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Study Report

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Version 1.0

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|  |  |
| --- | --- |
| **Study Title** | Informative title including a commonly used term indicating the study design and the medicinal product, substance or drug class concerned |
| **Study Report Version identifier** | Number to be added |
| **Date of last version of Study Report** | Date |
| **EU PAS register number** | Registration number in the EU PAS register; indicate “Study not registered” if the study has not (yet) been registered in the EU PAS register. |
| **Active substance** | List of pharmacotherapeutic group(s)) and active substance(s) subject to the study |
| **Medicinal product** | List of centrally authorised medicinal product(s) and/or, if possible, of nationally authorised products subject to the study |
| **Marketing authorisation holder(s)** | Marketing authorisation holder(s) which initiate(s), manage(s) or finance(s) the study |
| **Research question and objectives** | Summary of the research question and main objectives |
| **Country(-ies) of study** | List of countries where the study is to be conducted; if countries have not been identified yet, or if the list is not complete, this should be stated |
| **Author** | Name and contact details of the main author of the study protocol |

# DESCRIPTION OF STUDY TEAM

A table with the description of the Study team (by role, name and organisation). For off-the-shelf studies or routine repeated studies, it might be that a more lean composition of the study team is suggested (e.g. without need of Statistician, Clinical Domain Expert, etc)

| **Study team Role** | **Names** | **Organisation** |
| --- | --- | --- |
|  |  | *Organisation will either be members of the DARWIN EU® CC and/or Data sources* |
| Study Project Manager/Principal Investigator |  |  |
| Data Scientist |  |  |
| Epidemiologist |  |  |
| Clinical Domain Expert |  |  |
| Statistician |  |  |
| Data Manager |  |  |
| Data Analyst |  |  |

# DATA SOURCES

Information on data source(s) that have been used for the study (selected from the DARWIN EU® Database Catalogue). Additional Data Sources (not yet included in the DARWIN EU®Database Catalogue) might be considered depending on the study question.

More information on the data sources that have been used can be added to the appendix of the study report

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Country | Name of Database | Health Care setting (e.g. primary care, specialist care, hospital care) | Type of Data (EHR, claims, registries) | Number of active subjects |
|  |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

# ABSTRACT (Stand-alone summary of the Study Report)

Sections included in abstract are: title, rationale and background, research question and objectives, study design (see D1.3.8.1 Draft Catalogue of Data analytics), Setting, Subjects and study size (including drop-out), population, variables, results and discussion.

# LIST OF ABBREVIATIONS

# AMENDMENTS AND UPDATES

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Number | Date | Section of study protocol | Amendment or update | Reason |
| 1 | Date | Text | Text | Text |
| 2 | Date | Text | Text | Text |
| … | Date | Text | Text | Text |

# MILESTONES

|  |  |  |
| --- | --- | --- |
| **STUDY SPECIFIC DELIVERABLE** | **TIMELINE (planned)** | **TIMELINES (actual)** |
| Draft Study Protocol |  |  |
| Final Study Protocol |  |  |
| Creation of Analytical code |  |  |
| Execution of Analytical Code on the data |  |  |
| Draft Study Report |  |  |
| Final Study Report |  |  |
| Draft Manuscript (if agreed on |  |  |
| Final Manuscript (if agreed on |  |  |

# RATIONALE AND BACKGROUND

This section will provide background and explanation on the rationale for the study, the different methodological aspects to be addressed, potential challenges and opportunities.

# RESEARCH QUESTION AND OBJECTIVES

Description of the proposed objectives to be achieved in the study.

If applicable, the proposed objectives should be structured as primary and secondary objectives.

# AMENDMENTS and UPDATES

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Number | Date | Section of study protocol | Amendment or update | Reason |
| 1 | Date | Text | Text | Text |
| 2 | Date | Text | Text | Text |
| … | Date | Text | Text | Text |

# RESEARCH METHODS

This Information will be copied from the method section of the final Study Protocol.

## Study Setting and Data Sources

This section describes in which countries and using which data sources (selected from the DARWIN EU®Database Catalogue), the study ran

Information on data source(s) which were used are presented by means of a table:

## Study Period

Defines the period in which the study ran.

* 1. Follow-up

Describes the follow-up of individuals within the study, based on study specific criteria with regard to time of inclusion and time of exclusion of subjects within the study.

* 1. Study Population with in and exclusion criteria

This section describes how the study population was selected based on specific in and exclusion criteria.

* 1. Variables

Presentation of exposures, outcomes and relevant characteristics including risk factors, co-morbidities, co-medications, confounding variables and effect modifiers which were considered for the study. Concept lists/Vocabularies for diseases/outcomes/drug exposure that were used will be included as Supplementary Documents.

* 1. Study size

Results of the sample size calculation (if needed) based on the available data with regard to incidence of the condition of interest and the estimated risk estimate. If relevant, describe methods to attain the projected study size.

* 1. Data transformation

Data management and transformations, calculations or operations on the data, including how quantitative data were handled in the analyses and which groupings were chosen and why.

* 1. Statistical Methods
     1. Main summary Measures

Describes measures to summarize the data (e.g. mean, median, incidence rates, relative risk etc.)

* + 1. Main Statistical Methods

This section will describe the analysis approach and rationale for the choice of analysis, with reference to the D1.3.8.1 Draft Catalogue of Data analytics.

In principle the type of analysis by study type is fixed as can be observed from **Table 2**. In certain circumstances, depending on the study question, additional analysis might be considered but this would imply that studies fall within the category complex/very complex.

**Table 2**. Description of Study Types and Type of analysis

| **STUDY TYPE** | **STUDY CLASSIFICATION** | **TYPE OF ANALYSIS** |
| --- | --- | --- |
| Population Level DUS | Off-the-shelf (C1) | * Population-based incidence rates * Population-based prevalence of use of a drug/drug class |
| Patient Level DUS | Off-the-shelf (C1) | * characterisation of patient-level features * Frequency and % of indication/s * Estimation of minimum, p25, median, p75, and maximum initially prescribed or dispensed dose/strength * Estimation of minimum, p25, median, p75, and maximum treatment duration |
| Trend analyses and RMM effectiveness | Complex (C3) | * Incidence and prevalence rate/s of drug/s use over time * For patient-level analyses, standardised mean differences of each of the covariates for the comparison between new drug user/s in the pre-RMM vs post-RMM period will be obtained * measures of patient-level DUS (descriptives of treatment duration) will be provided |
| Population-level descriptive epidemiology | Off-the-shelf (C1) | * Incidence rates of the condition of interest * Prevalence rates of the condition of interest |
| Patient-level characterisation | Off-the-shelf (C1) | * large-scale characterisation * patient-level characteristics * Prognosis / progression to a pre-specified outcome * Standard care description |
| Time series analyses and Difference-in-difference studies | Complex (C3) | * Incidence and prevalence rate/s of disease over time, followed by segmented regression methods to estimate the impact of the proposed intervention/s * For difference-in-difference studies, parallel trends before the intervention will be identified. If confirmed, Difference-in-difference models will be used to subtract the difference of the unexposed group to the exposed one whilst controlling for time varying factors * For patient-level analyses, standardised mean differences of each of the covariates for the comparison between new cases diagnosed in the pre- vs post-intervention period will be obtained |
| Drug/Vaccine Safety Studies or Comparative Effectiveness Studies | Complex (C3) | SCCS design:   * Large-scale characterisation as well as pre-specified patient-level characteristics of SCCS participants at the time of diagnosis * Incidence rate/s during exposed and unexposed time * Diagnostics (event-exposure independence, power, residual confounding/systematic error) * (Adjusted)Incidence rate ratios and 95% confidence intervals using conditional Poisson regression models, comparing the exposed vs the baseline period (adjusting for age and seasonality). * Optionally, calibrated incidence rate ratios will be estimated |
| Comparative Effectiveness Studies | Complex (C3) | New cohort design:   * Large-scale characterisation of participants in the target and comparator cohorts * Large-scale propensity scores (LSPS) will be estimated * Incidence rate/s of each of the outcomes of interest in the target and comparator cohorts * Diagnostic/s: Covariate balance, Equipoise, Power, residual confounding/systematic error (optional) * Rate Ratios or Hazard Ratio/s and 95% confidence intervals using Poisson or Cox models respectively * Optionally, calibrated RR or HR will be estimated after empirical calibration using negative control outcomes |

Details of the applied analysis will be added from the D1.3.8.1 Draft Catalogue of Data analytics which provides more details on e.e. definitions, characterisation of participants/population, dealing with confounders, statistical models to be used etc.

* + 1. Missing Values

Describes how missing values are addressed

* + 1. Sensitivity Analysis

Describes whether sensitivity analyses have been performed on the data, how and why

# DATA MANAGEMENT

Methods for data collection, retrieval, collection and preparation. Statistical software(s) to be used in the study should be specified.

Note: Standard text will be generated on Data Management which will fit all studies run by the DARWIN EU®CC

# QUALITY CONTROL

Description of any mechanisms and procedures to ensure data quality and integrity, including accuracy and legibility of collected data and original documents, extent of source data verification and validation of endpoints, storage of records and archiving of the statistical programming performed to generate the results.

Note: This section will be automatically generated based on the DARWIN EU®Q/C processes

# RESULTS

* 1. Participants

Describes the number of study subjects who entered each stage of study ( e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing followed and analysed) Reasons for non-participation will be mentioned and flowcharts/diagrams to display this info wil be used.

* 1. Descriptive Data

Will provide Large-scale characterisation of participants. Depending on the Study Type, also patient level characterisation will be provided.

* 1. Outcome Data

Number of subjects with the outcomes of interest

* 1. Main Results

The presentation of the main results will be Study Type specific and Type of Analysis specific as described in the Draft Catalogue of Data analytics.

**Table 3** describes the main results by Study Type and Data Analytics

**Table 3**. Description of Presentation of Main Results by Study Classification and Type of Analysis

| **STUDY TYPE** | **STUDY CLASSIFICATION** | **TYPE OF ANALYSIS** | **PRESENTATION OF MAIN RESULTS** |
| --- | --- | --- | --- |
| Population Level DUS | Off-the-shelf (C1) | * Population-based incidence rates * Population-based prevalence of use of a drug/drug class | * Incidence of drug use (stratified by pre-specified criteria (age bands, sex, calendar year or month). * Prevalence of drug use (stratified by pre-specified criteria (age bands, sex, calendar year or month). |
| Patient Level DUS | Off-the-shelf (C1) | * characterisation of patient-level features * Frequency and % of indication/s * Estimation of minimum, p25, median, p75, and maximum initially prescribed or dispensed dose/strength * Estimation of minimum, p25, median, p75, and maximum treatment duration | * patient characteristics of patients initiating drug therapy * number of patients with information on indication of use (expressed as proportion) * information on dose and strength (expressed as minimum, p25, median, p75, and maximum) * treatment duration (expressed as minimum, p25, median, p75, and maximum) |
| Trend analyses and RMM effectiveness | Complex (C3) | * Incidence and prevalence rate/s of drug/s use over time * For patient-level analyses, standardised mean differences of each of the covariates for the comparison between new drug user/s in the pre-RMM vs post-RMM period will be obtained * measures of patient-level DUS (descriptives of treatment duration) will be provided | * Number of participants and total number of drug/s user/s in each source population during study period. (if needed by pre-specified strata) * Incidence rate/s of drug/s use over calendar time (month/year) highlighting the period before and after RMM * Prevalence of drug/s use over calendar time highlighting the period before and after RMM * Baseline characteristics of incident drug user/s at the time of therapy initiation, comparing those initiating treatment before vs after RMM date * Descriptive measures of treatment duration, stratified by date of therapy initiation (before vs after RMM) |
| Population-level descriptive epidemiology | Off-the-shelf (C1) | * Incidence rates of the condition of interest * Prevalence rates of the condition of interest | * Number of participants and total number of incident and/or prevalent cases in each data source during the study period. (might be presented by pre-specified strata where necessary/applicable) * Incidence rate/s of disease over calendar time (month/year) overall (and stratified by sex and age) * Prevalence of disease over calendar time (month/year) overall (and stratified by sex and age) |
| Patient-level characterisation | Off-the-shelf (C1) | * large-scale characterisation * patient-level characteristics * Prognosis / progression to a pre-specified outcome * Standard care description | * Baseline characteristics of patients newly diagnosed with a condition of interest, at the time of diagnosis/recording (might be presented by pre-specified strata where necessary/applicable) * Number and % with an outcome of interest in the x years following diagnosis * Kaplan-Meier or Cumulative Incidence Function plots of the probability of a pre-specified outcome following index diagnosis * Number and % treated with a pre-specified medicine or list of medicine/s within a pre-specified time period following an index diagnosis (presented by table as well as by figures/plots where relevant) |
| Time series analyses and Difference-in-difference studies | Complex (C3) | * Incidence and prevalence rate/s of disease over time, followed by segmented regression methods to estimate the impact of the proposed intervention/s * For difference-in-difference studies, parallel trends before the intervention will be identified. If confirmed, Difference-in-difference models will be used to subtract the difference of the unexposed group to the exposed one whilst controlling for time varying factors * For patient-level analyses, standardised mean differences of each of the covariates for the comparison between new cases diagnosed in the pre- vs post-intervention period will be obtained | * Number of participants and total number of cases in each source population during study period. (might be presented by pre-specified strata where necessary/applicable) * Incidence rate/s of disease over calendar time (month/year) highlighting the period before and after the intervention of interest (presented as figure)(numbers presented in table) * Prevalence of disease over calendar time (month/year) overall highlighting the period before and after intervention (presented as figure) (numbers presented in table) * Baseline characteristics of incident cases diagnosed before vs after exposure * Prevalence of key patient features among new cases diagnosed in the pre- (x axis) vs post-intervention (y axis) period |
| Drug/Vaccine Safety Studies or Comparative Effectiveness Studies | Complex (C3) | SCCS design:   * Large-scale characterisation as well as pre-specified patient-level characteristics of SCCS participants at the time of diagnosis * Incidence rate/s during exposed and unexposed time * Diagnostics (event-exposure independence, power, residual confounding/systematic error) * (Adjusted)Incidence rate ratios and 95% confidence intervals using conditional Poisson regression models, comparing the exposed vs the baseline period (adjusting for age and seasonality). * Optionally, calibrated incidence rate ratios will be estimated | * Baseline characteristics of SCCS participants (by pre-specified strata where applicable) * Number (of events) and incidence rate/s during baseline and exposed time periods * Diagnostic histogram of the distribution of time between event date and end of observation * Diagnostic table showing MDRR (minimum detectable rate ratio) for each of the study outcome/s * Unadjusted and age and season-adjusted incidence rate ratios (and 95% confidence intervals) (table and figure) * Calibrated incidence rate ratios and error bars (OPTIONAL) |
| Comparative Effectiveness Studies | Complex (C3) | New cohort design:   * Large-scale characterisation of participants in the target and comparator cohorts * Large-scale propensity scores (LSPS) will be estimated * Incidence rate/s of each of the outcomes of interest in the target and comparator cohorts * Diagnostic/s: Covariate balance, Equipoise, Power, residual confounding/systematic error (optional) * Rate Ratios or Hazard Ratio/s and 95% confidence intervals using Poisson or Cox models respectively * Optionally, calibrated RR or HR will be estimated after empirical calibration using negative control outcomes | * Baseline characteristics of participants in the target and comparator cohort, both before and after LSPS matching/weighting/stratification. * Number (of events) and incidence rate/s in the target and comparator cohorts after LSPS matching/weighting/stratification * Diagnostic plot of covariate balance * Diagnostic table showing MDRR for each of the study outcome/s in each target-comparator pair * Diagnostic plot of equipoise * RR or HRs after LSPS matching/weighting/stratification (table and figure) * Systematic error plot (OPTIONAL) * Calibrated RR or HR and error bars (OPTIONAL) |

The presentation of main results might diverse from what is specified above for complex/very complex studies.

Unplanned analyses performed secondarily, such as sub-group analyses or investigation of alternative exposure categories, should be clearly identified and presented as exploratory.

* 1. Other Analysis

Other analyses done, e.g. results of sensitivity analyses, analyses per data source or other relevant variables.

# MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

# DISCUSSION

* 1. Key Results
  2. Limitations of the research methods

Any potential limitations of the study design, data sources, and analytic methods, including issues relating to confounding, bias, generalisability, and random error will be discussed. The likely success of efforts taken to reduce errors should be discussed.

* 1. Interpretation

Overall interpretation of results considering objectives, limitations and findings from similar studies and other relevant evidence supporting or conflicting with the study results. For safety studies, results will be interpreted in relation to the safety issue leading the study to be imposed or initiated, their impact on the benefit-risk balance of the concerned product(s) and the information included in the summary of product characteristics and the risk management plan of the product(s).]

* 1. Generalisability

The generalisability (external validity) of the study results, considering the data source, characteristics of the study population, inclusion and exclusion criteria will be discussed

* 1. Other information

Any additional or complementary information on specific aspects not previously addressed will be added here

# CONCLUSION

Main conclusion of the study, deriving from the analysis of the data, including a statement regarding the impact of the study results on the benefit-risk balance of the product(s).]

# REFERENCES

References using an appropriate referencing convention.

# ANNEXES

**Appendix I:** List of Stand-Alone documents (e.g. lists with concept definitions (conditions & drugs), validation procedures, questionnaires, link to code lists and programming codes, etc.)

**Appendix II**: ENCePP checklist for study protocols

**Appendix III**: Other Additional Information