



## **Study Protocol P3-C2-004**

# **DARWIN EU® – Monitoring prescription of medicines for public health emergencies at risk of shortages**

10/04/2025

Version 4.0

|                                                                                   |                                                                 |                                    |
|-----------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------|
|  | <b>P3-C2-004 Study Protocol</b>                                 |                                    |
|                                                                                   | <b>Author(s):</b> M. Pineda-Moncusí, Y. Guo, D. Prieto-Alhambra | <b>Version:</b> V4.0               |
|                                                                                   |                                                                 | <b>Dissemination level:</b> Public |

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|                                                                                   | <b>Author(s):</b> M. Pineda-Moncusí, Y. Guo, D. Prieto-Alhambra | <b>Version:</b> V4.0               |
|                                                                                   |                                                                 | <b>Dissemination level:</b> Public |

| Study Title                            | DARWIN EU® – Monitoring prescription of medicines for public health emergencies at risk of shortages                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |          |  |            |       |          |             |                                    |         |                         |                             |         |              |            |         |                                 |                                      |         |            |                                 |         |             |                                 |         |            |                                  |         |                |            |         |           |             |         |                                        |                                      |         |                         |                             |         |
|----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------|--|------------|-------|----------|-------------|------------------------------------|---------|-------------------------|-----------------------------|---------|--------------|------------|---------|---------------------------------|--------------------------------------|---------|------------|---------------------------------|---------|-------------|---------------------------------|---------|------------|----------------------------------|---------|----------------|------------|---------|-----------|-------------|---------|----------------------------------------|--------------------------------------|---------|-------------------------|-----------------------------|---------|
| Protocol version                       | 4.0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |          |  |            |       |          |             |                                    |         |                         |                             |         |              |            |         |                                 |                                      |         |            |                                 |         |             |                                 |         |            |                                  |         |                |            |         |           |             |         |                                        |                                      |         |                         |                             |         |
| Date                                   | 10/04/2025                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |          |  |            |       |          |             |                                    |         |                         |                             |         |              |            |         |                                 |                                      |         |            |                                 |         |             |                                 |         |            |                                  |         |                |            |         |           |             |         |                                        |                                      |         |                         |                             |         |
| EU PAS number                          | EUPAS1000000473                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |          |  |            |       |          |             |                                    |         |                         |                             |         |              |            |         |                                 |                                      |         |            |                                 |         |             |                                 |         |            |                                  |         |                |            |         |           |             |         |                                        |                                      |         |                         |                             |         |
| Active substance                       | <table><tr><th>Antibiotic</th><th>Class</th><th>ATC code</th></tr><tr><td>Amoxicillin</td><td>Penicillins with extended spectrum</td><td>J01CA04</td></tr><tr><td>Amoxicillin/clavulanate</td><td>Combinations of penicillins</td><td>J01CR02</td></tr><tr><td>Azithromycin</td><td>Macrolides</td><td>J01FA10</td></tr><tr><td>Benzylpenicillin (Penicillin G)</td><td>Beta-lactamase sensitive penicillins</td><td>J01CE01</td></tr><tr><td>Cefotaxime</td><td>Third-generation cephalosporins</td><td>J01DD01</td></tr><tr><td>Ceftriaxone</td><td>Third-generation cephalosporins</td><td>J01DD04</td></tr><tr><td>Cefuroxime</td><td>Second-generation cephalosporins</td><td>J01DC02</td></tr><tr><td>Clarithromycin</td><td>Macrolides</td><td>J01FA09</td></tr><tr><td>Meropenem</td><td>Carbapenems</td><td>J01DH02</td></tr><tr><td>Phenoxymethylpenicillin (Penicillin V)</td><td>Beta-lactamase sensitive penicillins</td><td>J01CE02</td></tr><tr><td>Piperacillin/tazobactam</td><td>Combinations of penicillins</td><td>J01CR05</td></tr></table> <p>ATC = Anatomical Therapeutic Chemical</p> |          |  | Antibiotic | Class | ATC code | Amoxicillin | Penicillins with extended spectrum | J01CA04 | Amoxicillin/clavulanate | Combinations of penicillins | J01CR02 | Azithromycin | Macrolides | J01FA10 | Benzylpenicillin (Penicillin G) | Beta-lactamase sensitive penicillins | J01CE01 | Cefotaxime | Third-generation cephalosporins | J01DD01 | Ceftriaxone | Third-generation cephalosporins | J01DD04 | Cefuroxime | Second-generation cephalosporins | J01DC02 | Clarithromycin | Macrolides | J01FA09 | Meropenem | Carbapenems | J01DH02 | Phenoxymethylpenicillin (Penicillin V) | Beta-lactamase sensitive penicillins | J01CE02 | Piperacillin/tazobactam | Combinations of penicillins | J01CR05 |
| Antibiotic                             | Class                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | ATC code |  |            |       |          |             |                                    |         |                         |                             |         |              |            |         |                                 |                                      |         |            |                                 |         |             |                                 |         |            |                                  |         |                |            |         |           |             |         |                                        |                                      |         |                         |                             |         |
| Amoxicillin                            | Penicillins with extended spectrum                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | J01CA04  |  |            |       |          |             |                                    |         |                         |                             |         |              |            |         |                                 |                                      |         |            |                                 |         |             |                                 |         |            |                                  |         |                |            |         |           |             |         |                                        |                                      |         |                         |                             |         |
| Amoxicillin/clavulanate                | Combinations of penicillins                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | J01CR02  |  |            |       |          |             |                                    |         |                         |                             |         |              |            |         |                                 |                                      |         |            |                                 |         |             |                                 |         |            |                                  |         |                |            |         |           |             |         |                                        |                                      |         |                         |                             |         |
| Azithromycin                           | Macrolides                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | J01FA10  |  |            |       |          |             |                                    |         |                         |                             |         |              |            |         |                                 |                                      |         |            |                                 |         |             |                                 |         |            |                                  |         |                |            |         |           |             |         |                                        |                                      |         |                         |                             |         |
| Benzylpenicillin (Penicillin G)        | Beta-lactamase sensitive penicillins                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | J01CE01  |  |            |       |          |             |                                    |         |                         |                             |         |              |            |         |                                 |                                      |         |            |                                 |         |             |                                 |         |            |                                  |         |                |            |         |           |             |         |                                        |                                      |         |                         |                             |         |
| Cefotaxime                             | Third-generation cephalosporins                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | J01DD01  |  |            |       |          |             |                                    |         |                         |                             |         |              |            |         |                                 |                                      |         |            |                                 |         |             |                                 |         |            |                                  |         |                |            |         |           |             |         |                                        |                                      |         |                         |                             |         |
| Ceftriaxone                            | Third-generation cephalosporins                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | J01DD04  |  |            |       |          |             |                                    |         |                         |                             |         |              |            |         |                                 |                                      |         |            |                                 |         |             |                                 |         |            |                                  |         |                |            |         |           |             |         |                                        |                                      |         |                         |                             |         |
| Cefuroxime                             | Second-generation cephalosporins                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | J01DC02  |  |            |       |          |             |                                    |         |                         |                             |         |              |            |         |                                 |                                      |         |            |                                 |         |             |                                 |         |            |                                  |         |                |            |         |           |             |         |                                        |                                      |         |                         |                             |         |
| Clarithromycin                         | Macrolides                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | J01FA09  |  |            |       |          |             |                                    |         |                         |                             |         |              |            |         |                                 |                                      |         |            |                                 |         |             |                                 |         |            |                                  |         |                |            |         |           |             |         |                                        |                                      |         |                         |                             |         |
| Meropenem                              | Carbapenems                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | J01DH02  |  |            |       |          |             |                                    |         |                         |                             |         |              |            |         |                                 |                                      |         |            |                                 |         |             |                                 |         |            |                                  |         |                |            |         |           |             |         |                                        |                                      |         |                         |                             |         |
| Phenoxymethylpenicillin (Penicillin V) | Beta-lactamase sensitive penicillins                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | J01CE02  |  |            |       |          |             |                                    |         |                         |                             |         |              |            |         |                                 |                                      |         |            |                                 |         |             |                                 |         |            |                                  |         |                |            |         |           |             |         |                                        |                                      |         |                         |                             |         |
| Piperacillin/tazobactam                | Combinations of penicillins                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | J01CR05  |  |            |       |          |             |                                    |         |                         |                             |         |              |            |         |                                 |                                      |         |            |                                 |         |             |                                 |         |            |                                  |         |                |            |         |           |             |         |                                        |                                      |         |                         |                             |         |
| Medicinal product                      | N/A                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |          |  |            |       |          |             |                                    |         |                         |                             |         |              |            |         |                                 |                                      |         |            |                                 |         |             |                                 |         |            |                                  |         |                |            |         |           |             |         |                                        |                                      |         |                         |                             |         |
| Research question and objectives       | <p>This study aims to characterise the monthly use (prescription/dispensation) of 11 antibiotics to understand trends, cycles and seasonality in the use of those medicines; and to forecast the prescription rates of such medicines under assumed scenarios, which could help anticipate and prevent potential shortages, or manage them.</p> <p>1) To estimate monthly number of prescriptions of the 11 selected medicines during a 10-year period from the most recent data available (e.g., 2015-2024) overall and stratified by age and sex, in each of the databases.</p> <p>2) To conduct time series modelling by fitting an ARIMA model to data generated in objective 1 for short-term (12-month) forecasting.</p>                                                                                                                                                                                                                                                                                                                                                                                |          |  |            |       |          |             |                                    |         |                         |                             |         |              |            |         |                                 |                                      |         |            |                                 |         |             |                                 |         |            |                                  |         |                |            |         |           |             |         |                                        |                                      |         |                         |                             |         |
| Country(-ies) of study                 | Belgium, Finland, Germany, Netherlands, France and Spain                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |          |  |            |       |          |             |                                    |         |                         |                             |         |              |            |         |                                 |                                      |         |            |                                 |         |             |                                 |         |            |                                  |         |                |            |         |           |             |         |                                        |                                      |         |                         |                             |         |
| Author                                 | Marta Pineda Moncusí<br>Yuchen Guo<br>Daniel Prieto-Alhambra                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |          |  |            |       |          |             |                                    |         |                         |                             |         |              |            |         |                                 |                                      |         |            |                                 |         |             |                                 |         |            |                                  |         |                |            |         |           |             |         |                                        |                                      |         |                         |                             |         |

<sup>1</sup> This is a routine repeated study from [P2-C1-012, with EUPAS107932](#).

|                                                                                   |                                                                 |                                    |
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|  | <b>P3-C2-004 Study Protocol</b>                                 |                                    |
|                                                                                   | <b>Author(s):</b> M. Pineda-Moncusí, Y. Guo, D. Prieto-Alhambra | <b>Version:</b> V4.0               |
|                                                                                   |                                                                 | <b>Dissemination level:</b> Public |

## LIST OF ABBREVIATIONS

| Acronyms/terms | Description                                                 |
|----------------|-------------------------------------------------------------|
| ARIMA          | Autoregressive Integrated Moving Average predictive models  |
| CDM            | Common Data Model                                           |
| CDW            | Clinical Data Warehouse                                     |
| DA             | Disease Analyzer                                            |
| DARWIN EU®     | Data Analysis and Real World Interrogation Network          |
| DUS            | Drug Utilization Study                                      |
| EEA            | European Economic Area                                      |
| EHR            | Electronic Health Records                                   |
| EMA            | European Medicines Agency                                   |
| EU             | European Union                                              |
| GP             | General Practitioner                                        |
| H12O           | Hospital Universitario 12 de Octubre                        |
| IMASIS         | Institut Municipal Assistència Sanitària Information System |
| InGef RDB      | Institut für angewandte Gesundheitsforschung                |
| IPCI           | Integrated Primary Care Information                         |
| LPD            | Longitudinal Patient Data                                   |
| OMOP           | Observational Medical Outcomes Partnership                  |
| PHE            | Public Health Emergencies                                   |

|                                                                                   |                                                                 |                                    |
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|  | <b>P3-C2-004 Study Protocol</b>                                 |                                    |
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|                                                                                   |                                                                 | <b>Dissemination level:</b> Public |

## 1. TITLE

DARWIN EU® – Monitoring prescription of medicines for public health emergencies at risk of shortages

## 2. RESPONSIBLE PARTIES – STUDY TEAM

| Study team role                              | Names                                                                          | Organisation                                   |
|----------------------------------------------|--------------------------------------------------------------------------------|------------------------------------------------|
| Study Project Manager/Principal Investigator | Marta Pineda Moncusí                                                           | University of Oxford                           |
| Data Scientist                               | Yuchen Guo<br>Edward Burn                                                      | University of Oxford<br>University of Oxford   |
| Epidemiologist                               | Daniel Prieto Alhambra                                                         | University of Oxford and Erasmus MC University |
| Data Partner*                                | Names                                                                          | Organisation                                   |
| Local Study Coordinator/Data Analyst         | Romain Griffier<br>Guillaume Verdy                                             | CDW Bordeaux                                   |
|                                              | Juan Luis Cruz Bermudez<br>Noelia Garcia Barrio<br>Javier de la Cruz Bertolo   | H12O                                           |
|                                              | Angela Leis<br>Miguel Angel Mayer<br>Pujadas<br>Juan Manuel Ramirez<br>Anguita | IMASIS                                         |
|                                              | Josephine Jacob<br>Raeleesha Norris<br>Annika Vivirito<br>Alexander Harms      | InGef RDB                                      |
|                                              | Katia Verhamme                                                                 | IPCI                                           |
|                                              | Dina Vojinovic<br>Isabella Kaczmarczyk<br>James Brash                          | IQVIA DA Germany/IQVIA LPD Belgium             |

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

|                                                                                   |                                                                 |                                    |
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|  | <b>P3-C2-004 Study Protocol</b>                                 |                                    |
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|                                                                                   |                                                                 | <b>Dissemination level:</b> Public |

### 3. ABSTRACT

#### Title

DARWIN EU®– Monitoring prescription of medicines for public health emergencies at risk of shortages

#### Rationale and Background

The extended mandate of EMA reinforcing the role of the Agency in crisis preparedness and management of medicinal products and medical devices became applicable on 1st March 2022 ([Regulation on EMA's extended mandate becomes applicable | European Medicines Agency \(europa.eu\)](#)).

EMA is now responsible for monitoring medicine shortages that might lead to a crisis situation, as well as reporting shortages of critical medicines during public health emergencies (PHE). Such shortages would make it difficult or impossible to meet the treatment needs of individual patients or populations. The Agency has also the mandate to coordinate responses of EU / EEA countries to shortages of critical medical devices and in-vitro diagnostics in crisis situations.

Scientific and commercial data on monthly prescriptions of medicines that may be critical in PHE can help understanding trends and seasonal variations. In conjunction with time series and forecasting models, as well as data on medicines supply, such data will contribute to the on-going efforts of the Agency to better monitor and coordinate its response to shortages of critical medicines.

This study aims at generating monthly number of prescriptions of selected medicines over the last 10 years and to fit Autoregressive Integrated Moving Average (ARIMA) prediction models to such data.

#### Research question and objectives

This study aims to characterise the monthly use (prescription or dispensation) of 11 antibiotics used for public health emergencies that are considered at risk of shortages in order to understand trends, cycles and seasonality in the use of those medicines; and to forecast short-term prescription rates of such medicines under assumed scenarios, which could help anticipate and prevent potential shortages, or manage them.

The general research question is: What are the monthly number of prescriptions of selected medicines of importance for public health emergencies over the last 10 years?

The specific objectives of this study are:

- (i) To estimate monthly number of use prescriptions or dispensations of the 11 selected medicines during a 10-year period from the most recent data available, stratified by age and sex, in each of the databases.
- (ii) To conduct time series modelling by fitting an ARIMA model to data generated in objective 1 for short-term (12-month) forecasting.

#### Research Methods

##### Study design

- Population level cohort study (Objective 1, Population-level drug utilisation study on antibiotics)
- Population level cohort study (Objective 2, Time series modelling based on the Population-level drug utilisation study on antibiotics).

|                                                                                   |                                                                 |                                    |
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### Population

*Population-level drug utilisation of antibiotics:* All individuals present in the database in the last 10 years of available data will be included in the analysis. For this population, prescription or dispensation of antibiotics will be explored.

### Variables

*Drugs of interest:* list of 11 antibiotics that may be critical in PHE.

Calendar month, age, and sex will be used for stratification.

### Data sources

- 1) IQVIA DA Germany (Primary and Outpatient care)
- 2) IQVIA LPD Belgium (Primary Care Database)
- 3) IPCI (Netherlands, Primary Care Database)
- 4) IMASIS (Spain, Secondary Care Database)
- 5) CDW Bordeaux (France, Secondary Care Database)
- 6) H12O (Spain, Secondary Care Database)
- 7) InGef RDB (Germany, Primary and Secondary Care Database)

### Sample size

No sample size has been calculated. Based on a preliminary study feasibility assessment the expected number of prescriptions in the period investigated is expected to be between <1000 and 25 million across the seven data sources considered.

### Data analyses

*Population-level drug utilisation study on antibiotics:* monthly number of prescriptions of antibiotic use, as described in section 8.7.5.1 – Population-level drug utilisation study.

*Time series modelling:* forecast of the 12-month number of prescriptions/dispensations of antibiotic use after the end of available data in the data source using AutoRegressive Integrated Moving Average (ARIMA) models for time series analysis, as described in section 8.7.5.2.

|                                                                                   |                                                                 |                                    |
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|                                                                                   |                                                                 | <b>Dissemination level:</b> Public |

## 4. CHANGES COMPARED TO THE ORIGINAL STUDY AND UPDATES

This is a routinely repeated study from the P2-C1-012 study. The P2-C1-012 study was registered in the catalogue (<https://catalogues.ema.europa.eu/node/3890/administrative-details>) with the EU PAS register number EUPAS107932. The study code from P2-C1-012 is available in the GitHub repository: <https://github.com/darwin-eu-studies/P2-C1-012-DrugShortages>

The following updates are the changes included in the routinely repeated analysis P3-C2-004 when compared with P2-C1-012:

| Protocol Number | Number | Date       | Section of study protocol                                                                                     | Amendment or update                                                                                                                                     | Reason                                                                                                                                                                                                                                                                                            |
|-----------------|--------|------------|---------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| P3-C2-004       | 1.0    | 17/01/2025 | 3. ABSTRACT<br>7. RESEARCH QUESTION AND OBJECTIVES<br>8.7.5.2. Time Series modelling                          | Data fitted into the ARIMA models will be the IR numerators (i.e., monthly number of prescriptions rather than monthly incidence rates of prescription) | Prior study showed denominators are underestimated in databases with observation period calculated based on the last interaction of the patient to the healthcare system. Focusing on the numerator of the incidence rates enables the use of more recent data, which is critical for this study. |
| P3-C2-004       | 1.0    | 17/01/2025 | 3. ABSTRACT<br>7. RESEARCH QUESTION AND OBJECTIVES<br>8.2 Study Setting and Data Sources                      | Inclusion of the databases used for the repeated analysis.                                                                                              | The new routinely repeated analysis will reuse 3 databases from the original analysis and 4 new, mostly expanding use of the selected medicines in hospital care.                                                                                                                                 |
| P3-C2-004       | 1.0    | 17/01/2025 | 8.4 Study Population with inclusion and exclusion criteria<br>8.7.5.1 Population-level drug utilisation study | No sensitivity analysis for P3-C2-004                                                                                                                   | Given the learnings from the original analysis, a sensitivity analysis is not needed.                                                                                                                                                                                                             |
| P3-C2-004       | 1.0    | 05/02/2025 | 8.7 Analysis                                                                                                  | Validation and forecasted periods will be 12 months.                                                                                                    | We extended the forecasted period to 12 months to ensure results will be relevant (end of data availability in the study databases oscillated between June and August 2024).                                                                                                                      |

|                                                                                   |                                                                 |                                    |
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|                                                                                   |                                                                 | <b>Dissemination level:</b> Public |

## 5. MILESTONES

| STUDY SPECIFIC DELIVERABLE               | TIMELINES     |
|------------------------------------------|---------------|
| Final Study Protocol                     | 17/02/2025    |
| Creation of Analytical code              | February 2025 |
| Execution of Analytical Code on the data | March 2025    |
| Draft Study Report                       | April 2025    |
| Final Study Report                       | May 2025      |

## 6. RATIONALE AND BACKGROUND

The extended mandate of EMA reinforcing the role of the Agency in crisis preparedness and management of medicinal products and medical devices became applicable on 1st March 2022 ([Regulation on EMA's extended mandate becomes applicable | European Medicines Agency \(europa.eu\)](#)).

EMA is now responsible for monitoring medicine shortages that might lead to a crisis situation, as well as reporting shortages of critical medicines during public health emergencies (PHE). Such shortages would make it difficult or impossible to meet the treatment needs of individual patients or populations.[1] The Agency has also the mandate to coordinate responses of EU / EEA countries to shortages of critical medical devices and in-vitro diagnostics in crisis situations.

Scientific and commercial data on monthly prescriptions of medicines that may be critical in PHE can help understanding trends and seasonal variations. In conjunction with time series and forecasting models, as well as data on medicines supply, such data will contribute to the on-going efforts of the Agency to better monitor and coordinate its response to shortages of critical medicines.

This study aims at generating number of monthly prescriptions of selected medicines over the last 10 years of available data and to conduct a time series modelling by fitting Autoregressive Integrated Moving Average (ARIMA) models to such data to then forecast short-term (12-months) prescription numbers.

|                                                                                   |                                                                 |                                    |
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|  | <b>P3-C2-004 Study Protocol</b>                                 |                                    |
|                                                                                   | <b>Author(s):</b> M. Pineda-Moncusí, Y. Guo, D. Prieto-Alhambra | <b>Version:</b> V4.0               |
|                                                                                   |                                                                 | <b>Dissemination level:</b> Public |

## 7. RESEARCH QUESTION AND OBJECTIVES

**Table 1.** Primary and secondary research questions and objective.

### A. Primary research question and objective

|                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Objective:</b>                                                    | To estimate monthly number of prescriptions or dispensations of the 11 selected medicines during the last 10 years of available data, stratified by age and sex, in each of the databases.                                                                                                                                                                                                                                                                                                                                                |
| <b>Hypothesis:</b>                                                   | Not applicable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Population (<i>mention key inclusion-exclusion criteria</i>):</b> | The study cohort will comprise all individuals present in the database in a 10-year period from the most recent data available.                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Exposure:</b>                                                     | Eleven antibiotics identified as potentially critical in public health emergencies (PHE)                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Comparator:</b>                                                   | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Outcome:</b>                                                      | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <b>Time (<i>when follow up begins and ends</i>):</b>                 | Follow-up will start on a pre-specified calendar time point e.g., 1st of January for each month between the 10-year study period for the calculation of monthly number of prescriptions.<br><br>End of follow-up will be defined as the earliest of loss to follow-up, end of data availability, death, or end of the 10-year study period.                                                                                                                                                                                               |
| <b>Setting:</b>                                                      | Inpatient and outpatient setting using data from the following data sources:<br><br><ol style="list-style-type: none"> <li>1) IQVIA DA Germany (Primary and Outpatient care)</li> <li>2) IQVIA LPD Belgium (Primary Care Database)</li> <li>3) IPCI (Netherlands, Primary Care Database)</li> <li>4) IMASIS (Spain, Secondary Care Database)</li> <li>5) CDW Bordeaux (France, Secondary Care Database)</li> <li>6) H12O (Spain, Secondary Care Database)</li> <li>7) InGef RDB (Germany, Primary and Secondary Care Database)</li> </ol> |
| <b>Main measure of effect:</b>                                       | Monthly number of antibiotic prescriptions                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

### B. Secondary research question and objective

|                    |                                                                                                                                     |
|--------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| <b>Objective:</b>  | To conduct a time series modelling by fitting an ARIMA model to data generated in objective 1 for short-term (12-month) forecasting |
| <b>Hypothesis:</b> | Not applicable                                                                                                                      |

|                                                                                   |                                                                 |                                    |
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|  | <b>P3-C2-004 Study Protocol</b>                                 |                                    |
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|                                                                                   |                                                                 | <b>Dissemination level:</b> Public |

|                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Population (<i>mention key inclusion-exclusion criteria</i>):</b> | The study cohort will comprise the monthly number of prescriptions/dispensations of the 11 selected medicines during the last 10 years of available data, from the primary research question.                                                                                                                                                                                                                                                                                                                                      |
| <b>Exposure:</b>                                                     | Eleven antibiotics identified as potentially critical in PHE                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <b>Comparator:</b>                                                   | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Outcome:</b>                                                      | None                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <b>Time (<i>when follow up begins and ends</i>):</b>                 | We will use the overall (i.e., not stratified nor sensitivity analysis) monthly number of prescriptions/dispensations from the last 10 years of available data calculated in objective 1 to forecast the following 12-months.                                                                                                                                                                                                                                                                                                      |
| <b>Setting:</b>                                                      | Inpatient and outpatient setting using data from the following data sources: <ol style="list-style-type: none"> <li>1) IQVIA DA Germany (Primary and Outpatient care)</li> <li>2) IQVIA LPD Belgium (Primary Care Database)</li> <li>3) IPCI (Netherlands, Primary Care Database)</li> <li>4) IMASIS (Spain, Secondary Care Database)</li> <li>5) CDW Bordeaux (France, Secondary Care Database)</li> <li>6) H12O (Spain, Secondary Care Database)</li> <li>7) InGef RDB (Germany, Primary and Secondary Care Database)</li> </ol> |
| <b>Main measure of effect:</b>                                       | Forecast of the 12-month number of prescriptions/dispensations of antibiotic use after the end of study period                                                                                                                                                                                                                                                                                                                                                                                                                     |

## 8. RESEARCH METHODS

### 8.1 Study type and study design

Retrospective cohort studies will be conducted using routinely-collected health data from 7 databases. The study will comprise two consecutive parts:

- 1) A population-based cohort study will be conducted to address objective 1, assessing the monthly number of prescriptions of the 11 selected antibiotics.
- 2) A time series modelling study based on the Population-level drug utilisation study on antibiotics to address objective 2, fitting the time series data generated in objective 1 into an ARIMA model to then forecast prescription rates for the subsequent 12-months.

### 8.2 Study setting and data sources

#### 8.2.1 Data sources selected

Inpatient and outpatient setting using data from the following data sources:

- 1) IQVIA Disease Analyzer Germany [IQVIA DA] (Primary and Outpatient care)
- 2) IQVIA Longitudinal Patient Data Belgium [IQVIA LPD Belgium] (Primary Care Database)

|                                                                                   |                                                                 |                                    |
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|  | <b>P3-C2-004 Study Protocol</b>                                 |                                    |
|                                                                                   | <b>Author(s):</b> M. Pineda-Moncusí, Y. Guo, D. Prieto-Alhambra | <b>Version:</b> V4.0               |
|                                                                                   |                                                                 | <b>Dissemination level:</b> Public |

- 3) Integrated Primary Care Information [IPCI] (Netherlands, Primary Care Database)
- 4) Institut Municipal Assistència Sanitària Information System [IMASIS, Parc Salut Mar Barcelona - Hospital del Mar] (Spain, Secondary Care Database)
- 5) Clinical Data Warehouse of Bordeaux University Hospital [CDW Bordeaux] (France, Secondary Care Database)
- 6) Hospital Universitario 12 de Octubre [H120] (Spain, Secondary Care Database)
- 7) InGef Research Database [InGef RDB, Institut für angewandte Gesundheitsforschung] (Germany, Primary and Secondary Care Database)

Information on data source(s) planned to be used is described in a [Table 2](#).

### 8.2.2 Rationale for the data sources selected

In this routinely collected study we selected 7 databases onboarded for DARWIN EU® in 2025, representing 5 European countries. The selection of databases for this study was based on availability of data until at least June 2024. All selected databases fulfil the criteria required for a population-level drug utilisation study, as they systematically and adequately capture all drug prescriptions. Additionally, the proposed data sources capture the relevant data necessary to answer the research questions of this study, they have recent data covering the 10-year study period, and they cover different healthcare settings where the drugs of interest may be used (i.e., primary and secondary care).

Two databases include records from primary care (IPCI and IQVIA LPD Belgium), three from hospital (IMASIS, CDW Bordeaux and H120), one includes records from primary and outpatient care (IQVIA DA Germany), and one includes records from primary and hospital care (InGef RDB). Since certain medications observed in primary care may be not observed at secondary care, an vice versa, given the nature of their own indication, we have included data sources from both health care settings, and the administration path (primary and/or secondary care) will be considered when interpreting the results. We selected these three outpatient databases (IPCI, IQVIA LPD Belgium, and IQVIA DA Germany, covering primary care and outpatient specialist care) as many antibiotics, particularly beta-lactam antibiotics/combinations and macrolides, and are expected to be prescribed in that ambulatory health care setting. In addition, IMASIS, CDW Bordeaux, H120, and InGef RDB include in- and outpatient records from the hospital, where antibiotics used for the treatment of more severe conditions, including the third-generation cephalosporins and carbapenems, are expected to be administered during hospitalisation. This data sources also captures data on antibiotics that are expected to be initiated and prescribed for outpatient use following hospital discharge. With that, the diversity of healthcare systems enables us to capture all the antibiotics of interest with a relevant number of prescriptions ranged from <1000 to 25 million across data sources. While two of the databases included in the study are from the same country and may contain overlapped information of patients (IQVIA DA Germany and InGef RDB), they have a different coverage: IQVIA DA Germany captures a larger proportion of the German population and therefore it will provide a broader and more representative coverage of prescriptions in the German primary care, whereas InGef RDB will be particularly relevant for medications administered in hospital settings, which are not captured by IQVIA DA Germany.

The proposed data sources capture the relevant data necessary to answer the research questions of this study, they have recent data covering the 10-year study period, and they cover different healthcare settings where the drugs of interest may be used (i.e., primary and secondary care). Moreover, 4 of the 7 databases (CDW Bordeaux, IPCI, IMASIS and IQVIA DA Germany) were included for a previous DARWIN EU study which focussed on the use of antibiotics of the WHO Watch list (EUPAS103381).

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|  | <b>P3-C2-004 Study Protocol</b>                                 |                                    |
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Information on data source(s) planned to be used with a justification for their choice in terms of ability to capture the relevant data is described in a [Table 2](#).

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

| Country     | Name of Database  | Justification for Inclusion                                                       | Health Care setting       | Type of Data | Number of active subjects | Date last available record |
|-------------|-------------------|-----------------------------------------------------------------------------------|---------------------------|--------------|---------------------------|----------------------------|
| Germany     | IQVIA DA Germany  | Covers primary and secondary care setting where antibiotic prescriptions are used | Primary & Outpatient Care | EHR          | 41.9 million              | 01/06/2024                 |
| Belgium     | IQVIA LPD Belgium | Covers primary care setting where antibiotic prescriptions are used               | Primary Care              | EHR          | 8.5 million               | 01/09/2024                 |
| Netherlands | IPCI              | Covers primary care setting where antibiotic prescriptions are used               | Primary Care              | EHR          | 2.9 million               | 01/06/2024                 |
| Spain       | IMASIS            | Covers secondary care setting where antibiotic prescriptions are used             | Hospital                  | EHR          | 0.6 million               | 01/06/2024                 |
| France      | CDW Bordeaux      | Covers secondary care setting where antibiotic prescriptions are used             | Hospital                  | EHR          | 2 million                 | 01/08/2024                 |
| Spain       | H120              | Covers secondary care setting where antibiotic prescriptions are used             | Hospital                  | EHR          |                           | 01/08/2024                 |
| Germany     | InGef RDB         | Covers primary and secondary care setting where antibiotic prescriptions are used | Primary and Hospital Care | EHR          | 10 million                | 01/07/2024                 |

CDW = Clinical Data Warehouse, DA = Disease Analyzer, EHR = Electronic Health record. Exposure is based on prescription data, H120 = Hospital Universitario 12 de Octubre, IMASIS= Institut Municipal Assistència Sanitària Information System, IPCI = Integrated Primary Care Information, InGef RDB = Institut für angewandte Gesundheitsforschung, LPD = Longitudinal Patient Data.

#### **Institut Municipal Assistència Sanitària Information System [IMASIS, Parc Salut Mar Barcelona - Hospital del Mar] (Spain, Secondary Care Database)**

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 centre (Centre Dr. Emili Mira) and one social-healthcare centre (Centre Fòrum) including emergency room settings, which offer specific and varied 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. Diagnoses are coded using The International Classification of Diseases ICD-9-CM and ICD-10-CM.

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The average follow-up period per patient in years is 6.37 (SD±6.82). Most drug data mapped to the OMOP-CDM in IMASIS is obtained from EHR administration records, which serve as a primary source of medication-related information. These records are typically documented by nurses at the time of medication administration to ensure accurate tracking of drug usage in clinical settings. The recorded data includes details such as the drug name, dosage, route of administration, and the time of administration. This process helps maintain consistency and reliability in capturing real-world medication exposure, supporting both clinical decision-making and research initiatives. 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.[4]

#### **IQVIA Disease Analyzer Germany [IQVIA DA]**

DA Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings.[5] Data coverage includes more than 34M distinct person records out of a 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 patients have free choice of specialist. As a result, data are collected from visits to General (28.8%), Orthopaedic Surgery (13.4%), Otolaryngology (11.8%), Dermatology (11.2%), Obstetrics/Gynaecology (7.7%), various Neurology and Psychiatry (6.2%), Paediatric (7.0%), Urology (4.6%), Cardiology (3.7%), Gastroenterology (3.5%), Pulmonary (1.5%) and Rheumatology (0.7%) practices. Drugs are recorded as prescriptions of marketed products, and the information is derived mainly from the EHR prescription issue record, followed by the EHR administration record.

#### **IQVIA Longitudinal Patient Data Belgium [IQVIA LPD Belgium] (Primary Care Database)**

IQVIA LPD Belgium is a computerised network of GPs who contribute to a centralised database of anonymised data of patients with ambulatory visits. Currently, around 300 GPs from 234 practices are contributing to the database covering 1.1M patients from a total of 11.5M Belgians (10.0%). The database covers time from 2005 through the present. Observation time is defined by the first and last consultation dates. Drug information is derived from GP prescriptions, which are systematically recorded in the EHR prescription issue record. Drugs obtained over the counter by the patient outside the prescription system are not reported. No explicit registration or approval is necessary for drug utilisation studies.

There is some overlap between IQVIA DA Germany and InGef RDB databases. However, the IQVIA DA Germany database provides broader coverage of prescriptions in primary care, as it captures a larger proportion of the German population, whereas the InGef RDB database is particularly relevant for medications administered in hospital settings, which are not captured by IQVIA DA Germany.

#### **Integrated Primary Care Information [IPCI] (Netherlands, Primary Care Database)**

The Integrated Primary Care Information (IPCI) database is a longitudinal observational database containing routinely collected data from computer-based patient records of a selected group of GPs throughout the Netherlands (N=723). IPCI was started in 1992 by the department of Medical Informatics of the Erasmus University Medical Center in Rotterdam with the objective to enable better post marketing surveillance of drugs. The current database includes patient records from 2006 on, when the size of the database started to increase significantly. In 2016, IPCI was certified as Regional Data Center. Since 2019 the data is also standardised to the OMOP-CDM, enabling collaborative research in a large network of databases within the Observational Health Data Sciences and Informatics (OHDSI) community. The primary goal of IPCI is to enable medical research. In addition, reports are generated to inform GPs and their organizations about the

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provided care. Contributing GPs are encouraged to use this information for their internal quality evaluation. Since IPCI is a registration of GP systems, the majority of drug records are provided directly from GP prescriptions, with the occasional addition of few pharmacy dispensation records. Drugs that are captured as prescription records contain the information of the product, quantity, dosing directions, and strength. Additionally, prescription records may contain information on the indication of use, although this information is not always complete. Drugs not prescribed in the GP setting might be underreported.

#### **Clinical Data Warehouse of Bordeaux University Hospital [CDW Bordeaux] (France, Secondary Care Database)**

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). Drug information is primarily derived from the EHR administration record, followed by EHR prescription. Administration data consists of information filled out principally by nurses when a medication is administered to the patient. Administration and prescription records may contain some discrepancies, such as administrations without corresponding prescriptions or prescriptions that were not necessarily administered. Conversely, data from critical care units (ICUs) is managed using a separate software, and at present, only prescription data is integrated into the OMOP-CDM. The data from the hospital production information system are loaded daily into a CDW in i2b2 format. A specific ETL from i2b2 to OMOP has been set up to standardize the data in OMOP-CDM format. Currently, this ETL from i2b2 to OMOP is launched manually when needed (this ETL can be scheduled regularly if necessary). The data is integrated in the OMOP Common Data Model version 5.3.1 and is stored in Oracle version 19c.

#### **Hospital Universitario 12 de Octubre [H120] (Spain, Secondary Care Database)**

The main source of data for the OMOP database is the Electronic Health Record (EHR) of the Hospital Universitario 12 de Octubre, which has a reference population of about 450,000 patients. The data source contains information from the different healthcare domains (laboratory, prescriptions, treatments, administrative, diagnoses, etc.). In addition, information is also obtained from other data sources such as the pathological anatomy system, which provides information about sample analysis, and the cost system, containing information on the cost associated with a contact with the hospital. In the case of drug data, it is derived from multiple sources within the EHR, including structured data from inpatient and emergency prescriptions and natural language processing of EHR notes. Work for the inclusion of further data is ongoing, among others, radiological information or PROMs.

#### **Institut für angewandte Gesundheitsforschung Research Database [InGef RDB] (Germany, Primary and Secondary Care Database)**

<https://portal-dev.darwin-eu.org/>The InGef RDB database comprises anonymized longitudinal claims data of about 10 million individuals across more than 70 statutory health insurance providers (SHIs) throughout Germany. Data are longitudinally linked over a period of currently ten years. Patients can be traced across health care sectors. All patient-level and provider-level data in the InGef RDB research database are anonymised to comply with German data protection regulations and German federal law. German SHI claims data available in the InGef RDB database includes information on demographics (year of birth, gender, death date if applicable, region of residence on administrative district level); hospitalizations; outpatient services (diagnoses, treatments; specialties of physicians); dispensing of drugs; dispensings of remedies and aids; and sick leave and sickness allowance times. In addition, costs or cost estimates from

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SHI perspective are available for all important cost elements. All diagnoses in Germany are coded using the International Classification of Diseases, version 10 in the German Modification (ICD-10-GM). The persistence (membership over time) is rather high in the InGef RDB database: During a time period of 5 years (2009 to 2013), 70.6% of insurance members survived and remained insured with the same SHI without any gap in their observational time. Persons leaving one of the participating SHIs and entering another participating SHI, can be linked during yearly database consistency updates and are thus not lost over time. The InGef RDB database is dynamic in nature, i.e. claims data are updated in an ongoing process and new SHIs may join or leave the database. By law, only the last 10 years of data are allowed to be used. At every new release this window shifts, dropping older data and adding new data. Additionally, drug data in InGef RDB captures dispensation of medicines, with the records of the specific date of dispensation driven from the claims data based dispensing record. All drugs that are reimbursed by the German statutory health insurance are captured within the data. However, a minority of prescription records from outpatient procedure codes (OPS-code) that represents procedures where a drug was administered, and which have been mapped to the observation table instead of the drug table, do not have a specific date associated and therefore will not be included in this study. Additionally, over-the-counter medication cannot be found in the database.

There is some overlap between the InGef RDB and IQVIA DA Germany databases. However, the IQVIA DA Germany database provides broader coverage of prescriptions in primary care, as it captures a larger proportion of the German population, whereas the InGef RDB database is particularly relevant for medications administered in hospital settings, which are not captured by IQVIA DA Germany.

### 8.3 Study period and follow-up

The study will comprise the last 10 years of available data counting backwards from the respective latest date of data lock of the respective databases ([Table 3](#)).

Number of monthly prescriptions will be obtained directly from the numerators of the incidence rates estimates. To estimate the incidence rates, we require the appropriate population and their contributed observation time to first be identified. Study individuals in the denominator population will begin contributing person time on the respective date of the latest of the following: 1) study start date 2) date at which the observation period starts. Individuals will stop contributing person time at the earliest date of the following: 1) end of available data in each of the data sources or 2) 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 and 3 are included as denominators at the study start date as both are being observed in the data base from a prior date. Person ID 2 enters the study at the date of starting their period of observation, which was later than the study start date. Person ID 1 and 2 will be followed until the study end date (end of available data in each of the data sources) whilst Person ID 3 leaves when exiting the database (the end of observation period). Lastly, person ID 4 has two observation periods in the database. The first period contributes time from study start until end of observation period, and the second period starts contributing time again on the date of their second observation period start and exits at study end date.

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**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 <sup>1</sup> | Code Type | Diagnosis position | Incident with respect to... | Measurement characteristics/ validation | Source of algorithm |
|-------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|-------------------|---------------|----------------|---------------------------|-----------|--------------------|-----------------------------|-----------------------------------------|---------------------|
| All patients from the database eligible for the study | Patient present in the database during the study period (the 10-year period from the latest available data) | Multiple          | Incident      | n/a            | IP and OP                 | n/a       | n/a                | Specific antibiotics        | n/a                                     | n/a                 |

<sup>1</sup> IP = inpatient, OP = outpatient, OT = other, n/a = not applicable

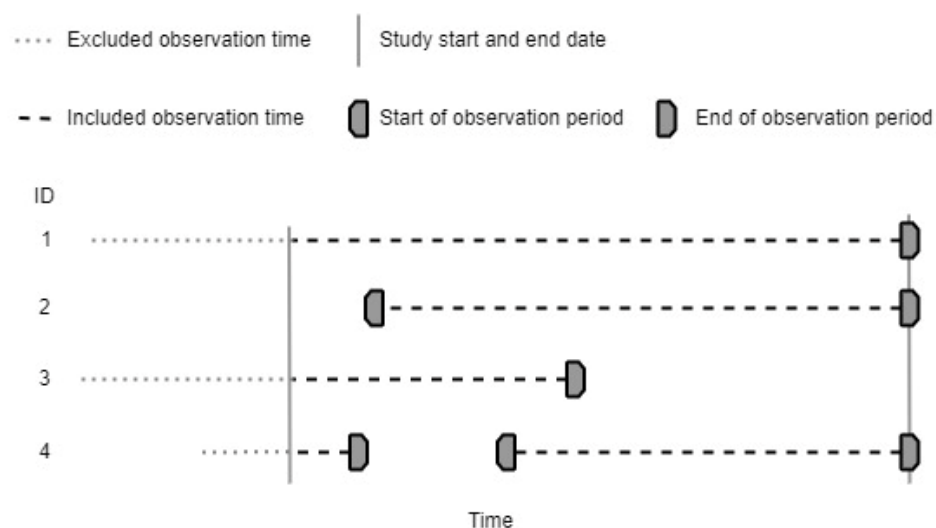


**Figure 1.** Included observation time for the denominator population.

|                                                                                   |                                                                 |                                    |
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|                                                                                   |                                                                 | <b>Dissemination level:</b> Public |

## 8.4 Study population with inclusion and exclusion criteria

The study cohort will comprise all individuals present in the database during the study period (the last 10 years of available data counting backwards from the respective latest date of data lock of the respective databases).

The operational definitions of the in and exclusion criteria are presented in **Table 4**.

**Table 4.** Operational definitions of inclusion criteria.

| Criterion                                                                                   | Details                                                          | Order of application | Assessment window | Care Settings <sup>1</sup>     | Code Type | Diagnosis position | Applied to study population:                  | Measurement characteristics /validation | Source for algorithm |
|---------------------------------------------------------------------------------------------|------------------------------------------------------------------|----------------------|-------------------|--------------------------------|-----------|--------------------|-----------------------------------------------|-----------------------------------------|----------------------|
| Observation period in the database during the 10-year period from the latest available data | All individuals present in the database during the study period. | After                | N/A               | PC, SC and Combination of both | N/A       | N/A                | All individuals within the selected databases | N/A                                     | N/A                  |

<sup>1</sup> PC = Primary Care, SC = Secondary Care, OT = other, n/a = not applicable

## 8.5 Variables

### 8.5.1. Exposure

For this study, the exposure of interest is use (during study period) of antibiotics identified as potentially critical in PHE. This list of antibiotics (with respective ATC code) is described in **Table 5**. Details of exposure are described in **Table 6**.

**Table 5.** Exposure of interest.

| Antibiotic                             | Class                                | ATC code |
|----------------------------------------|--------------------------------------|----------|
| Azithromycin                           | Macrolides                           | J01FA10  |
| Clarithromycin                         | Macrolides                           | J01FA09  |
| Penicillin V (phenoxymethylpenicillin) | Beta-lactamase sensitive penicillins | J01CE02  |
| Penicillin G (benzylpenicillin)        | Beta-lactamase sensitive penicillins | J01CE01  |
| Amoxicillin                            | Penicillins with extended spectrum   | J01CA04  |
| Amoxicillin + Clavulanic acid          | Combinations of penicillins          | J01CR02  |
| Ceftriaxone                            | Third-generation cephalosporins      | J01DD04  |
| Cefotaxime                             | Third-generation cephalosporins      | J01DD01  |
| Meropenem                              | Carbapenems                          | J01DH02  |
| Cefuroxime                             | Second-generation cephalosporins     | J01DC02  |
| Piperacillin + Tazobactam              | Combinations of penicillins          | J01CR05  |

|                                                                                   |                                                                 |                                    |
|-----------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------|
|  | <b>P3-C2-004 Study Protocol</b>                                 |                                    |
|                                                                                   | <b>Author(s):</b> M. Pineda-Moncusí, Y. Guo, D. Prieto-Alhambra | <b>Version:</b> V4.0               |
|                                                                                   |                                                                 | <b>Dissemination level:</b> Public |

**Table 6.** Operational definitions of exposure.

| Exposure group name(s)                                               | Details                                     | Wash out window | Assessment Window | Care Setting <sup>1</sup>      | Code Type | Diagnosis position | Applied to study populations:                                   | Incident with respect to... | Measurement characteristics/ validation | Source of algorithm |
|----------------------------------------------------------------------|---------------------------------------------|-----------------|-------------------|--------------------------------|-----------|--------------------|-----------------------------------------------------------------|-----------------------------|-----------------------------------------|---------------------|
| Antibiotics identified as potentially critical in PHE – users cohort | Preliminary code lists provided in Appendix | n/a             | Monthly           | PC, SC and Combination of both | RxNorm    | n/a                | All individuals present in the database during the study period | n/a                         | n/a                                     | n/a                 |

<sup>1</sup> PC = Primary Care, SC = Secondary Care, OT = other, n/a = not applicable

### 8.5.2. Outcome/s (where relevant)

None.

### 8.5.3. Other covariates, including confounders, effect modifiers and other variables (where relevant)

Covariates for stratification in population-level drug utilisation study:

- Age: age will be stratified in three groups (<18, 18-64, 65+).
- Time period: Monthly
- Sex

## 8.6 Study size

No sample size has been calculated for this study. The expected number of prescriptions across data sources is expected to be roughly between <1000 and 25 million.

## 8.7 Analysis

This section will describe the details of the analysis approach and rationale for the choice of analysis, with reference to the D1.3.8.1 Draft 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 as described in section 8.7.5.1 – Population-level drug utilisation study on antibiotics; and the fitting of the data generated in objective 1 into ARIMA models as described in section 8.7.5.2 – Time series modelling.

### 8.7.1 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

|                                                                                   |                                                                 |                                    |
|-----------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------|
|  | <b>P3-C2-004 Study Protocol</b>                                 |                                    |
|                                                                                   | <b>Author(s):</b> M. Pineda-Moncusí, Y. Guo, D. Prieto-Alhambra | <b>Version:</b> V4.0               |
|                                                                                   |                                                                 | <b>Dissemination level:</b> Public |

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.

### 8.7.2 Patient privacy protection

To prevent confidentiality issues, cell counts lower than 5 will be reported as “<5”.

### 8.7.3 Statistical model specification and assumptions of the analytical approach considered

#### Users cohorts

**Users** (for incidence rates estimation) will be selected based on their use (prescription or dispensation) of the respective drug of interest after the start of the study and/or in a pre-defined time window.

#### Missing Data

Individuals who are lost to follow-up or have end of observation period before the end of the study period will have missing follow-up between the time of loss to follow-up/end of observation period and the end of the study period (see the corresponding definitions in Section 8.3) and data on the prescription/dispensation of the medicines of interest will be missing. For these individuals, the time at risk of experiencing the event of interest (prescription of one of the medicines listed in Section 8.5.1) will be censored at the time of loss-to-follow-up/end of observation period and the estimated prescription rates will implicitly assume censoring occurs at random.

#### R-packages

We will use the R package “IncidencePrevalence” for the population-level estimation of drug utilisation. Additionally, we will use the R package “forecast” for the ARIMA modelling.

### 8.7.4 Methods to derive parameters of interest

#### Calendar time

Calendar time will be based on monthly periods of the index prescription/dispensation in the population level analysis (e.g., 01/01/2015 – 31/01/2015, 01/02/2015 – 30/02/2015, etc.).

#### Age

Age at index date will be calculated using January 1<sup>st</sup> of the year of birth as proxy for the actual birthday. The following age groups will be used for stratification: <18, 18-64, 65+.

#### Sex

Results will be presented stratified by sex.

|                                                                                   |                                                                 |                                    |
|-----------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------|
|  | <b>P3-C2-004 Study Protocol</b>                                 |                                    |
|                                                                                   | <b>Author(s):</b> M. Pineda-Moncusí, Y. Guo, D. Prieto-Alhambra | <b>Version:</b> V4.0               |
|                                                                                   |                                                                 | <b>Dissemination level:</b> Public |

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

### 8.7.5.1 Population-level drug utilisation study

Monthly number of prescriptions/dispensations will be obtained directly from the numerators of the incidence rates estimates (i.e., these estimates are produced by the IncidencePrevalence R package automatically after extraction of the relevant data for the numerator and the denominator of the incidence rate). Incidence calculations will be conducted separately for each antibiotic of interest using the methodology described below, which is included for the sake of completeness. However, please note in this study only the numerator (monthly number of prescriptions/dispensations) will be reported and analysed in the second objective. The estimated incidence rates will not be reported.

#### Incidence calculations

Monthly incidence rates of the antibiotics of interest will be calculated as the of number of **users** per 100,000 person-years of the population at risk of getting exposed during the period for each calendar year. Those study individuals who enter the denominator population will then contribute time at risk up to their first use (prescription or dispensation) 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 8.3 (Study period and Follow-up). Incidence rates will be given together with 95% Poisson exact confidence intervals.

An illustration of the calculation of incidence of antibiotic use is shown below in **Figure 2**.

Patient ID 1, 2 and 3 contribute time at risk between the study start and end date except when they become incident users of antibiotics. For Patient ID 2 and 5, use of antibiotics before study start will not be count as incident use. Patient ID 4 and 5 are not seen to use antibiotics between the study start and end date, and so contribute time at risk but no incident outcomes.

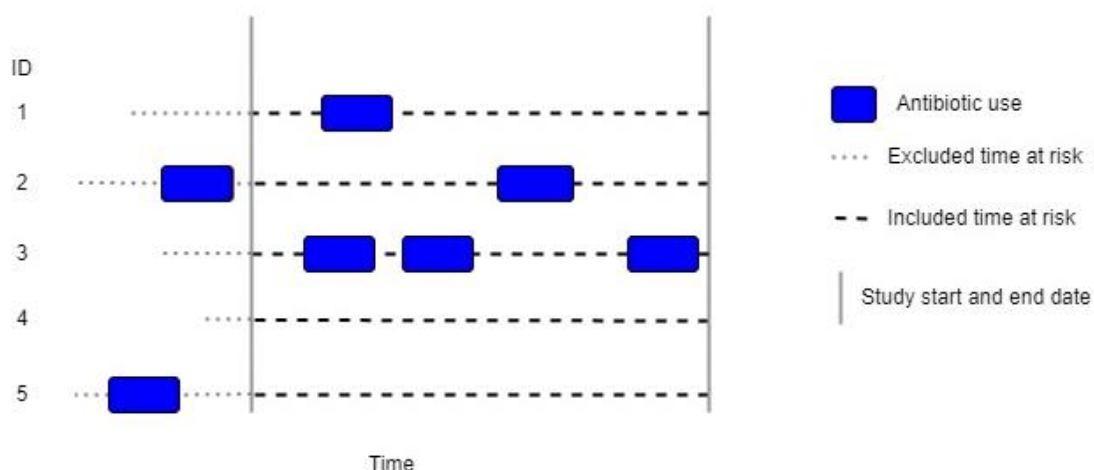


**Figure 2.** Incidence example for antibiotic use.

### 8.7.5.2 Time series modelling

We will conduct time series modelling where AutoRegressive Integrated Moving Average (ARIMA) models will be used to model trends and seasonality over time for the overall number of prescriptions/dispensations (i.e., the numerator of the IR estimates from the main analysis, without age and sex stratification), when no more than one month value will be censored to ensure the results will not be skewed by replacing the censored values with a value of 5.

|                                                                                   |                                                                 |                                    |
|-----------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------|
|  | <b>P3-C2-004 Study Protocol</b>                                 |                                    |
|                                                                                   | <b>Author(s):</b> M. Pineda-Moncusí, Y. Guo, D. Prieto-Alhambra | <b>Version:</b> V4.0               |
|                                                                                   |                                                                 | <b>Dissemination level:</b> Public |

These models will be characterized by varying combinations of autoregressive (AR) and moving average (MA) parameters, possibly on the integrated time series. The model selection and evaluation process are outlined in the following sub-sections:

1. First, ARIMA models will be fit using the `auto.arima()` function from the forecast R package, which considers stationary, seasonality and trend testing. A range of different combinations of AR and MA parameters will be assessed, and the best parsimonious model will be chosen based on the lowest Akaike's Information Criterion (AIC), together with diagnostic tools (e.g. plots of residuals).
2. Validation: The model's predictive accuracy will be assessed using out-of-sample validation techniques. Evaluation metrics will include the Mean Absolute Error (MAE) and Mean Absolute Percentage Error (MAPE). For the validation, we will remove the last 12 months of available data, fit ARIMA models to the remaining data, predict the next 12 months and compare the predictions with the actual observations. We note that while the ARIMA models fitted may well be different from the ones obtained using all available data, the obtained metrics will still inform of the validity of the general approach used to estimate the ARIMA models.
3. Forecasting: The selected ARIMA model(s) will be employed to forecast the numerator of the IR of prescriptions or dispensations for the next 12-months after end of data availability.

## 8.8 Evidence synthesis

Results from analyses described in Section 8.7 will be presented separately for each database and no meta-analysis of results will be conducted.

## 9. 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.

## 10. QUALITY CONTROL

### General database quality control

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

|                                                                                   |                                                                 |                                    |
|-----------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------|
|  | <b>P3-C2-004 Study Protocol</b>                                 |                                    |
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|                                                                                   |                                                                 | <b>Dissemination level:</b> Public |

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.

## 11. LIMITATIONS 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. Additionally, an unknown number of individuals will be present in both, InGef RDB and IQVIA DA Germany databases. However, since IQVIA DA Germany captures a larger proportion of the German population it will provide a broader and more representative coverage of prescriptions in the German primary care, whereas InGef RDB will be particularly relevant for medications administered in hospital settings, which are not captured by IQVIA DA Germany.

Forecasting with ARIMA models has several limitations. ARIMA assumes the homoscedasticity of the data (variance is constant over time) which might not hold even after integration of the time series. To overcome this limitation, we will evaluate the potential presence of heteroscedasticity in the data and, if necessary, mitigate its effect by applying a suitable transformation of the data prior to fitting the ARIMA model.

Given that each drug of interest for each country needs their own ARIMA model, model parameters will be initially estimated automatically using the function "*auto.arima*" from the R package *forecast* and finetuned if needed based on diagnostics. Additionally, we might not be able to capture all the exogenous variables into the models (e.g., having unexpected events leading to abnormal observations), which might impact model fitting. For example, COVID-19 pandemic might be an example of disruption that may negatively impact estimation and forecasting.

## 12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions will not be collected or analysed as part of this evaluation. The nature of this non-interventional evaluation, through the use of secondary data, does not fulfil the criteria for reporting adverse events, according to module VI, VI.C.1.2.1.2 of the Good Pharmacovigilance Practices

|                                                                                   |                                                                 |                                    |
|-----------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------|
|  | <b>P3-C2-004 Study Protocol</b>                                 |                                    |
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|                                                                                   |                                                                 | <b>Dissemination level:</b> Public |

([https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports\\_en.pdf](https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf))

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

## 13. GOVERNANCE BOARD ASPECTS

SIDIAP, IMASIS and CPRD will require to undergo their respective ethical approvals.

## 14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

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

## 15. REFERENCES

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|                                                                                   |                                                                 |                                    |
|-----------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------|
|  | <b>P3-C2-004 Study Protocol</b>                                 |                                    |
|                                                                                   | <b>Author(s):</b> M. Pineda-Moncusí, Y. Guo, D. Prieto-Alhambra | <b>Version:</b> V4.0               |
|                                                                                   |                                                                 | <b>Dissemination level:</b> Public |

## 16. ANNEXES

Appendix I: Preliminary code lists for the antibiotics identified as potentially critical in PHE.

| Antibiotic                                              | Class                                | ATC code | Ingredient ConceptID |
|---------------------------------------------------------|--------------------------------------|----------|----------------------|
| Amoxicillin                                             | Penicillins with extended spectrum   | J01CA04  | 1713332              |
| Amoxicillin/clavulanate (Amoxicillin + Clavulanic acid) | Combinations of penicillins          | J01CR02  | 1713332 + 1759842    |
| Azithromycin                                            | Macrolides                           | J01FA10  | 1734104              |
| Benzylpenicillin (Penicillin G)                         | Beta-lactamase sensitive penicillins | J01CE01  | 1728416              |
| Clarithromycin                                          | Macrolides                           | J01FA09  | 1750500              |
| Cefotaxime                                              | Third-generation cephalosporins      | J01DD01  | 1774470              |
| Ceftriaxone                                             | Third-generation cephalosporins      | J01DD04  | 1777806              |
| Cefuroxime                                              | Second-generation cephalosporins     | J01DC02  | 1778162              |
| Meropenem                                               | Carbapenems                          | J01DH02  | 1709170              |
| Phenoxymethylpenicillin (Penicillin V)                  | Beta-lactamase sensitive penicillins | J01CE02  | 1729720              |
| Piperacillin + Tazobactam                               | Combinations of penicillins          | J01CR05  | 1746114 + 1741122    |

ATC = Anatomical Therapeutic Chemical

Appendix II: ENCePP checklist for study protocols.

### ENCEPP Checklist for Study Protocols (Revision 1)

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

|                                                                                                  |
|--------------------------------------------------------------------------------------------------|
| <b>Study title:</b>                                                                              |
| Incidence, prevalence, and characterisation of medicines with suggested drug shortages in Europe |

|                                                          |
|----------------------------------------------------------|
| <b>EU PAS number:</b> EUPAS1000000473                    |
| <b>Study reference number (if applicable):</b> P3-C2-004 |

| Section 1: Milestones                                  | Yes                                 | No                       | N/A                      | Section Number |
|--------------------------------------------------------|-------------------------------------|--------------------------|--------------------------|----------------|
| 1.1 Does the protocol specify timelines for            |                                     |                          |                          | 6 - milestones |
| 1.1.1 Start of data collection <sup>1</sup>            | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                |
| 1.1.2 End of data collection <sup>2</sup>              | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                |
| 1.1.3 Progress report(s)                               | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                |
| 1.1.4 Interim report(s)                                | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                |
| 1.1.5 Registration in the EU PAS Register <sup>*</sup> | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                |

<sup>1</sup> 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.

<sup>2</sup> Date from which the analytical dataset is completely available.

|                                                                                   |                                                                 |                                    |  |
|-----------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------|--|
|  | <b>P3-C2-004 Study Protocol</b>                                 |                                    |  |
|                                                                                   | <b>Author(s):</b> M. Pineda-Moncusí, Y. Guo, D. Prieto-Alhambra | <b>Version:</b> V4.0               |  |
|                                                                                   |                                                                 | <b>Dissemination level:</b> Public |  |

| <b>Section 1: Milestones</b>         | <b>Yes</b>                          | <b>No</b>                | <b>N/A</b>               | <b>Section Number</b> |
|--------------------------------------|-------------------------------------|--------------------------|--------------------------|-----------------------|
| 1.1.6 Final report of study results. | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                       |

Comments:

| <b>Section 2: Research question</b>                                                                                                                             | <b>Yes</b>                          | <b>No</b>                | <b>N/A</b>                          | <b>Section Number</b>                 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|--------------------------|-------------------------------------|---------------------------------------|
| 2.1 Does the formulation of the research question and objectives clearly explain:                                                                               | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            | 7 – 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) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            |                                       |
| 2.1.2 The objective(s) of the study?                                                                                                                            | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            |                                       |
| 2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)                                             | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            |                                       |
| 2.1.4 Which hypothesis(-es) is (are) to be tested?                                                                                                              | <input type="checkbox"/>            | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                                       |
| 2.1.5 If applicable, that there is no <i>a priori</i> hypothesis?                                                                                               | <input type="checkbox"/>            | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                                       |

Comments:

| <b>Section 3: Study design</b>                                                                                                                                                                        | <b>Yes</b>                          | <b>No</b>                | <b>N/A</b>                          | <b>Section Number</b> |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|--------------------------|-------------------------------------|-----------------------|
| 3.1 Is the study design described? (e.g., cohort, case-control, cross-sectional, other design)                                                                                                        | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            | 8.1                   |
| 3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?                                                                                           | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            | 8.2                   |
| 3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)                                                                                                                  | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            | 8.7.5                 |
| 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))                           | <input type="checkbox"/>            | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                       |
| 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) | <input type="checkbox"/>            | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                       |

Comments:

| <b>Section 4: Source and study populations</b>           | <b>Yes</b>                          | <b>No</b>                | <b>N/A</b>               | <b>Section Number</b> |
|----------------------------------------------------------|-------------------------------------|--------------------------|--------------------------|-----------------------|
| 4.1 Is the source population described?                  | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 8.2                   |
| 4.2 Is the planned study population defined in terms of: |                                     |                          |                          | 8.3 and 8.4           |

|                                                                                   |                                                                 |  |                      |
|-----------------------------------------------------------------------------------|-----------------------------------------------------------------|--|----------------------|
|  | <b>P3-C2-004 Study Protocol</b>                                 |  |                      |
|                                                                                   | <b>Author(s):</b> M. Pineda-Moncusí, Y. Guo, D. Prieto-Alhambra |  | <b>Version:</b> V4.0 |
|                                                                                   | <b>Dissemination level:</b> Public                              |  |                      |

| <b><u>Section 4: Source and study populations</u></b>                                                                                           | <b>Yes</b>                          | <b>No</b>                | <b>N/A</b>               | <b>Section Number</b> |
|-------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|--------------------------|--------------------------|-----------------------|
| 4.2.1 Study time period                                                                                                                         | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                       |
| 4.2.2 Age and sex                                                                                                                               | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                       |
| 4.2.3 Country of origin                                                                                                                         | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                       |
| 4.2.4 Disease/indication                                                                                                                        | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                       |
| 4.2.5 Duration of follow-up                                                                                                                     | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |                       |
| 4.3 Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 8.4                   |

Comments:

| <b><u>Section 5: Exposure definition and measurement</u></b>                                                                                                                                         | <b>Yes</b>                          | <b>No</b>                | <b>N/A</b>                          | <b>Section Number</b> |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|--------------------------|-------------------------------------|-----------------------|
| 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) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            | 8.5.1                 |
| 5.2 Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)                                                                     | <input type="checkbox"/>            | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                       |
| 5.3 Is exposure categorised according to time windows?                                                                                                                                               | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            | 8.5.1                 |
| 5.4 Is intensity of exposure addressed? (e.g., dose, duration)                                                                                                                                       | <input type="checkbox"/>            | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                       |
| 5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?                                                   | <input type="checkbox"/>            | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                       |
| 5.6 Is (are) (an) appropriate comparator(s) identified?                                                                                                                                              | <input type="checkbox"/>            | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                       |

Comments:

| <b><u>Section 6: Outcome definition and measurement</u></b>                                                                                                                     | <b>Yes</b>               | <b>No</b>                | <b>N/A</b>                          | <b>Section Number</b> |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|--------------------------|-------------------------------------|-----------------------|
| 6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?                                                                          | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                       |
| 6.2 Does the protocol describe how the outcomes are defined and measured?                                                                                                       | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                       |
| 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) | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                       |

|                                                                                   |                                                                 |                                    |  |
|-----------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------|--|
|  | <b>P3-C2-004 Study Protocol</b>                                 |                                    |  |
|                                                                                   | <b>Author(s):</b> M. Pineda-Moncusí, Y. Guo, D. Prieto-Alhambra | <b>Version:</b> V4.0               |  |
|                                                                                   |                                                                 | <b>Dissemination level:</b> Public |  |

| <b><u>Section 6: Outcome definition and measurement</u></b>                                                                                                                                                              | <b>Yes</b>               | <b>No</b>                | <b>N/A</b>                          | <b>Section Number</b> |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|--------------------------|-------------------------------------|-----------------------|
| 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) | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                       |

Comments:

| <b><u>Section 7: Bias</u></b>                                                                                        | <b>Yes</b>               | <b>No</b>                | <b>N/A</b>                          | <b>Section Number</b> |
|----------------------------------------------------------------------------------------------------------------------|--------------------------|--------------------------|-------------------------------------|-----------------------|
| 7.1 Does the protocol address ways to measure confounding? (e.g., confounding by indication)                         | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                       |
| 7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)                                       | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                       |
| 7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias) | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                       |

Comments:

| <b><u>Section 8: Effect measure modification</u></b>                                                                                                      | <b>Yes</b>               | <b>No</b>                | <b>N/A</b>                          | <b>Section Number</b> |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|--------------------------|-------------------------------------|-----------------------|
| 8.1 Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect) | <input type="checkbox"/> | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                       |

Comments:

| <b><u>Section 9: Data sources</u></b>                                                                                                                                     | <b>Yes</b>                          | <b>No</b>                | <b>N/A</b>                          | <b>Section Number</b> |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|--------------------------|-------------------------------------|-----------------------|
| 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)                                               | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            | 8.2                   |
| 9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics) | <input type="checkbox"/>            | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                       |
| 9.1.3 Covariates and other characteristics?                                                                                                                               | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            | 8.2                   |
| 9.2 Does the protocol describe the information available from the data source(s) on:                                                                                      |                                     |                          |                                     |                       |

|                                                                                   |                                                                 |                                    |  |
|-----------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------|--|
|  | <b>P3-C2-004 Study Protocol</b>                                 |                                    |  |
|                                                                                   | <b>Author(s):</b> M. Pineda-Moncusí, Y. Guo, D. Prieto-Alhambra | <b>Version:</b> V4.0               |  |
|                                                                                   |                                                                 | <b>Dissemination level:</b> Public |  |

| <b>Section 9: Data sources</b>                                                                                                       | <b>Yes</b>                          | <b>No</b>                | <b>N/A</b>                          | <b>Section Number</b> |
|--------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|--------------------------|-------------------------------------|-----------------------|
| 9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)      | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            | 8.5.1                 |
| 9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)                                        | <input type="checkbox"/>            | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                       |
| 9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            | 8.5.3                 |
| 9.3 Is a coding system described for:                                                                                                |                                     |                          |                                     |                       |
| 9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)                              | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            | Appendix II           |
| 9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))        | <input type="checkbox"/>            | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                       |
| 9.3.3 Covariates and other characteristics?                                                                                          | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            | 8.5.3                 |
| 9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)                                 | <input type="checkbox"/>            | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                       |

Comments:

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| <b>Section 10: Analysis plan</b>                                                       | <b>Yes</b>                          | <b>No</b>                | <b>N/A</b>                          | <b>Section Number</b>     |
|----------------------------------------------------------------------------------------|-------------------------------------|--------------------------|-------------------------------------|---------------------------|
| 10.1 Are the statistical methods and the reason for their choice described?            | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            | 8.7                       |
| 10.2 Is study size and/or statistical precision estimated?                             | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            | 8.6 and Appendix I        |
| 10.3 Are descriptive analyses included?                                                | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            | 8.7                       |
| 10.4 Are stratified analyses included?                                                 | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            | 8.7.4                     |
| 10.5 Does the plan describe methods for analytic control of confounding?               | <input type="checkbox"/>            | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                           |
| 10.6 Does the plan describe methods for analytic control of outcome misclassification? | <input type="checkbox"/>            | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                           |
| 10.7 Does the plan describe methods for handling missing data?                         | <input type="checkbox"/>            | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                           |
| 10.8 Are relevant sensitivity analyses described?                                      | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            | 8.4., 8.5.1, 8.7.3, 8.7.5 |

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|-----------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------------------------|--|
|  | <b>P3-C2-004 Study Protocol</b>                                 |                                    |  |
|                                                                                   | <b>Author(s):</b> M. Pineda-Moncusí, Y. Guo, D. Prieto-Alhambra | <b>Version:</b> V4.0               |  |
|                                                                                   |                                                                 | <b>Dissemination level:</b> Public |  |

| <b><u>Section 11: Data management and quality control</u></b>                                                                                              | <b>Yes</b>                          | <b>No</b>                | <b>N/A</b>                          | <b>Section Number</b> |
|------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|--------------------------|-------------------------------------|-----------------------|
| 11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving) | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            | 9                     |
| 11.2 Are methods of quality assurance described?                                                                                                           | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/>            | 10                    |
| 11.3 Is there a system in place for independent review of study results?                                                                                   | <input type="checkbox"/>            | <input type="checkbox"/> | <input checked="" type="checkbox"/> |                       |

Comments:

| <b><u>Section 12: Limitations</u></b>                                                                                                                                                                                                                                                                             | <b>Yes</b>                                                                                             | <b>No</b>                                                                        | <b>N/A</b>                                                                                  | <b>Section Number</b> |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-----------------------|
| 12.1 Does the protocol discuss the impact on the study results of:<br>12.1.1 Selection bias?<br>12.1.2 Information bias?<br>12.1.3 Residual/unmeasured confounding?<br>(e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods). | <input checked="" type="checkbox"/><br><input checked="" type="checkbox"/><br><input type="checkbox"/> | <input type="checkbox"/><br><input type="checkbox"/><br><input type="checkbox"/> | <input type="checkbox"/><br><input type="checkbox"/><br><input checked="" type="checkbox"/> | 11                    |
| 12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)                                                                                                                        | <input type="checkbox"/>                                                                               | <input checked="" type="checkbox"/>                                              | <input type="checkbox"/>                                                                    |                       |

Comments:

| <b><u>Section 13: Ethical/data protection issues</u></b>                               | <b>Yes</b>                          | <b>No</b>                | <b>N/A</b>               | <b>Section Number</b> |
|----------------------------------------------------------------------------------------|-------------------------------------|--------------------------|--------------------------|-----------------------|
| 13.1 Have requirements of Ethics Committee/ Institutional Review Board been described? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 12                    |
| 13.2 Has any outcome of an ethical review procedure been addressed?                    | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 12                    |
| 13.3 Have data protection requirements been described?                                 | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 12                    |

Comments:

| <b><u>Section 14: Amendments and deviations</u></b>                             | <b>Yes</b>                          | <b>No</b>                | <b>N/A</b>               | <b>Section Number</b> |
|---------------------------------------------------------------------------------|-------------------------------------|--------------------------|--------------------------|-----------------------|
| 14.1 Does the protocol include a section to document amendments and deviations? | <input checked="" type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> | 4                     |

|                                                                                   |                                                                 |                      |
|-----------------------------------------------------------------------------------|-----------------------------------------------------------------|----------------------|
|  | <b>P3-C2-004 Study Protocol</b>                                 |                      |
|                                                                                   | <b>Author(s):</b> M. Pineda-Moncusí, Y. Guo, D. Prieto-Alhambra | <b>Version:</b> V4.0 |
|                                                                                   | <b>Dissemination level:</b> Public                              |                      |

Comments:

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| <b><u>Section 15: Plans for communication of study results</u></b>                          | <b>Yes</b>                          | <b>No</b>                           | <b>N/A</b>               | <b>Section Number</b> |
|---------------------------------------------------------------------------------------------|-------------------------------------|-------------------------------------|--------------------------|-----------------------|
| 15.1 Are plans described for communicating study results (e.g., to regulatory authorities)? | <input checked="" type="checkbox"/> | <input type="checkbox"/>            | <input type="checkbox"/> | 15                    |
| 15.2 Are plans described for disseminating study results externally, including publication? | <input type="checkbox"/>            | <input checked="" type="checkbox"/> | <input type="checkbox"/> |                       |

Comments:

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Name of the main author of the protocol:

Marta Pineda-Moncusí

Date: 18/02/2025

Signature:

MPM