Study Protocol P3-C1-006

09/07/2024

Version 3.0

Table of Contents

DOCUMENT HISTORY

VERSION	DATE	DESCRIPTION
V1.0	07/06/2024	**Submission to EMA**
V2.0	28/06/2024	**Second version following comments from EMA**
V3.0	09/07/2024	**Third version following comments from EMA**

Study Title	DARWIN EU® - Drug utilisation study on medicinal use of cannabis flos
Protocol version identifier	V3.0
Date of last version of protocol	09/07/2024
EU PAS register number	EUPAS1000000228
Active substance	Cannabis flos (dried, whole or fragmented, flowering tops of *Cannabis sativa* L.)
Medicinal product	Bedrocan, Bedrobinol, Bediol, Bedrolite, Bedica and any other *Cannabis flos* containing products, provided such products are available in the datasets of interest.
Research question and objectives	Research question What is the (real-world) use of Cannabis flos that is prescribed for medicinal purposes? Study objectives 1. To estimate incidence rates and prevalence of use of Cannabis flos, overall and stratified by pre-specified medicinal product of interest, age, sex and country/database, during the study period from 2014 to 2023. 2. To characterise the cohort of patients being treated with the Cannabis flos at the time of new prescription/dispensation of the selected medicinal products in terms of demographics, indication for prescribing/dispensing, comorbidities and comedication. Additionally, to determine duration of treatment with Cannabis flos products. All results will be stratified by pre-specified medicinal product of interest and database.
Country(ies) of study	Netherlands and Germany
Author	Dina Vojinovic d.vojinovic@darwin-eu.org

LIST OF ABBREVIATIONS

Acronyms/term	Description
CDM	Common Data Model
DA	Disease Analyzer
DARWIN EU®	Data Analysis and Real World Interrogation Network
DRE	Digital Research Environment
DOI	Declaration of interests
DQD	Data Quality Dashboard
DRE	Digital Research Environment
DUS	Drug Utilisation Study
ED	Emergency Department
EEA	European Economic Area
EHR	Electronic Health Records
EMA	European Medicines Agency
EU	European Union
GDPR	General Data Protection Regulation
HMPC	Committee on Herbal Medicinal Products
ICD	International Classification of Diseases
ID	Index date
IP	Inpatient
LPD	Longitudinal Patient Database
MA	Marketing Authorisation
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OP	Outpatient
RCT	Randomised Controlled Trial
SD	Standard deviation
SNOMED	Systematized Nomenclature of Medicine
WHO	World Health Organisation

1. TITLE

DARWIN EU® - Drug utilisation study on medicinal use of cannabis flos

2. RESPONSIBLE PARTIES – STUDY TEAM

The table below outlines the composition of the Study team, detailing the roles, names and organisations.

STUDY TEAM ROLE	NAMES	ORGANISATION
Principal Investigator/ Epidemiologist	Dina Vojinovic	IQVIA
Data Scientist	Isabella Kaczmarczyk	IQVIA
Data Partner*	**Names**	**Organisation**
Local Study Coordinator/Data Analyst	Katia Verhamme	Erasmus MC
	Mees Mosseveld	Erasmus MC
	James Brash	IQVIA

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

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

Title

DARWIN EU® - Drug utilisation study on medicinal use of cannabis flos

Rationale and background

Cannabis flos (dried, whole or fragmented, flowering tops of *Cannabis sativa* L.) is not registered as medicinal product in the European Union (EU). However, there are different regulatory strategies among EU member states that enable some specific exemptions for its use and its supply by pharmacies, as a controlled substance under physician's prescription only. Scientific data is needed to inform and support regulatory work including a possible establishment of an EU herbal monograph.

Research question and Objectives

Research question

What is the (real-world) use of Cannabis flos that is prescribed for medicinal purposes?

Study objectives

1. To estimate incidence rates and prevalence of use of Cannabis flos, overall and stratified by pre-specified medicinal product of interest, age, sex and country/database, during the study period

from 2014 to 2023.

2. To characterise the cohort of patients being treated with the Cannabis flos at the time of new prescription/dispensation of the selected medicinal products in terms of demographics, indication for prescribing/dispensing, comorbidities and comedication. Additionally, to determine duration of treatment with Cannabis flos products. Results will be stratified by pre-specified medicinal product of interest and database.

Research Methods

Study design

- Population-level cohort study (Objective 1, Population-level drug utilisation study on pre-specified medicinal products of interest).
- New drug user cohort study (Objective 2, Patient-level utilisation of selected medicinal products of interest with regard to demographics, indication of use, comorbidities, comedication and duration of treatment).

Population

Population-level utilisation of selected medicinal products of interest: Population-level drug utilisation analyses will include all individuals registered in the respective databases between 1st of January 2014 and 31st of December 2023, with at least 1 year of data visibility prior becoming eligible for study inclusion. This requirement of at least 1 year of prior data history will not hold for children <1 year of age.

Patient-level utilisation of selected medicinal products of interest: Patent-level drug utilization analyses will include new users of selected medicinal products registered in the respective databases between 1st of January 2014 and 31st of December 2023. Patients need to have at least 1 year of data visibility prior to the index date, and no use of the respective medicinal products in the previous 1 year. This requirement of at least 1 year of prior data history will not hold for children < 1 year of age.

Variables

Drug of interest

Cannabis flos (dried, whole or fragmented, flowering tops of *Cannabis sativa* L.)

Conditions of interest

Neuralgic pain, cancer, anxiety-related disorders, spasticity (multiple sclerosis (MS), spinal cord injury), neurological disorders (epilepsy, Tourette Syndrome, Huntington, Parkinson disease, amyotrophic later sclerosis (ALS), Alzheimer and other dementias), glaucoma, HIV, anorexia, sleep disorders (insomnia, sleep apnea), inflammatory bowel disease, fibromyalgia, rheumatoid arthritis.

Data sources

1. Integrated Primary Care Information Project (IPCI), the Netherlands
2. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany

Sample size

No sample size has been calculated for this drug utilisation descriptive study, as our primary focus is to investigate medicinal use of Cannabis flos, irrespective of the sample size. Based on a preliminary feasibility assessment, the expected number of person counts for the different products of the selected medication differ across databases and range from 230 in IQVIA DA Germany to 734 patients in IPCI.

Data analyses

Population-level utilisation of selected medicinal products of interest: Annual incidence rates (expressed as number of new users per 1,000 person-years) and annual period prevalence of use of Cannabis flos will be estimated. The statistical analyses will be performed based on OMOP-CDM mapped data using "*IncidencePrevalence*" R package. The results will be stratified by pre-specified medicinal product of interest, age, sex and database.

Patient-level utilisation of selected medicinal products of interest: Patient-level characterisation will be conducted at index date including large-scale characterisation (demographics, comorbidities and comedication) and frequency of indications for prescribing/dispensing Cannabis flos based on pre-specified list of diagnoses. Index date will be the date of incident prescription/dispensation of the selected medicinal products for each individual. Comorbidities, comedication and indications will be assessed at index date and in the period of 1 year prior to the index date. The duration of treatment with Cannabis flos will be calculated and summarized, providing the minimum, quartiles, and maximum. Statistical analyses will be conducted using the "*CohortCharacterisation*", "*PatientProfiles*" and "*DrugUtilization*" R packages based on OMOP-CDM mapped data. The analyses will be stratified by pre-specified medicinal product of interest and database.

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

4. AMENDMENTS AND UPDATES

NUMBER	DATE	SECTION OF STUDY PROTOCOL	AMENDMENT OR UPDATE	REASON

5. MILESTONES

Additional study specific deliverables (e.g. results of validation of new disease concepts, statistical analysis plan, etc.) might be requested but this will be on an individual basis.

STUDY SPECIFIC DELIVERABLE	TIMELINE
Draft Study Protocol	7th of June 2024
Final Study Protocol	July 2024
Creation of Analytical code	July 2024
Registration in HMA-EMA Catalogue	June 2024
Execution of Analytical Code on the data	August 2024
Interim Study Report (if applicable)	Not applicable
Draft Study Report	August 2024
Final Study Report	August/September 2024

6. RATIONALE AND BACKGROUND

Cannabis flos (dried, whole or fragmented, flowering tops of *Cannabis sativa* L.) is not registered as medicinal product in the European Union (EU). However, there are different regulatory strategies among EU member states that enable some specific exemptions for its use and its supply by pharmacies as a controlled substance, available only under physician's prescription.

Cannabis sativa extract, derived from the flowering top of the Cannabis sativa plant, contains various cannabinoids, including tetrahydrocannabinol (THC).[1] These cannabinoids possess potential anti-cachexic, muscle-relaxing, and analgesic properties. When administered, the cannabinoids bind to the CB1 cannabinoid G-protein coupled receptors located in both central and peripheral neurons. Activation of CB1 receptors inhibits adenyl cyclase, enhances multiple signal transduction pathways, and modulates the activity of various ion channels.[1] This results in analgesic effects, may prevent muscle spasms, and can potentially increase appetite.

To our knowledge, there are no observational studies examining the use of Cannabis flos products of profiling the individuals who use them in real-world setting. Furthermore, scientific data is needed to inform and support regulatory work including a possible establishment of an EU herbal monograph.

7. RESEARCH QUESTION AND OBJECTIVES

Research question

What is the (real-world) use of Cannabis flos that is prescribed for medicinal purposes?

Study objectives

1. To estimate incidence rates and prevalence of use of Cannabis flos, overall and stratified by pre-specified medicinal product of interest, age, sex and country/database, during the study period from 2014 to 2023.
2. To characterise the cohort of patients being treated with the Cannabis flos at the time of new prescription/dispensation of the selected medicinal products in terms of demographics, indication for prescribing/dispensing, comorbidities and comedication. Additionally, to determine duration of treatment with Cannabis flos products. Results will be stratified by pre-specified medicinal product of interest and database.

Description of the proposed objectives to be achieved in the study (**Table 1**).

Table 1. Primary and secondary research questions and objective.

A. Objective 1.

Objective:	**Objective 1:** To estimate incidence rates and prevalence of use of Cannabis flos, overall and stratified by pre-specified medicinal product of interest, age, sex and country/database, during the study period from 2014 to 2023.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	Population-level utilisation of selected medicinal products of interest will include all individuals registered in the respective database between 1st of January 2014 and 31st of December 2023, with at least 1 year of data visibility prior becoming eligible for study inclusion. This requirement of at least 1 year of prior data history will not hold for children <1 year of age.
Exposure:	n/a
Comparator:	None
Outcome:	Use of Cannabis flos (dried, whole or fragmented, flowering tops of *Cannabis sativa* L.) products Bedrocan, Bedrobinol, Bediol, Bedrolite, Bedica and any other Cannabis flos containing products, provided such products are available in the datasets of interest.
Time *(when follow up begins and ends):*	Follow-up will start on the respective date of the latest of the following: study start date (1st January 2014) or date at which individual has 1 year of prior history. End of follow-up will be defined as earliest of the following: end of observation period or end of study period (31st of December 2023), whichever occurs first.
Setting:	Outpatient setting using data from the following 2 data sources: IPCI (Netherlands) and IQVIA DA Germany (Germany).
Main measure:	Annual incidence rates (expressed as number of new users of Cannabis flos per 1,000 person-years) and annual period prevalence of Cannabis flos use, overall and stratified by pre-specified medicinal product of interest, age and sex.

	Annual incidence rates and annual period prevalence, for all products combined, will be stratified by age and sex, while annual incidence rates and annual period prevalence for each product stratum will be presented in an overall manner due to the limited sample size within each product stratum.

B. Objective 2.

Objective:	**Objective 2**: To characterise the cohort of patients being treated with the Cannabis flos at the time of new prescription/dispensation of the selected medicinal products in terms of demographics, indication for prescribing/dispensing, comorbidity and comedication and to determine duration of treatment with Cannabis flos. Results will be stratified by pre-specified medicinal product of interest and database.
Hypothesis:	Not applicable
Population *(mention key inclusion-exclusion criteria):*	Patient-level utilisation of selected medicinal products of interest will include new users of selected products registered in the respective database between 1st of January 2014 and 31st of December 2023, with at least 1 year of data visibility prior to index date. "New use" refers to a prescription/dispensation of the selected medicinal products in the study period and without any use of respective medicinal products in the previous 1 year. This requirement of at least 1 year of prior data history will not hold for children <1 year of age.
Exposure:	n/a
Comparator:	None
Outcome:	Use of Cannabis flos (dried, whole or fragmented, flowering tops of *Cannabis sativa* L.) products Bedrocan, Bedrobinol, Bediol, Bedrolite, Bedica and any other Cannabis flos containing products, provided such products are available in the datasets of interest.
Time *(when follow up begins and ends):*	Follow-up will start on the day of incident prescription/dispensation of Cannabis flos (index date). End of follow-up will be defined as earliest of end of observation period, end of study period (31st of December 2023) or end of treatment episode, whichever comes first.
Setting:	Outpatient setting using data from the following 2 data sources: IPCI (Netherlands) and IQVIA DA Germany (Germany).
Main measures:	Large-scale characterisation (demographics, comorbidity and comedication) for new users of Cannabis flos at the index date and in a 1 year prior to the index date, stratified by pre-specified medicinal products of interest. Frequency and % of indications for prescribing/dispensing Cannabis flos, based on pre-specified list of diagnoses, for new users of Cannabis flos at

	the index date and in 1 year prior to the index date, stratified by pre-specified medicinal product of interest. Duration of treatment of selected medicinal products of interest expressed as minimum, p25, median, p75 and maximum, stratified by pre-specified medicinal product of interest.

8. RESEARCH METHODS

8.1 Study type and Study Design

The Study Types with related Study Designs are described in the **Table 2** below and are selected from the Draft Catalogue of Data analytics.

A cohort study will be conducted using routinely collected health data from 2 databases. The study will comprise two consecutive parts:

- Population-based cohort study will be conducted to address objective 1, assessing incidence rates and prevalence of use of Cannabis flos, overall and stratified by pre-specified medicinal product of interest, age, sex and country/database.
- New drug user cohort study will be used to address objective 2; to characterise patient-level drug utilisation in terms of demographics, indication of use, comorbidities and comedication at the date of incident prescription/dispensation of pre-selected medicinal products of interest and duration of treatment with Cannabis flos.

Table 2. Description of Potential Study Types and Related Study Designs.

STUDY TYPE	STUDY DESIGN	STUDY CLASSIFICATION
Population Level DUS	Population Level Cohort	Off the shelf (C1)
Patient Level DUS	New drug/s user cohort	Off the shelf (C1)

8.2 Study Setting and Data Sources

This study will be conducted using routinely collected data from 2 databases in 2 EU countries. All databases were previously mapped to the OMOP Common Data Model (CDM).

1. Integrated Primary Care Information Project (IPCI), the Netherlands
2. IQVIA Disease Analyzer Germany (IQVIA DA Germany), Germany

For this study, 2 databases in the DARWIN EU® Database Catalogue were considered fit for purpose. The selection process was based on the size of the databases, the number of individuals prescribed/dispensed pre-specified medication of interest, geographical spread and the experience gained from databases that participated in other similar DARWIN EU® studies. Based on the feasibility assessment performed, the suggested databases have data on selected pre-specified medication of interest.

Information on these data sources with a justification for their choice in terms of ability to capture the relevant data is described in **Table 3.**

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

Table 4. Description of the selected Data Sources.

Country	Name of Database	Justification for Inclusion	Health Care setting (e.g. primary care, specialist care, hospital care)	Type of Data (EHR, claims, registries)	Number of active subjects	Data lock for the last update
Netherlands	IPCI	Database covers primary care setting where selected pre-specified medicinal products of interest may be prescribed/dispensed	Primary care	EHR	1.4 million	30/04/2024
Germany	IQVIA DA Germany	Database covers primary care/outpatient specialist care setting where selected pre-specified medicinal products of interest may be prescribed/dispensed	Primary care and outpatient specialist care	EHR	8.5 million	23/01/2024

IPCI = Integrated Primary Care Information Project; DA = Data Analyzer; EHR = Electronic Health Record.

Integrated Primary Care Information Project (IPCI), The Netherlands

IPCI is collected from electronic health records (EHR) of patients registered with their general practitioners (GPs) throughout the Netherlands.[2] The selection of 374 GP practices is representative of the entire country. The database contains records from 2.8 million patients out of a Dutch population of 17M starting in 1996.[2] The median follow-up is 4.7 years. The observation period for a patient is determined by the date of registration at the GP and the date of leave/death. The observation period start date is refined by many quality indicators, e.g., exclusion of peaks of conditions when registering at the GP. All data before the observation period is kept as history data. Drugs are captured as prescription records with product, quantity, dosing directions, strength and indication. Drugs not prescribed in the GP setting might be underreported. Indications are available as diagnoses by the GPs and, indirectly, from secondary care providers but the latter might not be complete. Approval needs to be obtained for each study from the Governance Board.[2]

IQVIA Disease Analyser (DA) Germany, Germany

DA Germany is collected from extracts of patient management software used by GPs and specialists practicing in ambulatory care settings.[3] Data coverage includes more than 34M distinct person records out of at total population of 80M (42.5%) in the country and collected from 2,734 providers. Patient visiting more than one provider are not cross identified for data protection reasons and therefore recorded as separate in the system. Dates of service include from 1992 through present. Observation time is defined by the first and last consultation dates. Germany has no mandatory GP system and patient have free choice of specialist. As a result, data are collected from visits to General, Paediatric Medicine, Obstetrics / Gynaecology, Orthopaedic Surgery, Dermatology, Otolaryngology, Diabetic medicine, Urology, Neuropsychiatry, Cardiology, Gastroenterology, Pulmonary Disease, Rheumatology, Neurology, Psychotherapy, Child and Adolescent Psychiatry and Psychiatry. Drugs are recorded as prescriptions of marketed products. No registration or approval is required for drug utilisation studies.

8.3 Study Period

The study period will be from 1st of January 2014 until the earliest of 31st December 2023 or respective lock for the last database update (see **Table 3** for more details on each database's latest data).

8.4 Follow-up

For population-level utilisation of selected medicinal products of interest, follow-up will start when study participants fulfil inclusion criteria (i.e. present in the database between 1st of January 2014 and 31st of December 2023 and with at least 1 year of data visibility (not for children < 1 year of age). End of follow-up will be defined as the earliest of end of observation period or end of study period (31st December 2023), whatever comes first.

For patient-level drug utilisation of pre-selected medication of interest, study participants will be followed from the date of incident prescription/dispensation of selected pre-specified medication of interest (index date) until end of observation period, end of the study period (31st of December 2023) or end of treatment episode, whatever comes first.

Operational definition of index date and other primary time anchors are described in **Table 4.**

Table 5. Operational Definition of Time 0 (index date) and other primary time anchors.

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care Setting [1]	Code Type[2]	Diagnosis position	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
All patients from the database eligible for the study – Incident use of Cannabis flos	Patients present in the database with at least 1 year of valid database history (except for children <1 year).	Multiple entries	Incident	[-365, ID]	OP	RxNorm	n/a	Use of selected pre-specified medicinal products	n/a	n/a
All patients from database eligible for the study – Prevalent use of Cannabis flos	Patients present in the database with at least 1 year of valid database history (except for children <1 year).	Multiple entries	Prevalent	n/a	OP	RxNorm	n/a	n/a	n/a	n/a
All participants from the database eligible for the study initiating treatment with the selected pre-specified medication of interest - Characterisation	Initiation of treatment with pre-selected medication of interest	Multiple entries	Incident	[-365, ID)	OP	RxNorm	n/a	Use of selected pre-specified medicinal products	n/a	n/a

[1] OP = outpatient

[2] The type(s) of clinical codes that are used to define the time 0 (or another primary anchor) criterion.

ID = index date; n/a = not applicable;

Both incidence and prevalence require an appropriate denominator population and their contributed observation time to first be identified. Study participants in the denominator population will begin contributing person time on the respective date of the latest of the following: 1) study start date (1st January 2014) or 2) date at which they have 1 year of prior history. Participants will stop contributing person time at the earliest date of the following: 1) study end date (31st December 2023) or 2) end of observation period.

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

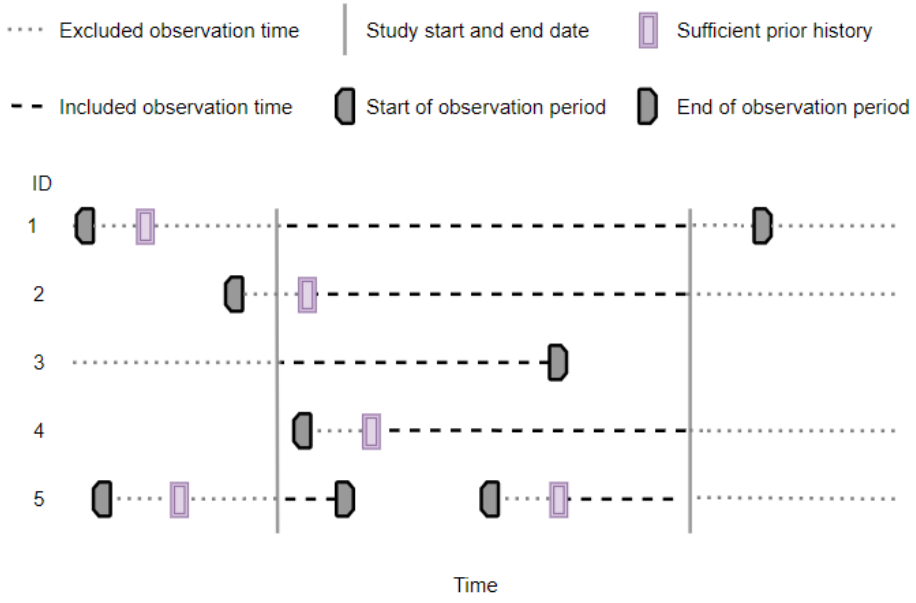


Figure 1. Included observation time for the denominator population

8.5 Study Population with inclusion and exclusion criteria

8.5.1 Population-level utilisation of selected medicinal products

The study cohort will include all individuals registered in the database between 1st of January 2014 and 31st of December 2023, with at least 1 year of data visibility prior to becoming eligible for study inclusion. This requirement of at least 1 year of prior data history will not hold for children <1 year of age.

Additional eligibility criteria will be applied for the calculation of incidence rates: The observation time of users of the selected pre-specified medication of interest is excluded during use and 1 year afterwards.

Additional eligibility criteria will be applied if incidence rates, and prevalence are stratified by age and sex. Age specific cohorts will have age-boundary eligibility criteria and sex specific cohorts will have sex eligibility criteria.

8.5.2 Patient-level utilisation of selected medicinal products

All new users of selected pre-specified medicine of interest in the period between 1st of January 2014 and 31st of December 2023 (or latest date available). Notably, all patients need to have at least 1 year of data visibility prior to the date of their new prescription/dispensing. "New use" refers to a prescription/dispensation of the selected medicinal products in the study period and without any use of respective medicinal products in the previous 1 year. This requirement of at least 1 year of prior data history will not hold for children <1 year of age. "New use" in children younger than 1 year will be defined as no prescription of the selected medicinal products ever before the index date.

The operational definitions of the inclusion and exclusion criteria are presented by means of **Table 5.**

Table 6. Operational Definitions of Inclusion Criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Observation period in the database during the period 2014-2023 (or the latest date available)	All individuals present in the period 2014-2023 (or the latest date available)	n/a	n/a	OP	n/a	n/a	All individuals within selected databases	n/a	n/a
Prior database history	Study participants will be required to have 1 year of prior history observed before contributing observation time (except for children < 1 year of age)	After*	365 days	OP	n/a	n/a	All individuals within selected databases	n/a	n/a
Washout period	Individuals who initiated treatment will be required to have not used selected pre-specified medication of interest 1 year before a "new" prescription	After*	365 days	OP	n/a	n/a	All individuals within selected databases	n/a	n/a

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

[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

*Order of application specifies whether the eligibility criterion is applied before or after selection of the study entry date. For example, selecting "before" means that all possible study entry dates are identified, and then one or more is chosen. For instance, selecting 'after' means that the first possible study entry date is chosen, followed by the application of the inclusion and/or exclusion criteria. If the patient does not meet the criterion, then the patient drops out.

8.6 Variables

8.6.1 Exposure

n/a

8.6.2 Outcome

For this study, outcome of interest is use (during study period) of Cannabis flos (dried, whole or fragmented, flowering tops of *Cannabis sativa L.)* products Bedrocan, Bedrobinol, Bediol, Bedrolite, Bedica and any other Cannabis flos containing products, provided such products are available in the datasets of interest.

The list of medication of interest is described in **Appendix I**. Details of exposure are described in by means of **Table 6.**

Table 6. Operational Definitions of Outcome.

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type	Diagnosis position[2]	Applied to study populations	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
Cannabis flos (dried, whole or fragmented, flowering tops of *Cannabis sativa* L.)	Preliminary code list provided in Appendix I	[-365, ID]	Calendar year	OP	RxNorm	n/a	All individuals present in the database during the study period	Previous use of selected pre-specified medication of interest	n/a	n/a

[1] OP = outpatient, n/a = not applicable

[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

ID = index date;

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

Covariates for population-level utilisation of selected medicinal products of interest

Covariates for stratification in population-level utilisation study will include:

- Calendar year
- Age categories: 0-17 years and 18 years and older
- Sex: male or female
- Pre-defined medicinal products of interest: bedrocan, bedrobinol, bediol, bedrolite, bedica and any other Cannabis flos containing products of interest, provided such products are available in the datasets of interest

Population-level utilisation for all products combined will be stratified by age and sex, while population level utilisation for each product stratum will be presented in an overall manner because of the limited sample size within each product stratum.

Covariates for patient-level utilisation of selected medicinal products of interest

Covariate for stratification in patient-level drug utilisation will include pre-selected medicinal products of interest:

- Bedrocan
- Bedrobinol
- Bediol
- Bedrolite
- Bedica
- Any other Cannabis flos containing products of interest, provided such products are available in the datasets of interest.

Other variables for patient-level utilisation of selected medicinal products of interest will include:

- A list of pre-specified conditions used to assess indication of use (the frequency of conditions of interest will be assessed at index date and within 1 year prior to the index date):
    - Cancer
    - Chemotherapy induced nausea and vomiting
    - Anxiety-related disorders
    - Neuralgic pain
    - Spasticity (multiple sclerosis (MS), spinal cord injury)
    - Neurological disorders (epilepsy, Tourette Syndrome, Huntington, Parkinson disease, Amyotrophic lateral sclerosis (ALS), Alzheimer and other Dementias)
    - Glaucoma
    - Human immunodeficiency virus (HIV) infection
    - Anorexia
    - Sleep disorders (insomnia, sleep apnea)
    - Inflammatory bowel disease
    - Fibromyalgia
    - Rheumatoid arthritis

- Top 10 of most frequent comorbidities from large-scale characterisation (the frequency of comorbidities will be assessed at index date and in 1 year prior to the index date).

- Top 10 of most frequent drugs in each data source from large-scale characterisation (the frequency of comedication will be assessed at index date and in 1 year prior to the index date).

The operational definition of the covariates is described in **Table 7**. Index date is the start of the (new) incident prescription during the study period. The preliminary list of concepts for prespecified conditions of interest are described in **Appendix I**.

Table 7. Operational Definitions of Covariates.

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations	Measurement characteristics/ validation	Source for algorithm
Indication of use	Check for pre-specified conditions of interest related to use of Cannabis flos	Counts	At ID and in window around ID [-365, ID]	OP	SNOMED	n/a	Persons with new use during the study period	n/a	n/a
Comorbidities	Large-scale patient characterisation with regard to underlying comorbidity	Counts	At ID and in window around ID [-365, ID]	OP	SNOMED	n/a	Persons with new use during the study period	n/a	n/a
Concomitant medication	Large-scale patient characterisation of new users with regard to concomitant medication	Counts	At ID and in window around ID [-365, ID]	OP	RxNorm	n/a	Persons with new use during the study period	n/a	n/a

ID = index date

[1] OP = outpatient, n/a = not applicable

[2] Specify whether a diagnosis code is required to be in the primary position (main reason for encounter)

8.7 Study size

No sample size has been calculated for this drug utilisation descriptive study, as our primary focus is to investigate medicinal use of Cannabis flos, irrespective of the sample size. Based on a preliminary feasibility assessment, the expected number of person counts for the different products of the selected medication differ across databases and range from 230 in IQVIA DA Germany to 734 patients in IPCI.

8.8 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 and prevalence, as described in section 8.8.5. The type of analysis by study type is presented in **Table8**.

Table 8. 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 pre-selected medicinal products of interest
Patient Level DUS	Off-the-shelf (C1)	- Characterisation of patient-level features - Frequency and % of indication/s - Frequency and % of comorbidities - Frequency and % of comedication - Estimation of minimum, p25, median, p75, and maximum treatment duration

8.8.1 Federated Network Analyses

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

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

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

8.8.2 Patient privacy protection

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

8.8.3 Statistical model specification and assumptions of the analytical approach considered

R-packages

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

Drug exposure calculations

Drug eras will be defined as follows: Exposure starts at date of the first prescription after a washout of 365 days. For each prescription, the estimated duration of use is retrieved from the drug exposure table in the CDM, using the start and end date of the exposure. Subsequent prescriptions will be combined into continuous exposed episodes (drug eras) using the following specifications:

Two drug eras will be merged into one continuous drug era if the distance in days between end of the first era and start of the second era is ≤ 30 days. The time between the two joined eras will be considered as exposed by the first era as shown in **Figure 2**, first row.

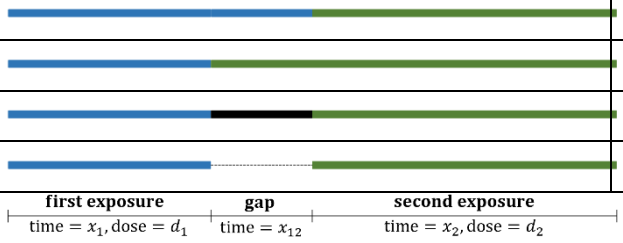
Gap era joint mode	Schematics	Dose in between	Cumulative dose	Cumulative time
"first"		d_1	$d_1 \cdot (x_1 + x_{12}) + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"second"		d_2	$d_1 \cdot x_1 + d_2 \cdot (x_2 + x_{12})$	$x_1 + x_{12} + x_2$
"zero"		0	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_{12} + x_2$
"join"		NA	$d_1 \cdot x_1 + d_2 \cdot x_2$	$x_1 + x_2$

Figure 2. Gap era joint mode.

New user cohort

New users will be selected based on their incident prescriptions of the respective drug of interest after the start of the study. For each patient, at least 1 year of data visibility will be required prior to a prescription. Individuals who initiate treatment are required to not have been exposed to the drug of interest for at least 1 year prior to the current prescription. If the start date of a prescription does not fulfil the exposure washout criteria of 1 year of no use, the whole exposure will be eliminated. New drug user cohort study will be used to characterise patient-level drug utilisation in terms of demographics, indication of use, comorbidities and comedication at the date of incident prescription/dispensation of pre-selected medicinal products of interest and duration of treatment with Cannabis flos.

8.8.4 Methods to derive parameters of interest

Age

Age at index date will be calculated using January 1st of the year of birth as proxy for the actual birthday. Date/month is either not present or cannot be made available for governance reasons. If available, date is often set to first of the month for patient's privacy. The following age groups will be used for stratification for population-level analyses: 0-17 and ≥ 18 years.

Sex

Results for population-level analyses will be presented stratified by sex.

Calendar time

Calendar time will be determined on the calendar year during which the index prescription was issued. The calendar time for subsequent prescriptions will be based on the year they are issued following the washout period of 365 days.

Indication

Indication will be determined based on recordings of pre-defined conditions (see 8.6.3 – other variables), at the date of the first prescription of the respective drug (index date) [primary definition] or during assessment windows 365 before index date. If none of the specific indications is recorded on index date or during the assessment window, but there is a record for any other condition, the person is considered having an "other" indication.

Characterisation of patient-level features

Large-scale patient-level characterisation will be conducted. Concepts in the "condition" domain will be assessed at index date and in the window around index date (1 year after index date). The top-10 conditions will be presented.

8.8.5 Methods planned to obtain point estimates with confidence intervals of measure of occurrence

Population-level drug utilisation study

Prevalence and incidence calculations will be conducted for Cannabis flos.

Incidence calculations

Annual incidence rates of the selected pre-specified medication of interest will be calculated as the number of new users of Cannabis flos after 1 year of no use per 1,000 person-years of the population at risk of getting exposed during the period for each calendar year. Those study participants who enter the denominator population will then contribute time at risk up to start of their new Cannabis flos prescription during the study period. Multiple prescriptions are allowed, with participants' time contributions paused during a defined outcome washout period of 365 days. Participants without drug exposure will contribute time at risk as described above. Time-at-risk of subjects who die will be censored at the time of death. Similarly, time at risk of subjects who are lost to follow-up will be censored at the time of loss to follow-up [last contact]. Subjects with data until the end of the study period without experiencing exposure will be administratively

censored at the end of the study period. Incidence rates will be given together with 95% Poisson confidence intervals.

An illustration of the calculation of incidence of selected pre-specified medication of interest is shown below in **Figure 3**. Patient ID 1 and 4 contribute time at risk up to the point at which they become incident users of selected pre-specified medication of interest. Patient ID 2 and 5 are not seen to use pre-specified medication of interest and so contribute time at risk but no incident outcomes. Meanwhile, patient ID 3 first contributes time at risk starting at the day when the washout period of a previous exposure, before study start, has ended, and ending when the next exposure of pre-specified medication of interest is starting. A second period of time at risk again starts after the washout period. For person ID 4, only the first and third exposures of pre-specified medication of interest count as incident use, while the second exposure starts within the washout period of the first exposure. The time between start of the first exposure until the washout period after the second exposure is not considered as time at risk.

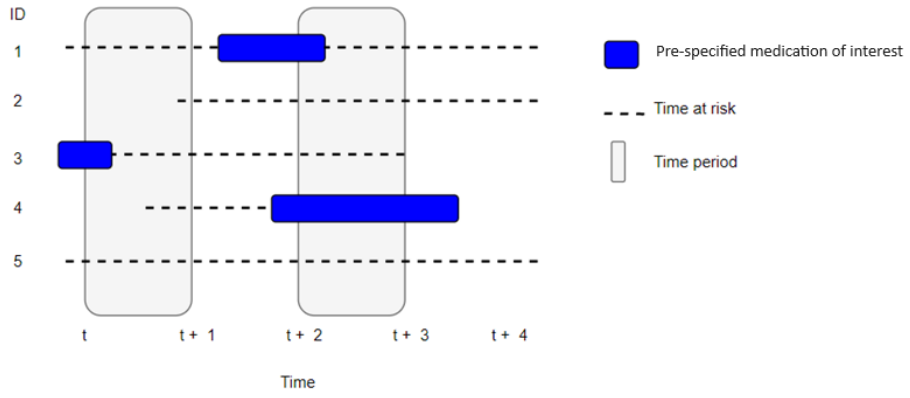


Figure 3. Incidence example.

Prevalence calculations

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

An illustration of the calculation of period prevalence is shown below in **Figure 4**. Between time t+2 and t+3, two of the five study participants are users of pre-selected medication of interest giving a prevalence of 40%. Meanwhile, for the period t to t+1 all five also have some observation time during the year with one of the five study participants being a user of pre-selected medication of interest.

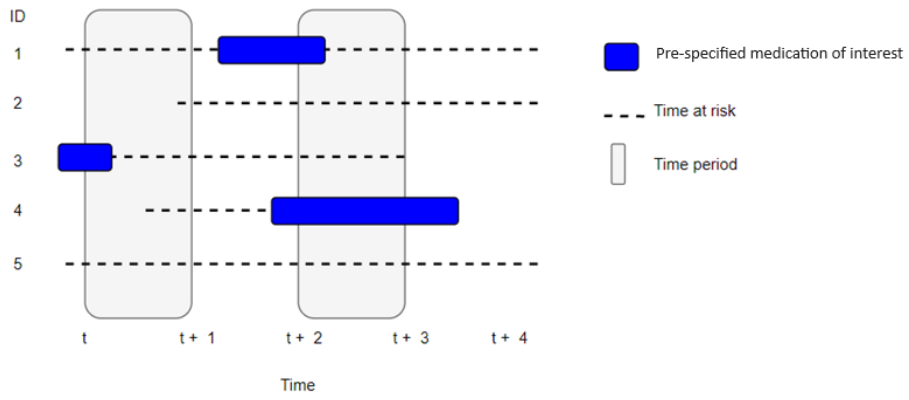


Figure 4. Period prevalence example.

Patient-level drug utilisation study

New drug user patient-level characteristics on index date

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

Indication

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

Treatment duration

Treatment duration will be calculated as the duration of each of treatment episode of the medication of interest during the study period. Treatment duration will be summarized providing the minimum, quartiles, maximum duration of treatment episodes. For databases, where duration cannot be calculated due to e.g., missing information on quantity or dosing, treatment duration will not be provided.

8.8.6 Methods to deal with missing data

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

8.8.7 Description of sensitivity analysis

n/a

8.9 Evidence synthesis

Results from analyses described in section 8.8 Data analysis will be presented separately for each database and no meta-analysis of results will be conducted.

9. DATA MANAGEMENT

9.1 Data management

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

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

9.2 Data storage and protection

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

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

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

10. QUALITY CONTROL

General database quality control

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

expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

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

The study code will be based on three R packages namely the "*IncidencePrevalence", "CohortCharacterisation",* "*PatientProfiles*" and *"DrugUtilization"* packages. 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 healthcare data, and it is important to consider several factors that may influence the interpretation of the results.

General limitations:

Medicinal product prescriptions: A recording of a prescription does not mean that the patient took the drug. Therefore, assumptions of actual use are made. *Characterisation/Indication*: The accuracy and consistency of pre-defined condition recording, crucial for patient characterisation and identification of the (potential) indication may vary across the databases included in the study. The actual reason for prescribing the drug of interest is not recorded as such in the databases. We assess indication via proxy based on a recording of pre-defined conditions recorded around the date of therapy initiation. Therefore, recording of potential indication might be incomplete.

Setting: For this study, we included data from 2 data sources (IPCI and IQVIA DA Germany). Results of these databases may not necessarily reflect prescription in other countries/databases.

Mapping: While OMOP provides mappings to established vocabularies like SNOMED CT and RxNorm, inaccuracies or gaps in these mappings can occur, impacting the accuracy and completeness of data analysis.

Study-specific limitations:

Unaccounted medicinal Cannabis flos use: There could be use of cannabis for medicinal purposes that is acquired without prescription (in the Netherlands in "coffee shops" for example). This would not be covered by the available data.

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

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

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

13. GOVERNANCE BOARD ASPECTS

Some of the data partners require approval from their respective IRB board, with the exception of IQVIA DA Germany which will not require any further specific approvals to undertake this study.

14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

14.1 Study Report

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

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

15. OTHER ASPECTS

n/a

16. REFERENCES

1. PubChem. *PubChem Compound Summary for , Cannabis sativa flowering top*. 2024; Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Cannabis-sativa-flowering-top.
2. Vlug, A.E., et al., *Postmarketing surveillance based on electronic patient records: the IPCI project.* Methods Inf Med, 1999. **38**(4-5): p. 339-44.
3. Rathmann W, B.B., Carius HJ, Kruppert S, Kostev K, *Basic characteristics and representativeness of the German Disease Analyzer database.* International Journal of Clinical Pharmacology and Therapeutics, 2018. **56**(10): p. 459-466.

17. ANNEXES

17.1 Appendix I: List of preliminary concept definitions

Preliminary list of source codes for exposure in each of participating databases is shown below. RxNorm concept IDs for 'Cannabis flos' products are unavailable as they have not been mapped yet.

Source code description	Source code ID	Source vocabulary	Excluded
CANNABIS FLOS BEDROCAN	2014884488	IPCI	-
CANNABIS FLOS SIMM 18	2014884496	IPCI	-
CANNABIS FLOS BEDROBINOL	2015009939	IPCI	-
CANNABIS FLOS BEDICA GRANULAAT	2015207439	IPCI	-
CANNABIS FLOS BEDIOL GRANULAAT	2015220478	IPCI	-
CANNABIS FLOS BEDROLITE GRANULAAT	2016019873	IPCI	-
CANNABIS FLOS BEDROCAN THEE SACHET 100MG AHZ	2016410742	IPCI	-
CANNABIS FLOS BEDICA GRANULAAT	2016730003	IPCI	-
CANNABIS FLOS BEDIOL GRANULAAT	2016730011	IPCI	-
CANNABIS FLOS BEDROCAN	2016730046	IPCI	-
CANNABIS FLOS BEDROLITE GRANULAAT	2016730062	IPCI	-
CANNABIS FLOS BEDROBINOL	2016747763	IPCI	-
CANNABIS FLOS BEDROCAN	2034093569	IPCI	-
CANNABIS FLOS SIMM 18	2034093577	IPCI	-
CANNABIS FLOS BEDROBINOL	2034360753	IPCI	-
CANNABIS FLOS BEDIOL GRANULAAT	2035009731	IPCI	-
CANNABIS FLOS BEDICA GRANULAAT	2035691168	IPCI	-
CANNABIS FLOS BEDROLITE GRANULAAT	2036744361	IPCI	-
CANNABIS FLOS BEDROCAN THEE SACHET 100MG AHZ	2037484747	IPCI	-
CANNABIS FLOS BEDROLITE GRANULAAT	2037663773	IPCI	-
CANNABIS FLOS BEDROCAN	2037663838	IPCI	-
CANNABIS FLOS BEDICA GRANULAAT	2037675712	IPCI	-
CANNABIS FLOS BEDIOL GRANULAAT	2037675720	IPCI	-
CANNABIS FLOS BEDROBINOL	2037675739	IPCI	-
CANNABIS FLOS BEDROCAN	2051621254	IPCI	-
CANNABIS FLOS SIMM 18	2051621262	IPCI	-
CANNABIS FLOS SIMM	2051681818	IPCI	-
CANNABIS FLOS BEDROBINOL	2051709968	IPCI	-
CANNABIS FLOS SIMM 18	2034093577	IPCI	-
CANNABIS FLOS BEDROBINOL	2034360753	IPCI	-
CANNABIS FLOS BEDIOL GRANULAAT	2035009731	IPCI	-
CANNABIS FLOS BEDICA GRANULAAT	2035691168	IPCI	-
CANNABIS FLOS BEDROLITE GRANULAAT	2036744361	IPCI	-
CANNABIS FLOS BEDROCAN THEE SACHET 100MG AHZ	2037484747	IPCI	-
CANNABIS FLOS BEDROLITE GRANULAAT	2037663773	IPCI	-

CANNABIS FLOS BEDROCAN	2037663838	IPCI	-
CANNABIS FLOS BEDICA GRANULAAT	2037675712	IPCI	-
CANNABIS FLOS BEDIOL GRANULAAT	2037675720	IPCI	-
CANNABIS FLOS BEDROBINOL	2037675739	IPCI	-
CANNABIS FLOS BEDROCAN	2051621254	IPCI	-
CANNABIS FLOS SIMM 18	2051621262	IPCI	-
CANNABIS FLOS SIMM	2051681818	IPCI	-
CANNABIS FLOS BEDROBINOL	2051709968	IPCI	-
CANNABIS FLOS BEDICA GRANULAAT	2051832204	IPCI	-
CANNABIS FLOS BEDIOL GRANULAAT	2051840908	IPCI	-
CANNABIS FLOS BEDROLITE GRANULAAT	2052423472	IPCI	-
CANNABIS FLOS BEDROCAN THEE SACHET 100MG AHZ	2052689073	IPCI	-
CANNABIS BLOEM SIMM 18	2061069841	IPCI	-
CANNABIS BLOEM BEDROCAN	2061069868	IPCI	-
CANNABIS BLOEM SIMM	2061075205	IPCI	-
CANNABIS BLOEM BEDROBINOL	2061076880	IPCI	-
CANNABIS BLOEM BEDICA	2061081477	IPCI	-
CANNABIS BLOEM BEDIOL	2061082015	IPCI	-
CANNABIS BLOEM BEDROLITE	2061117064	IPCI	-
CANNABIS BLOEM BEDROCAN KRUIDENTHEE 100MG	2061143510	IPCI	-
CANNABIS BLOEM SIMM 18	2062117935	IPCI	-
CANNABIS BLOEM BEDROCAN	2062117943	IPCI	-
CANNABIS BLOEM SIMM	2062121851	IPCI	-
CANNABIS BLOEM BEDROBINOL	2062123021	IPCI	-
CANNABIS BLOEM BEDICA	2062125857	IPCI	-
CANNABIS BLOEM BEDIOL	2062126292	IPCI	-
CANNABIS BLOEM BEDROLITE	2062150754	IPCI	-
CANNABIS BLOEM BEDROCAN KRUIDENTHEE 100MG	2062169897	IPCI	-
CANNABIS BLOEM BEDROCAN	2063083127	IPCI	-
CANNABIS BLOEM SIMM 18	2063083135	IPCI	-
CANNABIS BLOEM SIMM	2063084220	IPCI	-
CANNABIS BLOEM BEDROBINOL	2063084743	IPCI	-
CANNABIS BLOEM BEDICA	2063085855	IPCI	-
CANNABIS BLOEM BEDIOL	2063086096	IPCI	-
CANNABIS BLOEM BEDROLITE	2063093106	IPCI	-
CANNA.BL.BET.M A91 BEDROLITE 5G	803460	IQVIA DA	-
CANNA.BL.BET.M CA7 BEDROLITE 5G	803464	IQVIA DA	-
CANNA.BL.BET.M BDE BEDROLIT.1/9 5G	1974591	IQVIA DA	-
CANNA.BL.BET.M C0L BEDROLITE 5G	1974592	IQVIA DA	-
CANNA.BL.BET.M FO0 BEDROLITE 5G	36038896	IQVIA DA	-
CANNA.BL.BET.M CA7 BEDROLITE 20G	2043459080	IQVIA DA	-

CANNA.BL.BET.M D&N BEDROLITE 5G	2044482212	IQVIA DA	-
CANNA.BL.BET.M C0L BEDROCAN 5G	803177	IQVIA DA	-
CANNABIS BET.M C/H BEDROCAN	803448	IQVIA DA	-
CANNA.BL.BET.M CY+ BEDROCAN 5G	803455	IQVIA DA	-
CANNA.BL.BET.M CA7 BEDROCAN 100G	803462	IQVIA DA	-
CANNA.BL.BET.M CA7 BEDROCAN 10G	803463	IQVIA DA	-
CANNA.BL.BET.M FO0 BEDROCAN 5G	803468	IQVIA DA	-
CANNA.BL.BET.M AX0 BEDROCAN	803469	IQVIA DA	-
CAN.BL.BET.M CC4>> BEDROCAN	803470	IQVIA DA	-
CANNA.BL.BET.M A01 BEDROCAN	994793	IQVIA DA	-
CANNA.BL.BET.M CA7 BEDROCAN 5G	995708	IQVIA DA	-
CANNA.BL.BET.M CA7 BEDROCAN 20G	995709	IQVIA DA	-
CANNA.BL.BET.M AX0 BEDROCAN	1974588	IQVIA DA	-
CANNA.BL.BET.M B12 BEDROCAN 5G	1974590	IQVIA DA	-
CANNA.BL.BET.M CF& BEDROCAN 5G	1974611	IQVIA DA	-
CANNA.BL.BET.M C/A BEDROCAN 5G	1974624	IQVIA DA	-
CANNA.BL.BET.M LC4 BEDROCAN 5G	1974630	IQVIA DA	-
CANNA.BL.BET.M C0L BEDROCAN 400G	36038718	IQVIA DA	-
CANNA.BL.BET.M AX0 BEDROCAN	36038889	IQVIA DA	-
CANNA.BL.BET.M AX0 BEDROCAN	36038890	IQVIA DA	-
CANNA.BL.BET.M A98 BEDROCAN 5G	36038894	IQVIA DA	-
CANNA.BL.BET.M V&R BEDROCAN 5G	36038897	IQVIA DA	-
CAN.BL.BET.M AC9>> BEDROCAN	36038899	IQVIA DA	-
CAN.BL.BET.M ORI>> BEDROCAN	36038900	IQVIA DA	-
CANNA.BL.BET.M A01 BEDROCAN	36505180	IQVIA DA	-
CANNA.BL.BET.M A01 BEDROCAN	37595317	IQVIA DA	-
CANNA.BL.BET.M A01 BEDROCAN	37595318	IQVIA DA	-
CANNA.BL.BET.M E5A BEDROC.CANN. 5G BEDROCAN	2042697837	IQVIA DA	-
CANNA.BL.BET.M AX7 BEDROC.22/1 5G BEDROCAN	2043197173	IQVIA DA	-
CANNA.BL.BET.M A91 BEDROCAN 5G	2043198478	IQVIA DA	-
CANNA.BL.BET.M A91 BEDROCAN 5G	2043459193	IQVIA DA	-
CANNA.BL.BET.M AX7 BEDROC.22/1 10G BEDROCAN	2043461047	IQVIA DA	-
CANNA.BL.BET.M CFD BEDROCAN 5G	2044252006	IQVIA DA	-
CAN.BL.BET.M HM2>> BEDROC.22/1 5G BEDROCAN	2044252744	IQVIA DA	-
CANNA.BL.BET.M HDY BEDROC.22/1 5G BEDROCAN	2044253543	IQVIA DA	-
CANNA.BL.BET.M TSO BEDROCAN 5G	2045346951	IQVIA DA	-
CANNA.BL.BET.M NH1 BEDROCAN 10 5G	2045348074	IQVIA DA	-
CANNA.BL.BET.M S9P BEDROCAN 5G	2046069505	IQVIA DA	-
CANNA.BL.BET.M P+L BEDROCAN 5G	2046069506	IQVIA DA	-
CAN.BL.BET.M C2H>> BEDROC.22/1 5G BEDROCAN	2046883492	IQVIA DA	-
CANNA.BL.BET.M M4B BEDROCAN 5G	2046883564	IQVIA DA	-

CANNABIS BET.M AEX BEDROCAN 100G	2046883739	IQVIA DA	-
CANNA.BL.BET.M E5A BEDROC.ENUA 5G BEDROCAN	2046883917	IQVIA DA	-
CANNA.BL.BET.M G7E BEDROC.22/1 5G BEDROCAN	2046884292	IQVIA DA	-
CANNA.BL.BET.M FG6 BEDROBINOL 5G	803465	IQVIA DA	-
CANNA.BL.BET.M FO0 BEDROBINOL 5G	803467	IQVIA DA	-
CAN.BL.BET.M AC9>> BEDROBINOL	1974562	IQVIA DA	-
CANNA.BL.BET.M C0L BEDROBINOL 5G	36038717	IQVIA DA	-
CANNA.BL.BET.M B12 BEDROBINOL 5G	2046069455	IQVIA DA	-
CANNA.BL.BET.M C0L BEDIOL 5G	803176	IQVIA DA	-
CANNA.BL.BET.M D&N BEDIOL 5G	36038895	IQVIA DA	-
CANNA.BL.BET.M FO0 BEDIOL 5G	36506808	IQVIA DA	-
CANNA.BL.BET.M A01 BEDIOL 6.5/8 5G	37595319	IQVIA DA	-
CANNA.BL.BET.M VYD BEDIOL 5G	2042696660	IQVIA DA	-
CAN.BL.BET.M AC9>> BEDIOL 6.3/8 5G	2042698474	IQVIA DA	-
CANNABIS BET.M SB2 BEDIOL 5G	2043458780	IQVIA DA	-

Preliminary list of concepts for indication

Cancer

All malignant neoplastic disease and their descendants were included.

Concept name	Concept id	Descendants	Excluded
Malignant neoplastic disease	443392	Yes	-

Chemotherapy induced nausea and vomiting

Concept name	Concept id	Descendants	Excluded
Chemotherapy-induced nausea and vomiting	40385744	Yes	-

Anxiety-related disorders

Concept name	Concept id	Descendants	Excluded
Anxiety	441542	Yes	-

Neuralgic pain

Concept name	Concept id	Descendants	Excluded
Neurogenic pain	4133040	yes	-

Spasticity

Concept name	Concept id	Descendants	Excluded
Spasticity	4329728	Yes	-
X-linked intellectual disability, limb spasticity, retinal dystrophy, diabetes insipidus syndrome	37115758	Yes	-
Paroxysmal dystonic choreoathetosis with episodic ataxia and spasticity	37395940	Yes	-
Intellectual disability, spasticity, ectrodactyly syndrome	35622325	Yes	-
Hypomyelination with brain stem and spinal cord involvement and leg spasticity	36680577	Yes	-
Early-onset progressive neurodegeneration, blindness, ataxia, spasticity syndrome	36675179	Yes	-
Autosomal recessive cerebellar ataxia with late-onset spasticity	35622036	Yes	-

Spinal cord injury

Concept name	Concept id	Descendants	Excluded
Spinal cord injury	4235863	Yes	-

Multiple sclerosis

Concept name	Concept id	Descendants	Excluded
Multiple sclerosis	374919	Yes	-

Epilepsy

Concept name	Concept id	Descendants	Excluded
Seizure disorder	4029498	Yes	-
X-linked intellectual disability and epilepsy with progressive joint contracture and facial dysmorphism syndrome	36714067	Yes	-
Triple X syndrome, epilepsy, and hypogammaglobulinemia	4123240	Yes	-
Skeletal dysplasia with epilepsy and short stature syndrome	37398922	Yes	-
Myoclonic epilepsy myopathy sensory ataxia	44782474	Yes	-
Intellectual disability, epilepsy, bulbous nose syndrome	36715461	Yes	-
Autosomal recessive cerebellar ataxia, epilepsy, intellectual disability syndrome due to RUBCN deficiency	37204209	Yes	-
Alopecia, psychomotor epilepsy, periodontal pyorrhea, intellectual disability syndrome	36715349	Yes	-

Tourette Syndrome

Concept name	Concept id	Descendants	Excluded
Gilles de la Tourette's syndrome	379782	Yes	-

Parkinson disease

Concept name	Concept id	Descendants	Excluded
Parkinson disease	381270	Yes	-

Huntington's disease

Concept name	Concept id	Descendants	Excluded
Huntington chorea	374341	Yes	-

Amyotrophic lateral sclerosis

Concept name	Concept id	Descendants	Excluded
Amyotrophic lateral sclerosis	373182	Yes	-

Alzheimer disease and other dementias

Concept name	Concept id	Descendants	Excluded
Dementia	4182210	Yes	4047752, 4043381, 374341, 1340358
Inclusion body myopathy with early-onset Paget disease and frontotemporal dementia	45766396	Yes	-
GRN-related frontotemporal dementia	45765477	Yes	-
Frontotemporal dementia with parkinsonism-17	45765480	Yes	-
Frontotemporal dementia	4043378	Yes	-
Cerebral degeneration presenting primarily with dementia	4092747	Yes	-

Glaucoma

Concept name	Concept id	Descendants	Excluded
Glaucoma	437541	Yes	-
Neonatal diabetes, congenital hypothyroidism, congenital glaucoma, hepatic fibrosis, polycystic kidney syndrome	37110062	Yes	-
Imperforate pectinate glaucoma	4143359	Yes	-

Human immunodeficiency virus infection (HIV)

Concept name	Concept id	Descendants	Excluded
Human immunodeficiency virus infection	439727	Yes	-

World Health Organization human immunodeficiency virus infection clinical stage	604976	Yes	-
Parasitic infestation due to human immunodeficiency virus infection	606044	Yes	-
Non-Hodgkin lymphoma associated with Human immunodeficiency virus infection	40484012	Yes	-
Mycosis due to human immunodeficiency virus infection	3655580	Yes	-
Hepatitis B associated with Human immunodeficiency virus infection	40482214	Yes	-
Disorder of skin due to human immunodeficiency virus infection	606930	Yes	-
Bacterial infection due to human immunodeficiency virus infection	3654645	Yes	-

Anorexia

Concept name	Concept id	Descendants	Excluded
Loss of appetite	442165	Yes	-

Sleep disorders (including but not limited to insomnia, sleep apnea)

Concept name	Concept id	Descendants	Excluded
Sleep disorder	435524	Yes	-

Inflammatory bowel disease

Concept name	Concept id	Descendants	Excluded
Inflammatory bowel disease	4074815	Yes	-
Ulcerative colitis	81893	Yes	-
Crohn's disease	201606	Yes	-

Fibromyalgia

Concept name	Concept id	Descendants	Excluded
Fibromyalgia	40405599	Yes	-
Secondary fibromyalgia	46284893	Yes	-

Rheumatoid arthritis

Concept name	Concept id	Descendants	Excluded
Rheumatoid arthritis	80809	Yes	-
Juvenile rheumatoid arthritis	4253901	Yes	-
Deformity of hand due to rheumatoid arthritis	46273442	Yes	-
Deformity of foot due to rheumatoid arthritis	4334806	Yes	-

Dilated cardiomyopathy due to rheumatoid arthritis	4060405	Yes	-
Polyneuropathy in rheumatoid arthritis	4102493	Yes	-
Myopathy due to rheumatoid arthritis	4107913	Yes	-

17.2 APPENDIX II: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title:
DARWIN EU® - DARWIN EU® - Drug utilisation study on medicinal use of cannabis flos

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

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

Comments:

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

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

Comments:

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

Comments:

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

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.6
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorized according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☒	☐	☐	
5.5	Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

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

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☐	☐	☒	
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

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

Comments:

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

Section 9: Data sources	Yes	No	N/A	Section Number
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.8
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	8.7
10.3 Are descriptive analyses included?	☒	☐	☐	8.8
10.4 Are stratified analyses included?	☒	☐	☐	8.8
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	8.8

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.2
11.2 Are methods of quality assurance described?	☒	☐	☐	10.0
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	11
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.2

Comments:

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

Comments:

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

Comments:

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

Comments:

Name of the main author of the protocol: Dina Vojinovic

Date: 9th of July 2024

Signature: