonemoto N, Lebni JY, Younis MZ, Yousefifard M, Yousof HSA, Yu C, Yusefzadeh H, Zabeh E, Moghadam TZ, Bin Zaman S, Zamani M, Zandian H, Zangeneh A, Zerfu TA, Zhang Y, Ziapour A, Zodpey S, Murray CJL, Hay SI. Mapping 123 million neonatal, infant and child deaths between 2000 and 2017. Nature. 2019;574(7778):353-8.

4. Bassetti S, Tschudin-Sutter S, Egli A, Osthoff M. Optimizing antibiotic therapies to reduce the risk of bacterial resistance. Eur J Intern Med. 2022;99:7-12.

5. Watkins RR. Antibiotic stewardship in the era of precision medicine. JAC Antimicrob Resist. 2022;4(3):dlac066.

6. Pauwels I, Versporten A, Drapier N, Vlieghe E, Goossens H, Global PPSn. Hospital antibiotic prescribing patterns in adult patients according to the WHO Access, Watch and Reserve classification (AWaRe): results from a worldwide point prevalence survey in 69 countries. J Antimicrob Chemother. 2021;76(6):1614-24.

7. Vlug A, van der Lei J, Mosseveld B, van Wijk M, van der Linden P, MC S. Postmarketing surveillance based on electronic patient records: the IPCI project. Methods of information in medicine. 1999;38:339-44.

8. Brat GA, Weber GM, Gehlenborg N, Avillach P, Palmer NP, Chiovato L, Cimino J, Waitman LR, Omenn GS, Malovini A, Moore JH, Beaulieu-Jones BK, Tibollo V, Murphy SN, Yi SL, Keller MS, Bellazzi R, Hanauer DA, Serret-Larmande A, Gutierrez-Sacristan A, Holmes JJ, Bell DS, Mandl KD, Follett RW, Klann JG, Murad DA, Scudeller L, Bucalo M, Kirchoff K, Craig J, Obeid J, Jouhet V, Griffier R, Cossin S, Moal B, Patel LP, Bellasi A, Prokosch HU, Kraska D, Sliz P, Tan ALM, Ngiam KY, Zambelli A, Mowery DL, Schiver E, Devkota B, Bradford RL, Daniar M, Daniel C, Benoit V, Bey R, Paris N, Serre P, Orlova N, Dubiel J, Hilka M, Jannot AS, Breant S, Leblanc J, Griffon N, Burgun A, Bernaux M, Sandrin A, Salamanca E, Cormont S, Ganslandt T, Gradinger T, Champ J, Boeker M, Martel P, Esteve L, Gramfort A, Grisel O, Leprovost D, Moreau T, Varoquaux G, Vie JJ, Wassermann D, Mensch A, Caucheteux C, Haverkamp C, Lemaitre G, Bosari S, Krantz ID, South A, Cai T, Kohane IS. International electronic health record-derived COVID-19 clinical course profiles: the 4CE consortium. NPJ Digit Med. 2020;3:109.

9. Garcia-Gil Mdel M, Hermosilla E, Prieto-Alhambra D, Fina F, Rosell M, Ramos R. Construction and validation of a scoring system for the selection of high-quality data in a Spanish population primary care database (SIDIAP). Informatics in primary care. 2011;19(3):135-45.

10. Reyes C, Pistillo A, Fernandez-Bertolin S, Recalde M, Roel E, Puente D, Sena AG, Blacketer C, Lai L, Alshammari TM, Ahmed WU, Alser O, Alghoul H, Areia C, Dawoud D, Prats-Uribe A, Valveny N, de Maeztu G, Sorli Redo L, Martinez Roldan J, Lopez Montesinos I, Schilling LM, Golozar A, Reich C, Posada JD, Shah N, You SC, Lynch KE, DuVall SL, Matheny ME, Nyberg F, Ostropolets A, Hripcsak G, Rijnbeek PR, Suchard MA, Ryan P, Kostka K, Duarte-Salles T. Characteristics and outcomes of patients with COVID-19 with and without prevalent hypertension: a multinational cohort study. BMJ Open. 2021;11(12):e057632.

11. Rathmann W, Bongaerts B, Carius H, Kruppert S, Kostev K. Basic characteristics and representativeness of the German Disease Analyzer database. Int J Clin Pharmacol Ther. 2018;56(10):459-66.

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

14. ANNEXES

Appendix I: List of Stand-Alone documents (e.g., lists with concept definitions (conditions & drugs), validation procedures, questionnaires etc.)

Appendix II: ENCePP checklist for study protocols

Appendix III: Additional Information

APPENDIX I – TABLE 1: LIST WITH CONCEPT DEFINITIONS FOR INDICATION OF USE

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

Indication of use	Concept ID Included	Concept ID Excluded
	4287930, 619669, 443858, 4220824, 4170730, 4146602, 4087572, 444193, 4190297, 444237, 4105482, 196849, 4185273, 443772, 78916, 442542, 444111, 76848, 4245384, 4161947, 4266814, 4127735, 4047351, 4084286, 3655670, 40489336, 201093, 4174406, 4308468, 4306831, 4347179, 607157, 4180168, 4322630, 443796, 4043900, 4027538, 37017777, 4043718, 4344254, 200644, 133566, 37395594, 40484119, 4034650, 4121790, 761859, 4345453, 4180772, 4345448, 4173075, 36675187, 36675189, 76032, 4124848, 4080337, 4121789, 4120281	
Surgical Site Infection	437474	
Other Infection	432250	4028265, 132736, 4331670, 42537043, 42537216, 42537495, 4028070, 37396146, 255848, 256451, 4270490, 4253010, 42536600, 4309315, 40483549, 40481969, 40481970, 40480732, 40480731, 40482509, 4003305, 4001293, 4003303, 4001965, 4001294, 4003306, 36715562, 4151843, 141663, 74862, 80626, 4152591, 4002794, 761909, 37309799, 37309829, 37309798, 37309800, 37309830, 37309779, 37309778, 37309854, 37309869, 36717458, 607418, 4334028, 4262590, 4308690, 4291175, 762781, 4181583, 437486, 4110027, 4309954, 4122755, 37312548, 4066144, 4309214, 4336548, 4065984, 4042997, 4185761, 4136096, 4051481, 619673, 4185273, 4093433, 4171577, 4134613, 4193167, 4029803, 4058352, 193353, 43530817, 4050695, 4318386, 4029803, 439417, 4130006, 4116986, 4152958, 4155028, 4151520, 4095409, 36715560, 4110712, 37395724, 4327871, 4201370, 40483694, 4280729, 40547222,

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

Concept IDs include descendants unless highlighted as being excluded. By OMOP standards descendants automatically include the ancestor.

Before finalizing the concept sets, CohortDiagnostics will run on cohorts created using the initial concept sets to check code counts and patient characteristics which might give indications to adjust the concept sets.

APPENDIX I – TABLE 2: LISTS WITH CONCEPT DEFINITIONS FOR EXPOSURE

Prescriptions will be identified based on the relevant ingredient. Non-systemic products will be excluded from the code list.

Antibiotic	Class	ATC code	ConceptID
Arbekacin	Aminoglycosides	J01GB12	21603005
Aspoxicillin	Penicillins	J01CA19	40255264
Azithromycin	Macrolides	J01FA10	21602978
Azlocillin	Penicillins	J01CA09	21602828
Bekanamycin	Aminoglycosides	J01GB13	40255908
Biapenem	Carbapenems	J01DH05	21602924
Carbenicillin	Penicillins	J01CA03	21602822
Carindacillin	Penicillins	J01CA05	21602824
Cefaclor	Second-generation cephalosporins	J01DC04	21602886
Cefamandole	Second-generation cephalosporins	J01DC03	21602885
Cefbuperazone	Second-generation cephalosporins	J01DC13	40255561
Cefcapene-pivoxil	Third-generation cephalosporins	J01DD17	21602911
Cefdinir	Third-generation cephalosporins	J01DD15	21602909
Cefditoren-pivoxil	Third-generation cephalosporins	J01DD16	21602910
Cefepime	Fourth-generation cephalosporins	J01DE01	21602915
Cefetamet-pivoxil	Third-generation cephalosporins	J01DD10	21602904
Cefixime	Third-generation cephalosporins	J01DD08	21602902
Cefmenoxime	Third-generation cephalosporins	J01DD05	21602899
Cefmetazole	Second-generation cephalosporins	J01DC09	21602891
Cefminox	Second-generation cephalosporins	J01DC12	40255560
Cefodizime	Third-generation cephalosporins	J01DD09	21602903
Cefonicid	Second-generation cephalosporins	J01DC06	21602888
Cefoperazone	Third-generation cephalosporins	J01DD12	21602906
Ceforanide	Second-generation cephalosporins	J01DC11	21602893
Cefoselis	Fourth-generation cephalosporins	to be assigned	2000000002
Cefotaxime	Third-generation cephalosporins	J01DD01	21602895
Cefotetan	Second-generation cephalosporins	J01DC05	21602887
Cefotiam	Second-generation cephalosporins	J01DC07	21602889
Cefoxitin	Second-generation cephalosporins	J01DC01	21602883
Cefozopran	Fourth-generation cephalosporins	J01DE03	21602917
Cefpiramide	Third-generation cephalosporins	J01DD11	21602905
Cefpirome	Fourth-generation cephalosporins	J01DE02	21602916
Cefpodoxime-proxetil	Third-generation cephalosporins	J01DD13	21602907
Cefprozil	Second-generation cephalosporins	J01DC10	21602892
Cefsulodin	Third-generation cephalosporins	J01DD03	21602897

Antibiotic	Class	ATC code	ConceptID
Ceftazidime	Third-generation cephalosporins	J01DD02	21602896
Cefteram-pivoxil	Third-generation cephalosporins	J01DD18	715906
Ceftibuten	Third-generation cephalosporins	J01DD14	21602908
Ceftizoxime	Third-generation cephalosporins	J01DD07	
Ceftriaxone	Third-generation cephalosporins	J01DD04	21602898
Cefuroxime	Second-generation cephalosporins	J01DC02	21602884
Chlortetracycline	Tetracyclines	J01AA03	21602801
Cinoxacin	Quinolones	J01MB06	21603033
Ciprofloxacin	Fluoroquinolones	J01MA02	21603009
Clarithromycin	Macrolides	J01FA09	21602977
Clofoctol	Phenol derivatives	J01XX03	21603063
Clomocycline	Tetracyclines	J01AA11	21602809
Delafloxacin	Fluoroquinolones	J01MA23	715911
Demeclocycline	Tetracyclines	J01AA01	21602799
Dibekacin	Aminoglycosides	J01GB09	21603002
Dirithromycin	Macrolides	J01FA13	21602981
Doripenem	Carbapenems	J01DH04	21602923
Enoxacin	Fluoroquinolones	J01MA04	21603011
Ertapenem	Carbapenems	J01DH03	21602922
Erythromycin	Macrolides	J01FA01	21602970
Fidaxomicin	Macrolides	A07AA12	43534745
Fleroxacin	Fluoroquinolones	J01MA08	21603015
Flomoxef	Second-generation cephalosporins	J01DC14	40255562
Flumequine	Quinolones	J01MB07	21603034
Flurithromycin	Macrolides	J01FA14	21602982
Fosfomycin_oral	Phosphonics	J01XX01	21603061
Fusidic-acid	Steroid antibacterials	J01XC01	21603052
Garenoxacin	Fluoroquinolones	J01MA19	21603026
Gatifloxacin	Fluoroquinolones	J01MA16	21603023
Gemifloxacin	Fluoroquinolones	J01MA15	21603022
Grepafloxacin	Fluoroquinolones	J01MA11	21603018
Imipenem/cilastatin	Carbapenems	J01DH51	21602925
Isepamicin	Aminoglycosides	J01GB11	21603004
Josamycin	Macrolides	J01FA07	21602975
Kanamycin_IV	Aminoglycosides	J01GB04	21600610
Kanamycin_oral	Aminoglycosides	A07AA08	21602997
Lascufloxacin	Fluoroquinolones	J01MA25	947811
Latamoxef	Third-generation cephalosporins	J01DD06	21602900
Levofloxacin	Fluoroquinolones	J01MA12	21603019
Levonadifloxacin	Fluoroquinolones	J01MA24	947889
Lincomycin	Lincosamides	J01FF02	21602986

Antibiotic	Class	ATC code	ConceptID
Lomefloxacin	Fluoroquinolones	J01MA07	21603014
Loracarbef	Second-generation cephalosporins	J01DC08	21602890
Lymecycline	Tetracyclines	J01AA04	21602802
Meropenem	Carbapenems	J01DH02	21602921
Metacycline	Tetracyclines	J01AA05	21602803
Mezlocillin	Penicillins	J01CA10	21602829
Micronomicin	Aminoglycosides	to be assigned	2000000001
Midecamycin	Macrolides	J01FA03	21602972
Minocycline_oral	Tetracyclines	J01AA08	21602806
Miocamycin	Macrolides	J01FA11	21602979
Moxifloxacin	Fluoroquinolones	J01MA14	21603021
Nemonoxacin	Quinolones	J01MB08	1588669
Neomycin_IV	Aminoglycosides	J01GB05	21602998
Neomycin_oral	Aminoglycosides	A07AA01	21600603
Netilmicin	Aminoglycosides	J01GB07	21603000
Norfloxacin	Fluoroquinolones	J01MA06	21603013
Ofloxacin	Fluoroquinolones	J01MA01	21603008
Oleandomycin	Macrolides	J01FA05	21602973
Oxolinic-acid	Quinolones	J01MB05	21603032
Oxytetracycline	Tetracyclines	J01AA06	21602804
Panipenem	Carbapenems	J01DH55	21602926
Pazufloxacin	Fluoroquinolones	J01MA18	21603025
Pefloxacin	Fluoroquinolones	J01MA03	21603010
Penimepicycline	Tetracyclines	J01AA10	21602808
Pheneticillin	Penicillins	J01CE05	21602845
Pipemidic-acid	Quinolones	J01MB04	21603031
Piperacillin	Penicillins	J01CA12	21602866
Piperacillin/tazobactam	Beta-lactam/beta-lactamase-inhibitor_anti-pseudomonal	J01CR05	21602831
Piromidic-acid	Quinolones	J01MB03	21603030
Pristinamycin	Streptogramins	J01FG01	21602988
Prulifloxacin	Fluoroquinolones	J01MA17	21603024
Ribostamycin	Aminoglycosides	J01GB10	21603003
Rifabutin	Rifamycins	J04AB04	21603099
Rifampicin	Rifamycins	J04AB02	21603097
Rifamycin_IV	Rifamycins	J04AB03	21603098
Rifamycin_oral	Rifamycins	A07AA13	715872
Rifaximin	Rifamycins	A07AA11	21600613
Rokitamycin	Macrolides	J01FA12	21602980
Rolitetracycline	Tetracyclines	J01AA09	21602807

Antibiotic	Class	ATC code	ConceptID
Rosoxacin	Quinolones	J01MB01	21603028
Roxithromycin	Macrolides	J01FA06	21602974
Rufloxacin	Fluoroquinolones	J01MA10	21603017
Sarecycline	Tetracyclines	J01AA14	715904
Sisomicin	Aminoglycosides	J01GB08	21603001
Sitafloxacin	Fluoroquinolones	J01MA21	40256175
Solithromycin	Macrolides	J01FA16	1123620
Sparfloxacin	Fluoroquinolones	J01MA09	21603016
Spiramycin	Macrolides	J01FA02	21602971
Streptoduocin	Aminoglycosides	J01GA02	21602993
Streptomycin_IV	Aminoglycosides	J01GA01	21600606
Streptomycin_oral	Aminoglycosides	A07AA04	21602992
Sulbenicillin	Penicillins	J01CA16	21602835
Tazobactam	Beta-lactamase-inhibitors	J01CG02	21602860
Tebipenem	Carbapenems	J01DH06	715908
Teicoplanin	Glycopeptides	J01XA02	21603044
Telithromycin	Macrolides	J01FA15	21602983
Temafloxacin	Fluoroquinolones	J01MA05	21603012
Temocillin	Penicillins	J01CA17	21602836
Ticarcillin	Penicillins	J01CA13	21602832
Tobramycin	Aminoglycosides	J01GB01	21602995
Tosufloxacin	Fluoroquinolones	J01MA22	715910
Troleandomycin	Macrolides	J01FA08	21602976
Trovafloxacin	Fluoroquinolones	J01MA13	21603020
Vancomycin_IV	Glycopeptides	J01XA01	21600611
Vancomycin_oral	Glycopeptides	A07AA09	21603043

APPENDIX II – ENCEPP CHECKLIST

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
DARWIN EU® - DUS of Antibiotics in the 'Watch' category of the WHO AWaRe classification of antibiotics for evaluation and monitoring of use.

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

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]	☒	☐	☐	6 - milestones
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.	☒	☐	☐	

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

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8 – Research questions and objectives
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *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)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.1 and 9.7.5.1
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?	☒	☐	☐	9.4
4.2	Is the planned study population defined in terms of:				9.2.1
	4.2.1 Study time period	☒	☐	☐	
	4.2.2 Age and sex	☒	☐	☐	
	4.2.3 Country of origin	☒	☐	☐	
	4.2.4 Disease/indication	☒	☐	☐	
	4.2.5 Duration of follow-up	☒	☐	☐	
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	☒	☐	☐	9.2.3

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)	☒	☐	☐	9.3.1
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?	☒	☐	☐	9.3.1
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☒	☐	☐	9.7.3
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?	☐	☐	☒	
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 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:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☐	☐	☒	
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4 and 9.3.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4 and 9.7.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4 and 9.7.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4
9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.4
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?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☒	☐	☐	9.7.4
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?	☐	☐	☒	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.6

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)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
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:				9.9
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).	☐	☐	☒	
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)	☐	☒	☐	

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?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10
13.3 Have data protection requirements been described?	☒	☐	☐	10

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?	☒	☐	☐	5

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)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: Katia Verhamme

Date: 22/November/2022

Signature: _____