

Study Protocol – Incidence, prevalence, and characterisation of medicines with suggested drug shortages in Europe

27/10/2023

Version 2.0.

This document represents the views of the Pharmaco- and Device Epidemiology Group from University of Oxford

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DOCUMENT HISTORY

Version	Date	Description
V 0.1.	31/03/2023	**First version for review**
V 0.2.	30/05/2023	**Second version for review (for data partners)**
V 0.3.	07/08/2023	**Clean up including data partners suggestions**
V 1.0.	29/09/2023	**Version uploaded to EU PAS**
V 2.0	27/10/2023	**Addition of Data Partner into Appendix III - uploaded to EU PAS**

Study Title	Incidence, prevalence, and characterisation of medicines with suggested drug shortages in Europe
Protocol version identifier	2.0.
Date of last version of protocol	27 October 2023
EU PAS register number	EUPAS106954
Active substance	- Medicines suggest as being in shortage by regulatory agencies, including the latest list of medicines with ongoing shortage for at least 1 year by the European Medicines Agency (EMA): https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fwww.ema.europa.eu%2Fsites%2Fdefault%2Ffiles%2FMedicines_output_shortages.xlsx&wdOrigin=BROWSELINK - Suggested alternatives
Medicinal product	N/A
Research question and objectives	This study aims to characterise the incidence and prevalence of medicines with (suggested) shortages and their alternatives for the period 2010-2023, stratified by healthcare setting and time period in each database. Furthermore, we aim to describe incident and prevalent patients receiving a prescription / dispensation of a medicine with (suggested) shortages for the period 2010-2023, stratified by year in each database, including information on potential indication, treatment duration, and dosage.
Country(-ies) of study	Open to any data partner in EHDEN (data partners from the EHDEN consortium [EFPIA] may contribute data from outside Europe)
Author	Marta Pineda-Moncusí, Theresa Burkard, Daniel Prieto-Alhambra

LIST OF ABBREVIATIONS

Acronyms/terms	Description
CDM	Common Data Model
DA	Disease Analyzer
DUS	Drug Utilization Study
EFPIA	European Federation of Pharmaceutical Industries and Associations
EHDEN	European Health Data & Evidence Network
EHR	Electronic Health Records
EMA	European Medicines Agency
GP	General Practitioner
WHO	World Health Organization
OMOP	Observational Medical Outcomes Partnership
PCT	Primary Care Teams

1. TITLE

Incidence, prevalence, and characterisation of medicines with suggested drug shortages in Europe

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	Dr Daniel Prieto-Alhambra	University of Oxford
Principal Investigators	Dr Theresa Burkard Dr Marta Pineda-Moncusí	University of Oxford
Data Scientists	Dr Martí Català Sabaté Dr Edward Burn	University of Oxford
Epidemiologist	Dr Theresa Burkard Dr Marta Pineda-Moncusí	University of Oxford
Clinical Domain Experts	Dr Daniel Prieto-Alhambra Dr Theresa Burkard	University of Oxford
Data Partner*	**Names**	**Organisation**
List of Data Partners who confirmed their interest (by 30 of August 2023) is included in Annex III.		

*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

Incidence, prevalence, and characterisation of medicines with suggested drug shortages in Europe

Rationale and Background

Shortage of essential medicines has a harmful impact on patient's health by increasing mortality, adverse events, and therapy errors.

Since 2016, the European Medicines Agency (EMA) has published a public catalogue of medicines under surveillance due to shortage in more than one European country. The list includes information such as the reason for the shortage, and recommendations for patients, healthcare professionals and other stakeholders. The work of the task force that publish the catalogue of drug shortages was temporarily suspended between March 2020 and December 2021 due to the COVID-19 pandemic.

This study shall improve our understanding of drug shortages in routine health care delivery by showing trends over time as well as patient characteristics, including indication, treatment duration, and dose. The results will contribute to the European efforts to monitor use of critical medicines as part of the global fight against medicine shortage.

Research question and Objectives

The objectives of this study are:

(i) To investigate the incidence and prevalence of use of medicines with (suggested) shortage, including those listed as ongoing in the EMA shortages catalogue for ≥1 year and their alternatives by calendar year, stratified by healthcare setting for each database during the study period 2010-2023.

(ii) To describe the incident and prevalent patients (including but not limited to duration of usage of the medicines of interest, the potential indication for prescribing/dispensing it, and dosage) stratified by calendar year), in order to observe changes in patient's profiles

Research Methods

Study design

- Population level cohort study (Objective 1, Population-level drug utilisation study on medicines with [suggested] shortages and their alternatives)
- Patient level cohort study (Objective 2, Patient-level drug utilisation analysis describing patient characteristics, including duration of treatment, potential indication of the medicines of interest, and dose)

Population

Population-level drug utilisation study: All individuals present in the database in the period between 2010 and 2023 will be included. For this population, incidence and prevalence of use of medicines with (suggested) shortages and their alternatives will be explored.

Patient-level drug utilisation study: All new and prevalent users of medicines with (suggested) shortages and their alternatives in the period between 2010 and 2023. Patients can be eligible more than once during the study period.

Variables

Drug of interest: Drugs with (suggested) shortage, including ongoing shortages listed in the EMA shortages catalogue for ≥1 year, and their alternatives between 2010 and 2023 (see also section 9.3.1 – exposure)

Data sources

Open to any database from EHDEN data partners who finished their mapping to the OMOP CDM, this includes EHDEN consortium members (i.e. EFPIA).

Sample size

No sample size has been calculated.

Data analyses

Population-level drug utilisation study: annual period prevalence of the medicine use and annual incidence proportion, as described in section 9.7.5.1 – Population-level drug utilisation study.

Patient-level drug utilisation study: Large-scale patient-level characterisation will be conducted in incident and in prevalent users, defined as follows: I) in incident users, the index date will be the date of a prescription qualifying as a "new prescription" (i.e. after at least 30 days of non-use) of the specific medicine of interest for each person; II) the index date in prevalent users will be the earliest date of a prescription in the calendar year. Frequency of potential indication at index date will be assessed. Treatment duration will be estimated and the minimum, p25, median, p75, and maximum will be provided. Furthermore, daily dosage will be estimated and the minimum, p25, median, p75, and maximum will be provided. See for further description section 9.7.3 and 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 being masked.

5. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason

6. MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE
Draft Study Protocol	30/05/2023
Final Study Protocol	September 2023

Creation of Analytical code	Q3-Q4 2023
Execution of Analytical Code on the data	Q4 2023-Q1 2024
Interim Study Report (if applicable)	Not applicable
Draft Study Report	Q1-Q2 2024
Final Study Report	Q2-Q3 2024

7. RATIONALE AND BACKGROUND

The WHO considers affordable, safe, effective and quality medicines essential for people's health and for achieving a universal health coverage.[1] Shortages of essential medicines has a harmful impact on patient's health, increases the rates of mortality, adverse events and therapy errors, and also increases the economic costs of the treatment.[2] The WHO recognised the severity of global shortages of medicines and urged the Member States to develop strategies for diminishing its impact.[3, 4] Unfortunately, the COVID-19 outbreak exacerbated this phenomenon, and the COVID-19 vaccines were a perfect example to witness the consequences of drugs shortage:

During the first months of the pandemic, countries across the world went into lockdown and local and global transportations were reduced or stopped, affecting most of the stages of the manufactures' supply chain, including drugs production and distribution.[5, 6] Moreover, due to the uncertainty, patients started stockpiling.[7] Ultimately, the feasible production was insufficient to cover the worldwide demand of COVID-19 vaccines and there was an unequal distribution where countries with the greatest economic power were served first.[8]

Since 2016, the EMA publishes a public catalogue of medicines under surveillance due to shortages in more than one European country.[9, 10] The catalogue includes information such as the reason for the shortage, and recommendations for patients, healthcare professionals and other stakeholders. One of the most worrying and repeated reasons for their shortage is an increased demand of the product in Europe, for example antibiotics or cytarabine (a chemotherapy).

Medicines with increasing demand should be prioritized as key targets of stewardship programs and monitoring. Thus, the EMA shortages catalogue and further development of a centralised electronic platform for pharmaceutical companies and countries to report on shortages, the European shortages monitoring platform (ESMP), by 2025, shall enable monitoring the consumption, defining targets and monitoring the effects of stewardship policies that aim to optimize the use of medicines in shortage.

This study will improve our understanding of the use of medicines with shortages in routine health care delivery, including indication, treatment duration, doses, and trends over time. The use of a federated data network like EDHEN has the benefit to provide a more generalisable and complete picture of drug shortages in Europe. The results will contribute to the European efforts to monitor use of critical medicines as part of the global fight against medicine shortage.

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 medicines with (suggested) shortages and their alternatives stratified by annual period (calendar year) and healthcare setting for each database during the study period 2010-2023
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	The study cohort will comprise all individuals present in the database in the period 2010-2023. Additional eligibility criteria will be applied for the calculation of incidence proportion where observation time of the respective use of the medicine of interest is excluded during use and 30 days afterwards (wash out period).
Exposure:	Medicines with (suggested) shortages and their alternatives, including those with an ongoing shortage listed in the EMA catalogue for ≥1 year.
Comparator:	None
Outcome:	None
Time *(when follow up begins and ends):*	For the (suggested) medicines in shortages and their alternatives, follow-up will start as of eligibility of a patient or, if already eligible, on a pre-specified calendar time point e.g., 1st of January between 2010-2023 for the calculation of annual incidence proportions and period prevalence. End of follow-up will be defined as the earliest of loss to follow-up, end of data availability, death (where available), or end of the study period.
Setting:	GP/Primary care/outpatient, hospital/inpatient/outpatient, claims, disease registries/cohorts setting using data from data sources of EHDEN data partners.
Main measure of effect:	Incidence proportion and period prevalence of the use of medicines with (suggested) shortages and their alternatives

B. **Secondary research question and objective**

Objective:	To characterize the patients and the use of medicines regarding potential indication, treatment duration, and dosage.

Hypothesis:	Not applicable
Population ***(mention key inclusion-exclusion criteria):***	The study cohort will comprise the identified incident or prevalent users of the medicines with (suggested) shortage and their alternatives from the primary research question in the period 2010-2023.
Exposure:	Medicines with (suggested) shortage and their alternatives
Comparator:	None
Outcome:	None
Time ***(when follow up begins and ends):***	Patients will be followed-up during the eligible period from the index date (i.e., date of a new prescriptions) until the end of the drug use.
Setting:	GP/Primary care/outpatient, hospital/inpatient/outpatient, claims, disease registries/cohorts setting using data from data sources of EHDEN data partners.
Main measure of effect:	Potential indication of medicine use Duration of medicine use (expressed as minimum, p25, median, p75, and maximum) Daily dosage of medicine 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 open to any database from EHDEN data partners. The study will comprise two consecutive parts:

1. A population-based cohort study will be conducted to address objective 1, assessing the incidence and prevalence of the respective medicines of interest and their alternatives (if available).
2. A new drug user cohort and a prevalent user cohort will be used to address objective 2; to characterise patient-level drugs utilisation including the indication of use, duration of use, and dosage 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 (2010-2023, or latest data coverage).

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

9.2.2 Study period and follow-up

Study period:

The study period will be from the 1st of January 2010 (or earliest possible) until 31st December 2023 or the respective latest date of data coverage of the respective databases.

Follow-up:

Follow-up will start from the 1st of January 2010 (or earliest available eligibility), and end follow-up will be defined as the earliest of loss to follow-up, end of data availability, death (where available), or end of the study period.

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	Code Type	Diagnosis position	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
All patients from the database eligible for the study – **Analysis of Incident use of medicines of interest**	Patient present in the database during the study period (2010-2023) and with at least 30 day of non-use of the medicine of interest (wash out)	Multiple	Incident	[-30, -1]	Any	Nap	Nap	specific medicine	Nap	Nap
All patients from the database eligible for the study – **Analysis of Prevalent use of medicines of interest**	Patient present in the database during the study period (2010-2023)	Multiple	Prevalent	None	Any	Nap	Nap	Nap	Nap	Nap
Patients identified as incident users of the medicines of interest – **Characterisation of users of medicines of interest**	Patient present in the database during the study period (2010-2023) and with at least 30 day of non-use of the medicine of interest (wash out)	Multiple	Incident	[-30, -1]	Any	Nap	Nap	specific medicine	Nap	Nap
Patients identified as prevalent users of the medicines of interest – **Characterisation of users of medicines of interest**	Patient present in the database during the study period (2010-2023)	Multiple	Prevalent	None	Any	Nap	Nap	Nap	Nap	Nap

Nap = not applicable

Both incidence proportion and period prevalence require an appropriate denominator population. The denominator will be defined as any individual in the database who is present for ≥1 day in the time period (i.e., in the month, quarter or year of the measurement).

9.2.3 In- and exclusion criteria

9.2.3.1 Population-level drug utilisation study

The study cohort will comprise all individuals present in the period 2010-2023 (or the latest data coverage available).

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

9.2.3.2 Patient-level drug utilisation study

All new users of the medicines of interest, after 30 days of no use of the specific medicine, and all prevalent users of medicines of interest in the period between 01/01/2010 and 31/12/2023 (or latest date available).

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 2010-2023 (or the latest available)	Incident users (See under inclusion criterion)	After	N/A	Any	N/A	N/A	All individuals within the selected databases	N/A	N/A
Observation period in the database during the period 2010-2023 (or the latest available)	Prevalent users (See under inclusion criterion)	After	N/A	Any	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 medicines listed as (suggested) shortage, including those medicines listed as ongoing shortages for at least 365 days (cut off date 25.09.2023) in the EMA shortages catalogue (medicines under surveillance by the EMA due to shortage in more than one European country), and their alternatives.

The EMA shortages catalogue of medicines on ongoing and resolved shortages is available in:

a) The online EMA shortages catalogue browser: https://www.ema.europa.eu/en/medicines/ema_group_types/ema_document-supply_shortage/field_ema_shortage_status/0?sort=field_ema_computed_date_field&order=desc)

b) Live, as an excel spreadsheet: https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fwww.ema.europa.eu%2Fsites%2Fdefault%2Ffiles%2FMedicines_output_shortages.xlsx&wdOrigin=BROWSELINK

c) A downloadable table (name: Download table of medicine shortage): https://www.ema.europa.eu/en/medicines/download-medicine-data#shortages-section:~:text=Download%20table%20of%20medicine%20shortages

Alternative medicines comprise suggestions made directly in the announcement of EMA, or by using the ATC group in which a medicine was in, or recommendations from treatment guidelines / domain experts. The suggestions are made below in Table 5. Details of exposure are described in Table 6.

Table 5. Medicines listed as (suggested) shortages and alternatives

Medicines in (suggested) shortages	Suggested alternatives (as a group if more than 1 medicine) [ATC Code plus name]
Alteplase or Tenecteplase	B01AD01 streptokinase B01AD04 urokinase
Sarilumab	Any other biologic or targeted synthetic disease modifying anti-rheumatic drug (b/tsDMARD) excluding tocilizumab so we can use the same alternative: L04AA24 Abatacept L04AA29 Tofacitinib L04AA37 Baricitinib L04AA44 Upadacitinib L04AB01 Etanercept L04AB02 Infliximab L04AB05 Certolizumab L04AB06 Golimumab L04AC03 Anakinra

Verteporfin	Watchful wait or anti-VEGF (depending on the condition): S01LA04 ranibizumab S01LA08 bevacizumab
Tocilizumab	See alternatives for sarilumab
Varenicline	N07BA01 nicotine
ceftolozane / tazobactam (combination)	Ample of antibiotics as alternatives in the suggested medicines list already
C1-esterase inhibitor, human	B06AC02 icatibant B06AC03 ecallantide B06AC04 conestat alfa B06AC05 lanadelumab B06AC06 berotralstat
arsenic trioxide	L01BC01 cytarabine L01DB02 daunorubicin L01DB06 idarubicin L01XF01 tretinoin (oral formulation only) L01XY01 cytarabine / daunorubicin (combination)
belatacept	L04AA06 mycophenolic acid L04AA10 sirolimus L04AD01 ciclosporin L04AD02 tacrolimus
ganirelix	H01CC02 cetrorelix
tigecycline	Ample of antibiotics as alternatives in the suggested medicines list already
imiglucerase	A16AB10 velaglucerase alfa A16AB11 taliglucerase alfa
agalsidase beta	A16AB03 agalsidase alfa
azithromycin	Ample of antibiotics as alternatives in the suggested medicines list already
clarithromycin	Ample of antibiotics as alternatives in the suggested medicines list already
phenoxymethylpenicillin	Ample of antibiotics as alternatives in the suggested medicines list already
benzylpenicillin	Ample of antibiotics as alternatives in the suggested medicines list already
amoxicillin	Ample of antibiotics as alternatives in the suggested medicines list already
amoxicillin / clavulanic acid (combination)	Ample of antibiotics as alternatives in the suggested medicines list already

ceftriaxone	Ample of antibiotics as alternatives in the suggested medicines list already
cefotaxime	Ample of antibiotics as alternatives in the suggested medicines list already
meropenem	Ample of antibiotics as alternatives in the suggested medicines list already
cefuroxime	Ample of antibiotics as alternatives in the suggested medicines list already
piperacillin / tazobactam (combination)	Ample of antibiotics as alternatives in the suggested medicines list already

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
Medicines listed with (suggested) shortages	Preliminary code lists provided in Appendix I	[-30, -1] for incident use only	Calendar year for incidence/prevalence, Calendar year for large scale characterisation (alternatives will not be assessed here)	Any	Rx Norm	N/A	All individuals present in the database during the study period who have had a prescription / dispensation of the medicine of interest during the study period: 20010-2023.	Previous medicine use (of the specific drug 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:

- Period:
    - Calendar year for Medicines listed as (suggested) shortages and their alternatives.

    If calendar year stratifications do not allow to observe the changes once the shortage was declared, monthly or quarterly period (i.e., 01/01/2020 – 31/03/2020, 01/04/2020 – 30/06/2020, etc.) will be used as alternative.
- Healthcare setting: primary care, secondary care (if a database contains both), data types (e.g. claims versus electronic health care records or registry data)
- For stratification
    - Age bands: <18, 18-64,>=65 years old.
    - Sex

9.3.3.2 Covariates in patient-level drug utilisation study:

- For stratification:
    - Calendar year for 2010 – 2023

- For patient description:
    - Age: we will use <18, 18-64,>=65 age bands. If feasible, use of 5-year age bands, with the exception of under 25-year-olds (i.e., 0-1, 2-11, 12-17, 18-24, 25-29 etc. 85+), will be discussed.
    - Sex
    - Top 10 of comorbidities from large-scale patient characterisation
    - Indications (included in Appendix I)

The operational definition of the covariates is described in the table below. Index dates are the start dates of every "new prescription" (after a 30 day wash out period), or the first prescription in a calendar year (prevalent use) during the study period:

Table 7: Operational Definitions of Covariates

Characteristic	Details	Type of variable	Assessment window	Care Settings	Code Type	Diagnosis Position	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Indication of Use	Check for conditions of interest related to use of the medications of interest	Counts	At index date, around index date: [-30, 7], Clinical history from any time before (because treatments are so diverse)	Any	SNOMED	N/A	Persons with new use during the study period and, separately, in prevalent users	N/A	N/A
Comorbidity	Large-scale patient-level characterisation with regard to underlying comorbidity	Counts	At index date (clinical history from any time before).	Any	SNOMED	N/A	Persons with new use during the study period and, separately, in prevalent users	N/A	N/A

9.4 Data sources

This study will be conducted using routinely collected data from any healthcare setting, open to any database from EHDEN Data Partners who had finished the mapping to the OMOP CDM (including EHDEN consortium members [EFPIA]).

Up to date (March 2023), there are 187 Data Partners from 29 different countries who had mapped or are currently mapping their databases to the OMOP CDM. The list is available at: https://www.ehden.eu/datapartners/.

9.5 Study size

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

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

9.7 Data Analysis

The analysis will include calculation of population-based incidence and prevalence, as described in section 9.7.5.1 – Population-level drug utilisation study, characterisation of patient-level features for users of the medicines of interest, frequency of potential indications, and descriptive statistics of treatment duration and dosage of the medicines, 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, and values will be rounded to the reassert multiple of 5 when necessary to ensure values can't be deducted.

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.

New user cohorts

New users will be selected based on their new prescription of the respective drug of interest in a pre-defined time windows (calendar year periods e.g.). 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.

Prevalent user cohort

Prevalent users will be selected based on first prescription in the calendar year of interest.

9.7.4 Methods to derive parameters of interest

Calendar time

Calendar time will be based on calendar year of the index prescription in the population level analysis and patient level analysis respectively. If necessary, for those medicines that calendar year stratifications do not allow to observe the changes once the shortage was declared due to a reduced follow-up, monthly or quarterly period (i.e., 01/01/2010 – 31/03/2010, 01/04/2010 – 30/06/2010, etc.) will be considered as alternative time periods.

Indication

Potential indications will be determined based on index date, a time window before and after the new prescription of the respective drug (index date) during the assessment window (-30 days to 7 days), and any time before index date.

Characterisation of patient-level features

Large-scale patient-level characterisation will be conducted, including age and sex. Co-variates will be extracted for the following time intervals: Concepts in the "condition" domain will be assessed for any time before and until index date. The top-10 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 medicine of interest.

Prevalence calculations

Prevalence will be calculated as a calendar year prevalence and summarises the total number of individuals who use the drug of interest during the given period (year) divided by the population at risk of getting

exposed during that period. 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 1**. Between time t+2 and t+3, two of the five study participants are users of medicines of interest giving a prevalence of 40%. Meanwhile, for the period t to t+1 all five also have some observation time during the time with one of the five study participants being a user of a medicine of interest, giving a prevalence of 20%.

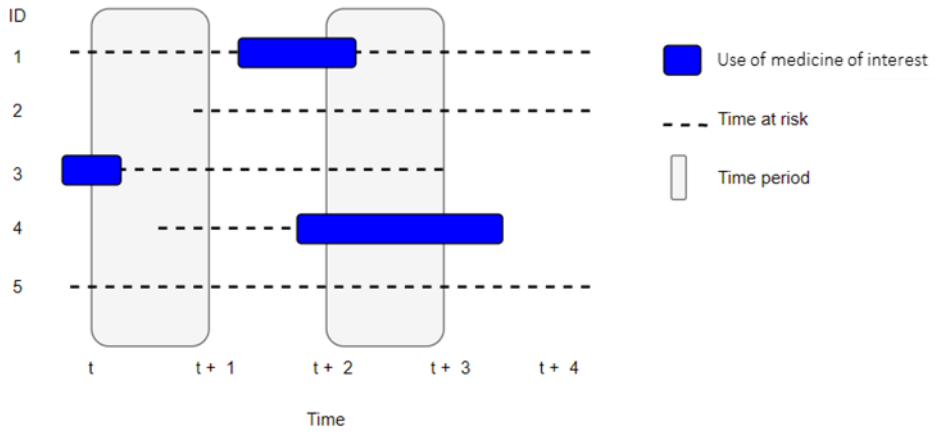


Figure 1: Period prevalence example for use of medicines with (suggested) shortage

Incidence calculations

Annual incidence proportion of the medicines of interest will be calculated as the number of **new users** after 30 days of no use divided by the population at risk of getting exposed during that period. Incidence proportions will be given together with 95% Poisson confidence intervals.

9.7.5.2 Patient-level drug utilisation study

New drug user patient-level characteristics on index date

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

Prevalent drug user patient-level characteristics on first calendar year prescription acting as "index date"

First prescription date of the calendar year will count as "index date". For each concept extracted at index date, the number of persons (N, %) with a record within the pre-specified time windows (i.e. per calendar year) will be provided.

Characterization of prevalent and new users will include the following characteristics:

Most frequent comorbidities

Concepts in the "condition" domain will be assessed for any time before and until index date. The top-10 will be reported.

Age

Sex

Indication

We will assess the diagnosis within pre-specified time windows (defined in 9.7.4). The number of persons (N, %) with a record of a potential indication within each time window will be provided. If a person has a record of more than one potential indication, that person will be included in both indication groups.

Treatment duration

Treatment duration will be calculated as the duration of the drug exposure of the new dispensation / prescription of a medicine of interest. Treatment duration will be summarized providing the minimum, p25, median, p75, and maximum treatment duration. For databases, where duration cannot be calculated due to missing information, treatment duration will not be provided.

Dosage

Daily dosage of treatment will be calculated per medicine of interest and administration route. Dose will be summarized providing the minimum, p25, median, p75, and maximum dose. For databases, where duration cannot be calculated due to missing information, dose will not be provided.

9.7.6 Description of sensitivity analyses.

None.

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). 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

A pharmacist will review the codes of the medicine of interest. 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 does not mean that the patient actually received the drug, especially in the situation of a shortage. This implies that we may miss the correct start date of a drug shortage when assessing incidence and prevalence of the medicines of interest in prescription data, i.e. the start date may be delayed. 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, treatment duration will not be provided. The same is true for dosage.

In addition, the recording of events used for patient characterisation and (potential) indication may vary across databases (e.g. some only record chronic conditions once, others several times).

Time at risk of population denominator may be incorrect for hospitals and registers, therefore we have selected to estimate incidence proportion instead of incidence rates to not rely on “time at risk”.

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, the data partners 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.

For each collaborator, the output files will be stored according to the specific legislation of each database, such as the use of Remote Research Environments. 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

The results will be compiled into a manuscript. Due to the scope of this research, we target this manuscript to be submitted into a high impact journal.

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14. ANNEXES

Appendix I: List of Stand-Alone documents (e.g., list of drugs & indications)

Appendix II: ENCePP checklist for study protocols.

Appendix III: list of data partners who confirmed their interest.

APPENDIX I - LISTS WITH CONCEPT DEFINITIONS FOR EXPOSURE & INDICATIONS

Prescriptions will be identified based on the relevant ingredient.

Indications will be identified based on the following conditions

	Drug (cohort) of interest	**Class**	**ATC code**	**Indication**
1	Alteplase or Tenecteplase	B01AD Enzymes	B01AD02 B01AD11	acute myocardial infarction, acute massive pulmonary embolism with haemodynamic instability, acute ischaemic stroke, catheter use (i.e. hemodialysis, hypovolemic shock, blood transfusion, platelet transfusion, chemotherapy)
2	Sarilumab	L04AC Interleukin inhibitors	L04AC14	moderately to severely active rheumatoid arthritis (RA), COVID-19
3	Verteporfin	S01LA Antineovascularisation agents	S01LA01	exudative (wet) age-related macular degeneration (AMD), used to perform ocular photodynamic therapy (PDT) in patients with choroidal neovascularization (CNV), central serous chorioretinopathy (CSC), polypoidal choroidal vasculopathy (PCV) and several other chorioretinal diseases
4	Tocilizumab	L04AC Interleukin inhibitors	L04AC07	rheumatoid arthritis, giant cell arteritis, juvenile idiopathic polyarthritis, systemic juvenile idiopathic arthritis, COVID-19
5	Varenicline	N07BA Drugs used in nicotine dependence	N07BA03	Smoking (cessation)
6	ceftolozane / tazobactam (combination)	J01DI Other cephalosporins and penems	J01DI54	bacteraemia, complicated intra-abdominal infections (e.g. appendiceal perforation, peri-appendiceal abscess), Complicated urinary tract infections (including pyelonephritis), pneumonia
7	C1-esterase inhibitor, human	B06AC Drugs used in hereditary angioedema	B06AC01	Hereditary angioedema type I and II (HAE)
8	arsenic trioxide	L01XX Other antineoplastic agents	L01XX27	low-to-intermediate risk acute promyelocytic leukaemia (APL)
9	belatacept	L04AA Selective immunosuppressants	L04AA28	Implants and transplants (prevent rejection)
10	ganirelix	H01CC Anti-gonadotropin-releasing hormones	H01CC01	prevention of premature luteinising hormone (LH) surges in women undergoing controlled ovarian hyperstimulation (COH) for assisted reproduction techniques (ART)

	Drug (cohort) of interest	Class	ATC code	Indication
11	tigecycline	J01AA Tetracyclines	J01AA12	Complicated skin and soft tissue infections (cSSTI), excluding diabetic foot infections, Complicated intra-abdominal infections (cIAI)
12	imiglucerase	A16AB Enzymes	A16AB02	non-neuronopathic (Type 1) or chronic neuronopathic (Type 3) Gaucher disease
13	agalsidase beta	A16AB Enzymes	A16AB04	Fabry disease (α-galactosidase A deficiency).
14	azithromycin	J01FA Macrolides S01AA Antibiotics	J01FA10 S01AA26	acute bacterial sinusitis, acute bacterial otitis media, pharyngitis, tonsillitis, acute exacerbation of chronic bronchitis, mild to moderately severe community acquired pneumonia, skin and soft tissue infections, uncomplicated Chlamydia trachomatis urethritis and cervicitis
15	clarithromycin	J01FA Macrolides	J01FA09	Lower respiratory tract infections for example, acute and chronic bronchitis, and pneumonia; Upper respiratory tract infections for example, sinusitis and pharyngitis; community acquired respiratory infections ; skin and soft tissue infections of mild to moderate severity (e.g. folliculitis, cellulitis, erysipelas) ; eradication of H. pylori in patients with duodenal ulcers;
16	phenoxymethylpenicillin	J01CE Beta-lactamase sensitive penicillins	J01CE02	Streptococcal infections: Pharyngitis ; Scarlet fever ; Skin and soft tissue infections (e.g. erysipelas) ; Pneumococcal infections: Pneumonia ; Otitis media ; Vincent's gingivitis and pharyngitis ; Prophylaxis of rheumatic fever and/or chorea ; Prophylaxis of pneumococcal infection (e.g. in asplenia and inpatients with sickle cell disease

	Drug (cohort) of interest	Class	ATC code	Indication
17	benzylpenicillin	J01CE Beta-lactamase sensitive penicillins S01AA Antibiotics	J01CE01 S01AA14	erysipelas ; syphilis: early syphilis (primary and secondary); latent syphilis (except for neurosyphilis and presence of pathological CSF findings); yaws; pinta; Prophylaxis of rheumatic fever (chorea, rheumatic carditis), poststreptococcal glomerulonephritis, erysipelas
18	amoxicillin	J01CA Penicillins with extended spectrum	J01CA04	Acute bacterial sinusitis; Acute otitis media; Acute streptococcal tonsillitis and pharyngitis; Acute exacerbations of chronic bronchitis; Community acquired pneumonia; Acute cystitis; Asymptomatic bacteriuria in pregnancy; Acute pyelonephritis; Typhoid and paratyphoid fever; Dental abscess with spreading cellulitis; Prosthetic joint infections; Helicobacter pylori eradication; Lyme disease; prophylaxis of endocarditis.
19	amoxicillin/clavulanic acid (combination)	J01CR Combinations of penicillins, incl. beta-lactamase inhibitors	J01CR02	Acute bacterial sinusitis; Acute otitis media; Acute exacerbations of chronic bronchitis ; Community acquired pneumonia; Cystitis; Pyelonephritis; Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis; Bone and joint infections, in particular osteomyelitis.
20	ceftriaxone	J01DD Third-generation cephalosporins	J01DD04	Bacterial Meningitis; Community acquired pneumonia; Hospital acquired pneumonia; Acute otitis media; Intra-abdominal infections; Complicated urinary tract infections (including pyelonephritis); Infections of bones and joints; Complicated skin and soft tissue infections; Gonorrhoea; Syphilis; Bacterial endocarditis; acute exacerbations of chronic obstructive

	Drug (cohort) of interest	Class	ATC code	Indication
				pulmonary disease; disseminated Lyme borreliosis (early (stage II) and late (stage III)) ; pre-operative prophylaxis of surgical site infections; neutropenic patients with fever that is suspected to be due to a bacterial infection; bacteraemia;
21	Cefotaxime	J01DD Third-generation cephalosporins	J01DD01	Infections of the lower respiratory tract; Infections of the kidneys and urinary tract; Infections of the skin and soft tissue; Genital infections caused by gonococci; Intra-abdominal infections (including Peritonitis); Lyme-borreliosis (especially stages II and III); Acute Meningitis; Sepsis; Endocarditis ; Peri-operative prophylaxis in surgical procedures such as colorectal, gastrointestinal, prostatic, urogenital and gynaecological surgery; infections caused by Pseudomonas;
22	Meropenem	J01DH Carbapenems	J01DH02	Severe pneumonia, including hospital and ventilator-associated pneumonia; Broncho-pulmonary infections in cystic fibrosis; Complicated urinary tract infections; Complicated intra-abdominal infections; Intra- and post-partum infections; Complicated skin and soft tissue infections; Acute bacterial meningitis; neutropenic patients with fever; bacteraemia;
23	Cefuroxime	S01AA Antibiotics J01DC Second-generation cephalosporins	S01AA27 J01DC02	Antibiotic prophylaxis of postoperative endophthalmitis after cataract surgery; Community acquired pneumonia; Acute exacerbations of chronic bronchitis; Complicated urinary tract infections, including pyelonephritis; Soft-tissue infections: cellulitis, erysipelas and wound infections; Intra-abdominal infections; Prophylaxis against infection in gastrointestinal

	Drug (cohort) of interest	Class	ATC code	Indication
				(including oesophageal), orthopaedic, cardiovascular, and gynaecological surgery (including caesarean section);
24	Piperacillin / Tazobactam (combination)	J01CR Combinations of penicillins, incl. beta-lactamase inhibitors	J01CR05	Severe pneumonia including hospital-acquired and ventilator-associated pneumonia; Complicated urinary tract infections (including pyelonephritis); Complicated intra-abdominal infections; Complicated skin and soft tissue infections (including diabetic foot infections); bacteraemia; neutropenic patients with fever
25	streptokinase or urokinase	B01AD Enzymes	B01AD01 B01AD04	*Alternative of alteplase or Tenecteplase (same indications)*
26	Abatacept or Tofacitinib or Baricitinib or Upadacitinib or Etanercept or Infliximab or Certolizumab or Golimumab or Anakinra	L04AA Selective immunosuppressants L04AB Tumor necrosis factor alpha (TNF-α) inhibitors L04AC Interleukin inhibitors	L04AA24 L04AA29 L04AA37 L04AA44 L04AB01 L04AB02 L04AB05 L04AB06 L04AC03	*Alternative of sarilumab or tocilizumab (same indications)*
27	Ranibizumab or bevacizumab	S01LA Antineovascularisation agents	S01LA04 S01LA08	*Alternative of verteporfin (same indications)*
28	nicotine	N07BA Drugs used in nicotine dependence	N07BA01	*Alternative of varenicline (same indications)*
29	Icatibant or Ecallantide or	B06AC Drugs used in hereditary angioedema	B06AC02 B06AC03	*Alternative of C1-esterase inhibitor (same indications)*

	Drug (cohort) of interest	Class	ATC code	Indication
	conestat alfa or lanadelumab or berotralstat		B06AC04 B06AC05 B06AC06	
30	Cytarabine or Daunorubicin or idarubicin or tretinoin (oral formulation only) or cytarabine / daunorubicin (combination)	L01B ANTIMETABOLITES L01D CYTOTOXIC ANTIBIOTICS AND RELATED SUBSTANCES L01X OTHER ANTINEOPLASTIC AGENTS	L01BC01 L01DB02 L01DB06 L01XF01 L01XY01	*Alternative of arsenic trioxide (same indications)*
31	mycophenolic acid or sirolimus or ciclosporin or tacrolimus or	L04AA Selective immunosuppressants L04AD Calcineurin inhibitors	L04AA06 L04AA10 L04AD01 L04AD02	*Alternative of belatacept (same indications)*
32	cetrorelix	H01CC Anti-gonadotropin-releasing hormones	H01CC02	*Alternative of ganirelix (same indications)*
33	velaglucerase alfa taliglucerase alfa	A16AB Enzymes	A16AB10 A16AB11	*Alternative of imiglucerase (same indications)*
34	agalsidase alfa	A16AB Enzymes	A16AB03	*Alternative of agalsidase beta (same indications)*

APPENDIX II – ENCEPP CHECKLIST

ENCePP Checklist for Study Protocols (Revision 1)

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:
Incidence, prevalence, and characterisation of medicines with suggested drug shortages in Europe

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.	☒	☐	☐	

Comments:

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

[2] Date from which the analytical dataset is completely available.

Section 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	☒	☐	☐	

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
	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)	☐	☐	☒	

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

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

Comments:

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

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☐	☒	☐	9.4
	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?	☒	☐	☐	9.3.3
9.2	Does the protocol describe the information available from the data source(s) on:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	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)	☒	☐	☐	9.7.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Appendix I. Table I
9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3.3. and 9.7.4
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?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.8
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: _____

Date: 29/September/2023

Signature: _____

APPENDIX III – LIST OF DATA PARTNERS WHO CONFIRMED THEIR INTEREST (BY 02 OF OCTOBER 2023)

DP Counts	Data Partner	Country	Type of Data	Date when interest was expressed
1	FIMIM	Spain	Hospital	23-May
2	HIC (Health Informatics Centre)	Scotland, UK	Primary Care and Hospital	23-May
3	CEGEDIM	France	Primary Care	12-Jul
4	CPRD Aurum	UK	Primary Care, linked to hospital data	25-May
5	CSS	Denmark	Hospital	21-Jul
6	HULAFE (Fundación para la Investigación del Hospital Universitario La Fe de la Comunidad Valenciana)	Spain	Hospital	31-May
7	H12O	Spain	Hospital	22-May
8	KCL (King's College London)	UK	Stroke and renal registers	20-Jul
9	IDIAP	Spain	Primary Care, linked to hospital data	01-Jun
10	UTARTU (University of Tartu)	Estonia	Claims	28-Aug
11	Auria	Finland	Hospital	24-May
12	UK National Neonatal Research Database	UK	Hospital	07-Jun
13	Marina Salud S.A.	Spain	Hospital	07-Aug
14	SIMG (Società Italiana di Medicina Generale e delle Cure Primarie)	Italy	Primary Care	02-Jun
15	Barts Heath	UK	Hospital	25-May
16	Istanbul University	Turkey	Hospital	30-May
17	Parc Sanitari Sant Joan de Déu	Spain	Hospital	21-Jul
18	Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico	Italy	Hospital	23-Aug
19	Clinical Center of Serbia	Serbia	Hospital	16-Jun
20	Lille University Hospital	France	Hospital	01-Jun
21	Charité - Universitätsmedizin	Germany	Hospital	18-May
22	Hasselt University (Multiple Sclerosis DataConnect)	Belgium	Multiple Sclerosis registry	02-Jul
23	IKNL (Netherlands Comprehensive Cancer Organisation)	Netherlands	Cancer registry	06-Jun
24	MEB KI (Karolinska Institutet)	Finland	Registry	13-Jun
25	Hospital District of Helsinki and Uusimaa	Finland	Hospital	07-Jun
26	University Medicine Dresden	Germany	Hospital	26-Jul
27	GOSH	UK	Hospital	06-Jun

28	Fondazione Istituto Nazionale dei Tumori	Italy	Cancer registry	20-Jul
29	Optimum Patient Care Limited	UK	Primary care	20-Jul
30	National Scientific Programme "E-Health in Bulgaria"	Bulgaria	Diabetes registry	21-Jul
31	University Clinical Center Nis	Serbia	Hospital	23-May
32	Clinical-hospital center Zvezdara	Serbia	Hospital	21-Jun
33	Hospital da Luz Learning Health	Portugal	Hospital	03-Jun
34	ATS Bergamo	Italy	Hospital	20-Jul
35	AP-HM (Assistance Publique - Hôpitaux de Marseille)	France	Hospital	24-Jul
36	Fundació Institut d´Investigació Sanitària Illes Balears	Spain	Hospital	01-Jun
37	University of Turku	Finland	Hospital	02-Aug
38	IACS (Instituto Aragonés de Ciencias de la Salud)	Spain	Research data registers	25-May
39	Registo Portugues de Doentes Reumaticos	Portugal	RA register	20-Jul
40	University Hospital of Parma	Italy	Hospital	20-Jul
41	Clinical Center of Montenegro	Montenegro	Hospital	19-Jun
42	Instituto de Medicina Molecular	Portugal	Rheumatic diseases registry	24-Jul
43	Unidade Local de Saúde de Matosinhos	Portugal	Primary Care and Hospital	29-May
44	University of Ulm, ZIBMT	Germany		21-May
45	Bologna	Italy	Hospital	01-Jun
46	FTGM (Fondazione Toscana Gabriele Monasterio)	Italy	Hospital	20-Jul
47	AEMPS (Agencia Española de Medicamentos y Productos Sanitarios; *Engl. Spanish Agency of Medicines and Medical Devices*)	Spain	Registry	06-Jul
48	FISABIO-HSRU	Spain	Primary Care and Hospital	23-May
49	EGAS MONIZ HEALTH ALLIANCE	Portugal	Hospital	22-May
50	UZ Brussel	Belgium	Hospital	09-Aug
51	University Hospital Antwerp	Belgium	Hospital	05-Jul
52	Servicio Navarro de Salud Osasunbidea (SNS-O)	Spain	Primary Care and Hospital	22-May
53	AZ Groeninge	Belgium	Hospital	20-Jul
54	Viecuri	Netherlands	Hospital	20-Jul
55	University of Gothenburg	Sweden		25-May
56	BHF Data Science	UK	Primary Care and Hospital	29-May
57	Clinical Practice Research Datalink (CPRD) GOLD	UK	Primary Care	30-Aug
58	The Integrated Primary Care Information Project (IPCI)	Netherlands	Primary Care	30-Aug
59	Boehringer-Ingelheim	TBD	TBD	09-Aug
60	Pfizer	TBD	TBD	09-Aug
61	UCB	TBD	TBD	09-Aug
62	ROCHE	TBD	TBD	09-Aug

63	Johnson & Johnson	TBD	TBD	31-Aug
64	Bayer	TBD	TBD	31-Aug
65	Novartis	TBD	TBD	02-Oct

TBD = To be determined