Study Protocol

P3-C1-010 DARWIN EU® - Incidence of suicidality in patients with specific chronic skin conditions

20/08/2024

Version 3.0

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Study Title	DARWIN EU® - Incidence of suicidality in patients with specific chronic skin conditions
Protocol version identifier	3.0
Date of last version of protocol	20/08/2024
EU PAS number	EUPAS1000000294
Active substance	n/a
Medicinal product	n/a
Research question and objectives	Research questions: What are the background incidence rates of suicidality-related events (completed suicide, attempted suicide, suicidal ideation, and intentional self-harm) in patients with acne and psoriasis and in the general population, overall and stratified by sex, age categories, calendar year, and in individuals with or without history of mental health disorders? Objectives: 1. To assess the background incidence rates of suicidality-related events in acne patient, overall and stratified by sex, age categories, calendar year, and in individuals with or without history of mental health disorders 2. To assess the background incident rates of suicidality-related events in psoriasis patients, overall and stratified by sex, age categories, calendar year, and in individuals with or without history of mental health disorders 3. To assess the background incident rates of suicidality-related events in general population, overall and stratified by sex, age categories, calendar year, and in individuals with or without history of mental health disorders.
Country(ies) of study	Netherlands, Spain, United Kingdom, Croatia
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LIST OF ABBREVIATIONS

Acronyms/term	Description
CDM	Common Data Model
CC	Coordinating centre
COVID-19	Coronavirus disease-2019
CPRD	Clinical Practice Research Datalink
DARWIN EU®	Data Analysis and Real-World Interrogation Network
DOI	Declaration Of Interests
DRE	Digital Research Environment
EHR	Electronic Health Records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GDPR	General Data Protection Regulation
GP	General Practitioner
ICD	International Classification of Diseases
IP	Inpatient
IPCI	Integrated Primary Care Information
IRR	Incidence Rate Ratio
NAJS	The National Public Health Information System Croatia
OHDSI	Observational Health Data Sciences and Informatics
OMOP	Observational Medical Outcomes Partnership
OP	Outpatient
RxNorm	Medical prescription normalized
SD	Standard deviation
SIDIAP	The Information System for Research in Primary Care
SNOMED	Systematized Nomenclature of Medicine
VID	The Valencia Health System Integrated Database

1. TITLE

DARWIN EU® - Incidence of suicidality in patients with specific chronic skin conditions

2. RESPONSIBLE PARTIES – STUDY TEAM

STUDY TEAM ROLE	NAMES	ORGANISATION
Study Project Manager/Principal Investigator	Marzyeh Amini Katia Verhamme	Erasmus MC
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Data Partner*	**Names**	**Organisation**
IPCI	Katia Verhamme	Erasmus MC
SIDIAP	Talita Duarte-Salles Anna Palomar Agustina Giuliodori Picco	IDIAPJGol
CPRD GOLD	Antonella Delmestri	University of Oxford
NAJS	Jakov Vuković Ivan Pristaš Anamaria Jurčević Marko Čavlina Antea Jezidžić Pero Ivanko	The Croatian National Institute of Public Health
VID	Gabriel Sanfélix Francisco Sanchez-Saez	Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunidad Valenciana (FISABIO)

*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® - Incidence of suicidality in patients with specific chronic skin conditions

Rationale and background

Chronic skin conditions like acne and psoriasis cause significant physical and psychological distress, leading to social stigmatization and an increased risk of mental health issues, including depression and anxiety. Concerns about their link to suicidality-related events are rising. Several signals of suicidal ideation associated with treatments for acne and/or other skin disorders have been discussed. For these signals, it is difficult to estimate the extent of the confounding by indication as the underlying patient population is widely believed to be at increased risk of suicide related conditions. Despite this, there is insufficient data in the literature regarding the background rates of such outcomes in these populations and most studies focusing on broader mental health outcomes. This study aims to evaluate suicide-related drug safety signals associated with treatments for the conditions of acne and psoriasis. Understanding of the background rate of suicidality in patients with these conditions and the extent to which this differs from the general population will aid in the assessment of such signals.

Research questions

What are the background incidence rates of suicidality-related events (completed suicide, attempted suicide, suicidal ideation, and intentional self-harm) in patients with acne and psoriasis and in the general population, overall and stratified by sex, age categories, and by calendar year? Results will further be stratified in individuals with and individuals without a medical history of mental health disorders at start of follow-up.

Objectives

1. To assess the incidence rate of i) completed suicide, ii) attempted suicide, iii) suicide ideation, iv) intentional self-harm, v) suicide-related events (i.e. completed suicide, attempted suicide, and suicidal ideation), vi) composite outcomes (combination of any of the above-mentioned events) *in patients with acne* stratified by sex, age category (12-<18 years, 18-30, 31-40, 41-50 etc, >=81 years), calendar year, and history of mental health disorders.
2. To assess the incidence rate of i) completed suicide, ii) attempted suicide, iii) suicide ideation, iv) intentional self-harm, v) suicide-related events (i.e. completed suicide, attempted suicide, and suicidal ideation), vi) composite outcomes (combination of any of the above-mentioned events) before *in patients with psoriasis* stratified by sex, age category (12-<18 years, 18-30, 31-40, 41-50 etc, >=81 years), calendar year, and history of mental health disorders
3. To assess the incidence rate of i) completed suicide, ii) attempted suicide, iii) suicide ideation, iv) intentional self-harm, v) suicide-related events (i.e. completed suicide, attempted suicide, and suicidal ideation), vi) composite outcomes (combination of any of the above-mentioned events) before *in the general population* stratified by sex, age category (12-<18 years, 18-30, 31-40, 41-50 etc, >=81 years), calendar year, and history of mental health disorders.

Research methods

Study design

Population level cohort study.

Population

The study population will include all individuals present in the database during the study period (2010 to the most recent data available) and with at least one year of database history.

Within this population 2 sub-cohorts will be nested namely one on individuals newly diagnosed with acne and one consisting of individuals newly diagnosed with psoriasis.

Patients with a history of attempted suicide, suicide ideation and intentional self-harm will NOT be excluded from the study, but results will be provided, stratified by presence (or absence) of a medical history of mental health disorders prior to start of follow-up.

Outcomes

Outcomes of interest are i) completed suicide, ii) attempted suicide, iii) suicide ideation or iv) intentional self-harm, v) suicide-related events (i.e. completed suicide, attempted suicide, and suicidal ideation), vi) composite outcomes (combination of any of the above-mentioned events).

Variables

Sex, age, and calendar year.

Presence (yes/no) medical history of mental health disorders (i.e. anxiety, depression, bipolar disorder, post-traumatic stress disorder, eating disorders, and psychotic disorders).

Data sources

1. Clinical Practice Research Datalink (CPRD) GOLD, United Kingdom
2. Integrated Primary Care Information (IPCI), Netherlands
3. The Information System for Research in Primary Care (SIDIAP), Spain
4. The Valencia Health System Integrated Database (VID), Spain
5. The National Public Health Information System (NAJS), Croatia

Sample size

No sample size has been calculated as this is a descriptive Disease Epidemiology Study where we are interested in the incidence rates of suicidality in patient with chronic skin conditions.

Analytical methods

For the calculation of the incidence rates of the outcomes of interest, the *"IncidencePrevalence"* R package will be used. A minimum cell counts of 5 will be used when reporting results, with any smaller count reported as "<5". All analyses will be reported by country/database, overall and stratified by sex, age category, calendar year, and by presence (yes/no) of a medical history of mental health disorders when possible (minimum cell count reached). Incidence rates will be given together with 95% Poisson confidence intervals.

4. AMENDMENTS AND UPDATES

NUMBER	DATE	SECTION OF STUDY PROTOCOL	AMENDMENT OR UPDATE	REASON
None	-	-	-	-

5. MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE
Draft Study Protocol	July 2024
Final Study Protocol	August 2024
Creation of Analytical code	September 2024
Execution of Analytical Code on the data	September 2024
Interim Study Report (if applicable)	Not applicable
Draft Study Report	October 2024
Final Study Report	December 2024

6. RATIONALE AND BACKGROUND

Chronic skin conditions like acne and psoriasis cause significant physical and psychological distress, leading to social stigmatization and an increased risk of mental health issues, including depression and anxiety.[1] The impact of these conditions extends beyond physical symptoms, often affecting self-esteem and social interactions, which can exacerbate psychological distress. Increasingly, there are concerns about the link between these skin conditions and suicidality-related events.[2,3] Several studies have noted signals of suicidal ideation associated with treatments for acne and other skin disorders. However, estimating the extent of confounding by indication remains challenging, as patients with chronic skin conditions are already believed to be at an elevated risk for suicide-related conditions due to the inherent psychological burden of their illnesses.[4,5]

There is limited data in the literature regarding the background rates of suicidality in patients with chronic skin conditions, with most research focusing on broader mental health outcomes. This gap in knowledge hampers the ability to accurately assess the risk of suicide-related events linked to specific treatments. This knowledge is crucial for developing comprehensive treatment plans that address both the physical and psychological needs of patients with chronic skin conditions.[6,7]

The study is intended to help the assessment of potential suicide-related drug safety signals associated with the treatments for conditions associated with specific chronic skin conditions. Knowledge of the background rate of suicidality in patient with these conditions and the extent to which this differs from the general population will aid in the assessment of safety signals occurring in relation to treatments for these conditions.

7. RESEARCH QUESTION AND OBJECTIVES

The proposed objectives to be achieved in the study are described in **Table 1**.

Table 1. Primary and secondary research questions and objective.

A. Primary research question and objective.

Objective:	1. To assess the incidence rate of the outcomes of interest i) completed suicide, ii) attempted suicide, iii) suicide ideation, iv) intentional self-harm, v) suicide-related events, and vi) composite endpoints in *patients with acne* stratified by sex, age category (12-<18 years, 18-30, 31-40, 41-50 etc, >=81 years), by calendar year, and in individuals with or without a history of mental health disorders. 2. To assess the incidence rate of the outcomes of interest i) completed suicide, ii) attempted suicide, iii) suicide ideation, iv) intentional self-harm, v) suicide-related events, and vi) composite endpoints in *patients with psoriasis* stratified by sex, age category (12-<18 years, 18-30, 31-40, 41-50 etc, >=81 years), by calendar year, and in individuals with or without a history of mental health disorders. 3. To assess the incidence rate of the outcomes of interest i) completed suicide, ii) attempted suicide, iii) suicide ideation, iv) intentional self-harm, v) suicide-related events, and vi) composite endpoint in *the general population* stratified by sex, age category (12-<18 years, 18-30, 31-40, 41-50 etc, >=81 years), by calendar year, and in individuals with or without a history of mental health disorders.
Hypothesis:	n/a
Population *(mention key inclusion-exclusion criteria):*	The study population will include all individuals present in the database during the study period (2010 to the most recent data available) and with at least one year of database history. Within this population 2 sub-cohorts will be nested namely one on individuals newly diagnosed with acne and one consisting of individuals newly diagnosed with psoriasis. Patients with a history of attempted suicide, suicide ideation and intentional self-harm prior to the study start will NOT be excluded from the study but results will be provided overall and stratified by presence (or absence) of medical history of these mental health disorders.
Exposure:	n/a
Comparator:	n/a

Outcome:	Outcomes of interest are i) completed suicide, ii) attempted suicide, iii) suicide ideation or iv) intentional self-harm, v) suicide-related events (i.e. completed suicide, attempted suicide, suicidal ideation), and vi) composite outcomes (combination of any of the above-mentioned events).
Time *(when follow up begins and ends):*	Objectives 1-2: Follow-up will start on 1st January of 2010, the date of acne and/or psoriasis diagnosis, or 365 days of database history whichever comes last until the earliest date of the study outcome of interest, death, end of observation period (the most recent data available) in the database, or end of data availability of data source whichever is earlier. Objective 3: Follow-up will begin on January 1st January of 2010, or 365 days of prior history and continue up until the first of outcome of interest, loss to follow-up, death, end of observation period (the most recent data available) in the database, or end of data availability of data source whichever is earlier.
Setting:	Outpatient setting using data from the following 5 data sources: CPRD GOLD (UK), IPCI (the Netherlands), SIDIAP (Spain), VID (Spain), NAJS (Croatia)
Main measure of effect:	Incidence rates of suicidality-related events (with 95% confidence intervals)

8. RESEARCH METHODS

8.1 Study type and study design

This will be a population level disease epidemiology study classified as "*off the shelf*" and as described in the DARWIN EU® Complete Catalogue of Standard Data Analyses (**Table 2**). The incidence rates of suicidality-related events in patients with acne and in patients with psoriasis will be described and compared to the general population, overall and stratified by sex, age categories and calendar year. Further on, results will be stratified in individuals with and individuals without a history of mental health conditions at start of follow-up.

Table 2. Description of potential study types and related study designs.

STUDY TYPE	STUDY DESIGN	STUDY CLASSIFICATION
Population-level descriptive epidemiology	Population-level cohort	Off the shelf (C1)

8.2 Study setting and data sources

This study will be conducted using routinely collected data from 5 primary and secondary care data sources in 5 European countries. All data were a priori mapped to the OMOP CDM.

- Clinical Practice Research Datalink (CPRD GOLD), United Kingdom
- The Integrated Primary Care Information (IPCI), the Netherlands
- Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain
- Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunidad Valenciana (VID), Spain
- The National Institute of Public Health (NAJS), Croatia

Detailed information on data sources is described in **Table 3**.

Data Selection

The selection of databases for this study was performed based on data reliability, availability of the study variables, and relevance for the proposed research question among those databases onboarded and availability within DARWIN EU®. The selected databases fulfil the criteria required for the availability of key information on outcomes, and covariates, while covering different settings and regions of Europe. Outpatient setting complemented with hospitalisations, was the preferred setting for this study as patient with chronic skin conditions are treated almost exclusively in this setting. Similarly, it is expected that the outcome should be captured as well, especially in databases that have information on hospital admissions.

Records on outcomes will be available in all databases, and counts were obtained during the feasibility stage and are detailed in **Table 3**.

Table 3. Description of the selected data sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data (EHR, claims, registries)	Number of active subjects	Feasibility count of acne*	Feasibility count of psoriasis*	Feasibility count of suicide or suicide attempt*	Data lock for the last update
United Kingdom	CPRD GOLD	Information on medical conditions, outcomes of interest and covariates is available within the patient records (as documented in the feasibility request). Use of CPRD contributes to geographical diversity of data sources included. Adequate data availability over the study period and continuous follow-up of the patients included.	PC and information on specialist care/ hospital discharge	EHR	17M	655,400	260.800	98,300	01/01/2024
The Netherlands	IPCI	Information on medical conditions, outcomes of interest and covariates is available within the patient records (as documented in the feasibility request). Use of IPCI contributes to geographical diversity of data sources included.	PC	EHR	2.9M	76,600	40,100	8,200	30/04/2024

		Adequate data availability over the study period and likely continuous follow-up of the patients included.							
Spain	SIDIAP	Information on medical conditions, outcomes of interest and covariates is available within the patient records (as documented in the feasibility request). Use of SIDIAP contributes to geographical diversity of data sources included. Adequate data availability over the study period and likely continuous follow-up of the patients included within the database.	PC and information on hospital discharge	EHR	8.5M	191,900	136,600	32,100	30/06/2023
Spain	VID	Information on medical conditions, outcomes of interest and covariates is available within the patient records (as documented in the feasibility request). Use of VID contributes to geographical diversity of data sources included. Adequate data availability over the study period and likely continuous follow-up	PC, outpatient specialist care, and inpatient	EHR and registries	2M	77,100	22,900	8,900	01/01/2022

		of the patients included within the database.	care.						
Croatia	NAJS	Information on medical conditions, outcomes of interest and covariates is available within the patient records (as documented in the feasibility request). Use of NAJS contributes to geographical diversity of data sources included. Adequate data availability over the study period and likely continuous follow-up of the patients included within the database.	PC, outpatient specialist care, and inpatient care	Registries	5.4M	176,900	85,900	6,600	17/11/2023

PC= primary care, SC= secondary care, EHR= Electronic Health Care Record

*Based on counts from feasibility assessment

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

The Clinical Practice Research Datalink (CPRD) GOLD is a database of anonymised electronic health records (EHR) from General Practitioner (GP) clinics in the UK that use the Vision® software system for their management.[8] The source population encompasses 98% of the UK, registered with GPs responsible for non-emergency care and referrals. Participating GPs provide CPRD EHR for all registered patients who did not specifically request to opt out of data sharing. Covering 4.6% of the current UK population, GOLD includes 4.9% of contributing GP practices, providing comprehensive information within its defined source population. GOLD contains data from all four UK constituent countries and the current regional distribution of its GP practices is 5.7% in England, 55.6% in Scotland, 28.4% in Wales, and 10.2% in Northern Ireland (May 2022).

GOLD data include patient's demographic, biological measurements, clinical symptoms and diagnoses, referrals to specialist/hospital and their outcome, laboratory tests/results, and prescribed medications. GOLD has been assessed and found broadly representative of the UK general population in terms of age, gender, and ethnicity.[8] GOLD has been widely used internationally for observational research to produce nearly 3,000 peer-reviewed publications, making GOLD the most influential UK clinical database so far.[9-11].

In terms of quality checks, the integrity, structure and format of the data is reviewed. Collection-level validation ensures integrity by checking that data received from practices contain only expected data files and ensures that all data elements are of the correct type, length and format. Duplicate records are identified and removed.[8] Transformation-level validation checks for referential integrity between records ensure that there are no orphan records included in the database (for example, that all event records link to a patient), while research-quality-level validation covers the actual content of the data. CPRD provides a patient-level data quality metric in the form of a binary 'acceptability' flag.[8] This is based on recording and internal consistency of key variables including date of birth, practice registration date and transfer out date.

The Integrated Primary Care Information (IPCI), the Netherlands

The Integrated Primary Care Information (IPCI) database is a longitudinal observational database containing routinely collected data extracted from computer-based patient records of a selected group of general practitioners (GPs) across the Netherlands.[12] IPCI was started in 1992 by the department of Medical Informatics of the Erasmus University Medical Centre in Rotterdam. The current database includes patient records from 2006 on, when the size of the database started to increase significantly. The demographic composition of the IPCI population mirrors that of the general Dutch population in terms of age and sex. Although the geographical spread is limited, GP practices are located in urban and non-urban areas.

Patient-level data includes demographic information, patient's complaints and symptoms, diagnoses, laboratory test results, lifestyle factors and correspondence with secondary care, such as referral and discharge letters. For complaints, symptoms and diagnoses, Dutch GPs use International Classification of Primary Care (ICPC-1) coding, an international standard developed and updated by the World Organization of Family Doctors' (WONCA) International Classification Committee.

IPCI data quality has been previously documented and IPCI has proved valuable for epidemiological studies.[13-17] In terms of quality control, extensive quality control steps are performed prior to each data release. These include comparison of patient characteristics between practices and checks to identify abnormal temporal data patterns in practices. Additional checks include over 200 indicators related to population characteristics (e.g. reliability of birth and mortality rates) and medical data (e.g. availability of durations of prescriptions, completeness of laboratory results, availability of hospital letters and

prescriptions, proportion of patients with blood pressure measurement, etc).[12] Based on this information, two quality scores have been created. Practices with low scores have been excluded.

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

The Information System for Research in Primary Care (SIDIAP) is a dynamic database of pseudo-anonymized electronic health records of the primary care patient population in Catalonia, Spain.[18] It contains data of approximately 80% of the Catalan population registered in over 280 primary care practices throughout Catalonia since 2005.

The database contains data recorded in primary care centres on a daily basis. Additionally, it integrates data from external sources including biomarkers data from laboratories and records of drug prescription and dispensation. The dataset covers demographics, all-cause mortality, disease diagnoses classified under the International Classification of Diseases 10th revision (ICD-10), prescription and dispensation records of drugs, results of laboratory tests, socio-economic indicators, vaccination records, lifestyle information, parent–child linkage and various clinical parameters. Additional data from other data sources such as hospital discharges, mental health centres or specific disease registries can be obtained through diverse linkages. The demographic composition within SIDIAP closely mirrors that of the broader Catalan population, encompassing a representative spectrum of geographic distribution, age, and sex proportions. The database is updated every 6 months.

SIDIAP data quality has been previously documented and SIDIAP has proved valuable for epidemiological studies.[19-28] In terms of data integrity and reliability, SIDIAP has been subject to rigorous evaluation. Quality checks have been implemented including central identification of duplicate patient ID and visual inspection for temporal patterns in the registry of a certain variable. Furthermore, the data undergoes assessment for availability (longitudinally and reliability), plausibility (range checks and unusual values) and consistency using visualization tools. Specifically, for biochemistry data, consistency for measurements taken in different laboratories is assessed, and unit conversion is undertaken when needed.

National Public Health Information System (NAJS), Croatia

The National Public Health Information System (Nacionalni javnozdravstveni informacijski sustav - NAJS) is an organised system of information services by the Croatian Institute of Public Health (CIPH). This database was established in 1998, with nationwide coverage, representing approximately 5.4 million inhabitants. Settings covered include public primary, secondary/outpatient, and inpatient care. Data is retrieved primarily from EHR and holds information on demographics, inpatient and outpatient visits, conditions and procedures, drugs (outpatient and inpatient prescriptions), measurements, and inpatient and outpatient dates of death. NAJS provides linkage between medical and public health data collected and stored in health registries and other health data collections, including cancer registry, mortality, work injuries, occupational diseases, communicable and non-communicable diseases, health events, disabilities, psychosis and suicide, diabetes, drug abuse and others. The CDM population comprises all publicly insured persons residing in Croatia starting in 2015.

Valencia Health System Integrated Dataset (VID), Valencia, Spain

The Valencia Health System Integrated Dataset (VID) is a set of multiple, public, population-wide electronic databases for the Valencia Region, the fourth most populated Spanish region, with about 5 million inhabitants and an annual birth cohort of 48 000 newborns, representing 10.7% of the Spanish population and around 1% of the European population. The VID provides exhaustive longitudinal information, including sociodemographic and administrative data (sex, age, nationality, etc.), clinical (diagnoses, procedures, diagnostic tests, imaging, etc.), pharmaceutical (prescription, dispensing) and healthcare

utilisation data from hospital care, emergency departments, specialised care (including mental and obstetrics care), primary care and other public health services. It also includes a set of associated population databases and registries of significant care areas such as cancer, rare diseases, vaccines, congenital anomalies, microbiology (including COVID-19 test results registry), and public health databases from the population screening programmes. All the information in the VID databases can be linked individually through a single personal identification code. The databases were initiated at different times, but overall, the VID provides comprehensive individual-level data fed by all the databases from 2008 to 2022. This database only includes data of women aged 12-55 years, which is the data they have currently mapped and is readily available for study purposes.

8.3 Study period

The study period is from 01/01/2010 to the most recent data available for each contributing data source (see **Table 3**).

8.4 Follow-up

Objectives 1-2: Follow-up will start on 1st January of 2010, the date of new diagnosis of acne (objective 1) or the date of new diagnosis of psoriasis (objective 2) or 365 days of database history whichever comes last until the earliest date of the study outcome of interest, death, or end of observation period (the most recent data available) in the database.

Objective 3: Follow-up will begin on January 1st January of 2010, or 365 days of prior history and will continue up until the earliest of the following: loss to follow-up, death, or end of observation period (the most recent data available) in the database.

Table 4. 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	Diagnosis position	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
Individuals with incident acne (objective 1)	Date of newly diagnosis of acne during follow-up	Single entry	Incident	Any time prior to study entry date	OP	Clinical finding, time	n/a	Prior acne diagnosis	n/a	n/a
Individuals with incident psoriasis (objective 2)	Date of newly diagnosis of psoriasis during follow-up	Single entry	Incident	Any time prior to study entry date	OP	Clinical finding, time	n/a	Prior psoriasis diagnosis	n/a	n/a
General population (Objective 3)	i) study start date (1st January 2010), ii) date at which they have sufficient prior data availability (365 days)	Single entry	General population	n/a	OP	Time of fulfilling inclusion criteria	n/a	n/a	n/a	n/a

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

An example of entry and exit into the denominator population is shown in **Figure 1**. In this example, person ID 1 already has sufficient prior history before the study start date and the observation period ends after the study end date, so this person will contribute during the complete study period. Person IDs 2 and 4 enter the study only when they have sufficient prior history. Person ID 3 leaves when exiting the database (the end of the 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.

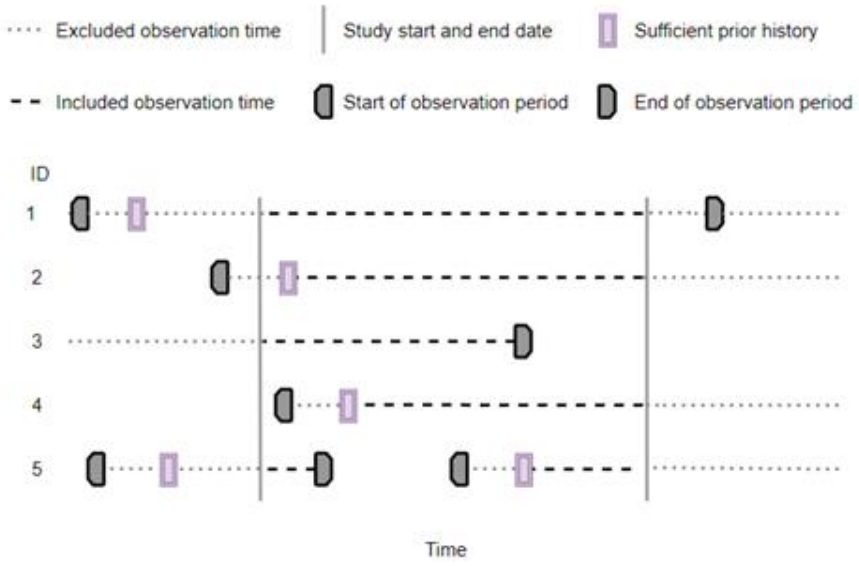

Figure 1. Included observation time for the denominator population.

8.5 Study population with inclusion and exclusion criteria

The study population will include all individuals observed in one of the participating data sources during the study period (01/01/2010 and the most recent data available); when the study end date is not reached in a data source, study end for that data source will be the last date of available date. Study participants are required to have at least 365 days of prior history before contributing observation time. This is to ensure a minimum prior observation time to identify history of mental history, acne and/or psoriasis and to identify a history of any of the outcomes of interest at the time at which a participant enters the study.

Within this population, two sub-cohorts will be nested: one comprising individuals newly diagnosed with acne and the other consisting of individuals newly diagnosed with psoriasis.

The concept definition of acne and psoriasis are described in **Table S1**, **Appendix I**.

The operational definitions of the inclusion and exclusion criteria are presented by means of **Table 5** and **Table 6**, respectively.

Table 5. Operational definitions of inclusion criteria.

Criterion	Details	Assessment window	Care Settings[1]	Code Type	Diagnosis position	Applied to study populations:
Observation period in the database during the period 2010-the most data available	All individuals present in the period 2010-the most recent data available	n/a	OP	n/a	n/a	All cohorts
Prior database history of one year	Study participants will be required to have a year of prior history observed before contributing observation time	[-365, -1]	OP	n/a	n/a	All cohorts
Acne	Diagnosis record of acne	Any time prior	OP	SNOMED	n/a	Acne cohort
Psoriasis	Diagnosis record of psoriasis	Any time prior	OP	SNOMED	n/a	Psoriasis cohort

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

Table 6. Operational definitions of exclusion criteria.

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position	Applied to study populations:
n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

8.6 Variables

8.6.1 Exposure/s

n/a.

8.6.2 Outcome/s

The outcomes of interest for the acne and/or psoriasis cohort as well as for the general population cohort are as follows:

a) Completed suicide
b) Attempted suicide
c) Suicide ideation
d) Intentional self-harm
e) Suicide-related events (i.e. completed suicide, attempted suicide, suicidal ideation)
f) Composite outcome (combination of any of the above-mentioned events)

All preliminary lists of codes for identifying the outcomes of interest are available in **Table S2**, **Appendix I**.

The operational definition of the outcomes is presented in the **Table 7**.

Table 7. Operational definitions of outcome.

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type	Diagnosis Position	Applied to study populations	Measurement characteristics/validation	Source of algorithm
Completed suicide	Condition record of completed suicide	Yes	Binary	[-inf , -1]	OP	SNOMED	n/a	All cohorts	n/a	n/a
Suicide attempt	Condition record of suicide attempt	Yes	Binary	[-inf , -1]* No wash out will be applied for event occurring before index date	OP	SNOMED	n/a	All cohorts	n/a	n/a
Suicide ideation	Condition record of suicide ideation	Yes	Binary	[-inf , -1]* No wash out will be applied for event occurring before index date	OP	SNOMED	n/a	All cohorts	n/a	n/a
Intentional self-harm	Condition record of intentional self-harm	Yes	Binary	[-inf , -1]* No wash out will be applied for event occurring	OP	SNOMED	n/a	All cohorts	n/a	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type	Diagnosis Position	Applied to study populations	Measurement characteristics/validation	Source of algorithm
				before index date						
Suicide-related events	Condition record of suicidal ideation, attempted suicide, completed suicide	Yes	Binary	[-inf , -1]* No wash out will be applied for event occurring before index date	OP	SNOMED	n/a	All cohorts	n/a	n/a
Composite outcome	Condition record of any events of completed suicide, attempted suicide, suicide ideation, and intentional self-harm	Yes	Binary	[-inf , -1]* No wash out will be applied for event occurring before index date	OP	SNOMED	n/a	All cohorts	n/a	n/a

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

* Infinite wash out is applied because we will only include the first outcome after start of follow-up, however patients with the history of these three outcomes (i.e. suicide attempt, suicide ideation, intentional self-harm) before the index date are allowed to be included in the study.

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

- sex (male/ female).
- age at index date namely
    - 12-17 years
    - 18-30 years
    - 31-40 years
    - 41-50 years
    - 51-60 years
    - 61-70 years
    - 71-80 years
    - >= 81 years

In addition, we will identify the following pre-specified mental health disorders of interest:

- Depression
- Anxiety
- Bipolar disorder
- Post-traumatic stress disorder
- Eating disorders
- Psychotic disorders

The preliminary concept ids of mental health disorders are described in **Table S1**, **Appendix I**.

The operational definition of the covariates is described in the **Table 8**.

Table 8. Operational definitions of covariates.

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position	Applied to study populations	Measurement characteristics/ validation	Source for algorithm
Demographics	Age at index date and sex	Binary, numeric continuous	All history	OP	n/a	n/a	All cohorts	n/a	n/a
Mental health disorders of interest	Diagnosis record	Binary	All history	OP	SNOMED	n/a	All cohorts	n/a	n/a

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

8.7 Study size

No sample size has been calculated as this is a descriptive Disease Epidemiology Study where we are interested in the incidence rates of suicidality in patient with chronic skin conditions. Based on a preliminary feasibility assessment the expected number of acne and psoriasis records in the included databases for this study were approximately 1,177,900 and 546,300, respectively. The expected number of suicidality-related events will be 154,100. These numbers are based on the overall number of conditions registries in each database with no filter by study period or inclusion and exclusion criteria.

8.8 Analysis

Table 9. Description of study types and type of analysis.

STUDY TYPE	STUDY CLASSIFICATION	TYPE OF ANALYSIS
Population-level descriptive epidemiology	Off-the-shelf (C1)	- Incidence rate of the condition of interest

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 RStudio 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 and the Study Dissemination Phase can start. All results are locked and timestamped for reproducibility and transparency.

8.8.2 Patient privacy protection

A minimum cell counts of 5 will be used when reporting results, with any smaller counts reported as “<5” to comply with privacy protection regulations.

8.8.3 Statistical model specification and assumptions of the analytical approach considered

R-packages

The incidence rates will be calculated based on OMOP-CDM mapped data using the “IncidencePrevalence” R package, developed by DARWIN EU®.[29]

Incidence rates of the outcomes of interest will be calculated as the number of newly diagnosed individuals with the outcome of interest divided by the person-years as contributed by the population at risk of the outcome during the period for each calendar year. Follow-up is censored upon the end of the observation period, the outcome of interest or upon death whichever comes first. Incidence rates will be given together with 95% Poisson confidence intervals. **Figure 2** represents an example of incidence rate estimation.

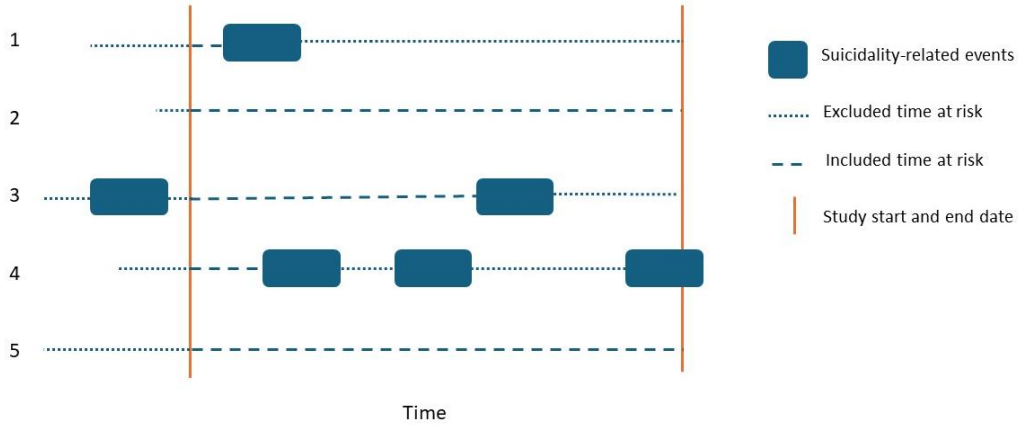

Figure 2. Example of incidence rate estimation.

Patient IDs 1, 3, and 4 contribute time at risk between the study start until they have an incident outcome of interest. Patient IDs 2 and 5 contribute time at risk between the study start and end date as no outcome of interest is observed between this period nor before the study start date. Infinite wash out is applied because only the first outcome after follow-up will be included, however patients with the history of outcomes (i.e. suicide attempt, suicide ideation, intentional self-harm) before the index date are allowed to be included in the study.

Incidence rates will be further stratified by:

- Sex
- Age groups (12-<18, 18-30, 31-40, 41-50 etc, >=81). Wider age groups might be used if most of the subgroups have event count less than 5.
- Calendar time will be based on the calendar year of the occurrence of outcome of interest
- Presence/absence of medical history of mental health disorders (i.e. depression, anxiety, post-traumatic stress disorder, eating disorder, and psychotic disorders) at index date.

8.8.4 Output

Output will include the following:

PDF report including an executive summary, and the following tables and figures

- Table 1. Number of participants, total number of incident cases and total time at risk in each data source during the study period. Number of participants per pre-specified strata will be included where necessary/applicable.
- Figure 1. Incidence rate/s of the outcome of interest over calendar time (year) in the incident acne population, psoriasis population, and the general population
- Figure 2. Incidence rate/s of the outcome of interest over calendar (year) stratified by sex in the incident acne population, psoriasis population, and the general population
- Figure 3. Incidence rate/s of the outcome of interest over calendar (year) stratified by age category in the incident acne population, psoriasis population, and the general population
- Figure 4. Incidence rate/s of the outcome of interest over calendar (year) stratified by history of mental health disorders in the incident acne population, psoriasis population, and the general population

- Table 2. Numbers reported in Figures 1, Figures 2, Figures 3, and Figures 4.

Interactive dashboard will be generated by incorporating all the results (tables and figures) included in the pdf report mentioned above.

8.9 Evidence synthesis

Results from analyses described in section 8.8 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 have previously mapped their data to the OMOP common data model. This enables the use of standardised analytics and using DARWIN EU tools across the network since the structure of the data and the terminology system is harmonised. The OMOP CDM was 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 and will use standardised analytics wherever possible. Each data partner will execute the study code against their database containing patient-level data, and then return the results (csv files) 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 individuals which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

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

The output files are stored in the DARWIN Remote Research Environment. These output files do not contain any data that allow identification of subjects included in the study. The RRE implements further security measures 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.

11. LIMITATIONS OF THE RESEARCH METHODS

The study will be informed by routinely collected health care data; therefore, data quality issues must be considered. In particular, the recording of the outcome events may vary across databases. While relatively few false positives would be expected, false negatives may be more likely, especially for databases without patient-level linkage to secondary care data. This is because the recording of suicide and suicide related events are often under-reported in primary care records. However, severe events are more likely to be known to the clinician and are therefore more likely to be recorded. Moreover, the documentation of co_morbidities, necessary for patient -level characterization, may vary across databases.

Furthermore, the COVID-19 pandemic (from 2020-2022) introduces a unique challenge. Changes in healthcare utilization patterns, routine clinical practices, and information recording during the pandemic might potentially distort estimates for the years 2020 and 2021. Disruptions in healthcare services and altered patient behaviours could influence the representation of suicidality-related events data during this period. A significant increase in suicidal thoughts and behaviours was reported during the COVID-19 pandemic. Factors such as loneliness, anxiety, depression, financial instability, and reduced social support contributed to this increase. For instance, a meta-analysis found higher rates of suicidal ideation (10.81%), suicide attempts (4.68%), and self-harm (9.63%) during the pandemic compared to pre-pandemic levels.[30] Consequently, the results from this period will be interpreted with caution.

Additionally, the results estimated from this study will only reflect the populations from the included data sources. Electronic health records have certain inherent limitations because they were collected for clinical purpose rather than primarily for research use. Consequently, using five primary care data sources from the UK, Spain, Croatia and the Netherlands limits generalisability to those countries.

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

CPRD GOLD and SIDIAP require ethical approvals from their local Institutional Review Boards to perform this study.

14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

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

15. OTHER ASPECTS

Not applicable.

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17. ANNEXES

Appendix I: – Concepts set for study variables

Table S1. List of conditions definitions.

Phenotype	Concept name	Concept id (including descendants)	Exclude concept id	Vocabulary
Acne	Acne	141095	42599382, 42598971	SNOMED
Psoriasis	Psoriasis	140168		SNOMED
Depression	Depressive disorder	440383		SNOMED
	Depressed mood	40546087		
Anxiety	Anxiety	441542		SNOMED
Bipolar	Bipolar disorder	436665		SNOMED
Eating disorder	Eating disorder	439002	4143677, 46285098	SNOMED
Psychotic disorder	Psychotic disorder	436073		SNOMED

Table S2. List of outcome definitions.

Phenotype	Concept name	Concept id (including descendants)	Exclude concept id	Vocabulary
Suicide	Suicide	440925		SNOMED
Suicide attempt	Suicide attempt	4219484	4206010	SNOMED
	Injury due to suicide attempt	4257906		
	Self-administered poisoning	4181216		
	Intentional overdose	607149		
Suicide ideation	Threatening suicide	4216115	602870, 4190444	SNOMED
	Suicidal thoughts	4273391		
	Harmful thoughts	4037303		
	Feeling suicidal	4021339		
	At risk for suicide	4021336		

Phenotype	Concept name	Concept id (including descendants)	Exclude concept id	Vocabulary
	Suicide risk	37399733		
Intentional self-harm	Self-inflicted injury	439235	440925, 42536693, 42573140	SNOMED
	Self-injurious behaviour	4092411		
	Late effect of self-inflicted injury	435446		
	Intentionally harming self	4303690		
Suicide-related events	Suicide	440925	4206010, 602870, 4190444	SNOMED
	Suicide attempt	4219484		
	Injury due to suicide attempt	4257906		
	Self-administered poisoning	4181216		
	Intentional overdose	607149		
	Threatening suicide	4216115		
	Suicidal thoughts	4273391		
	Harmful thoughts	4037303		
	Feeling suicidal	4021339		
	At risk for suicide	4021336		
	Suicide risk	37399733		
Composite outcome	Suicide	440925	4206010, 602870, 4190444, 42536693, 42573140	SNOMED
	Suicide attempt	4219484		
	Injury due to suicide attempt	4257906		
	Self-administered poisoning	4181216		
	Intentional overdose	607149		
	Threatening suicide	4216115		
	Suicidal thoughts	4273391		
	Harmful thoughts	4037303		
	Feeling suicidal	4021339		
	At risk for suicide	4021336		
	Suicide risk	37399733		

Phenotype	Concept name	Concept id (including descendants)	Exclude concept id	Vocabulary
	Self-inflicted injury	439235		
	Self-injurious behaviour	4092411		
	Late effect of self-inflicted injury	435446		
	Intentionally harming self	4303690		

Appendix II: ENCePP checklist for study protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

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

Study title:
DARWIN EU® - Incidence of suicidality in patients with specific chronic skin conditions

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

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	8.3
1.1.2 End of data collection[2]	☒	☐	☐	8.3
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.	☒	☐	☐	5

Comments:

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

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
	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)	☒	☐	☐	6
	2.1.2 The objective(s) of the study?	☒	☐	☐	7
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.5
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	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)	☒	☐	☐	12

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	8.2
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	☒	☐	☐	8.5
	4.2.3 Country of origin	☒	☐	☐	8.2

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
	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 categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.6.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☐	☐	☒	
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☐	☐	☒	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.6.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.6.2
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	

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

Comments:

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

Comments:

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

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.2
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.2
	9.1.3 Covariates and other characteristics?	☒	☐	☐	8.2
9.2	Does the protocol describe the information available from the data source(s) on:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.2
9.2.2 Outcomes? (e.g. date of occurrence, multiple events, severity measures related to event)	☒	☐	☐	8.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.2
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.2
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.2
9.3.3 Covariates and other characteristics?	☒	☐	☐	8.2
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?	☒	☐	☐	8.5
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)	☐	☐	☒	
11.2 Are methods of quality assurance described?	☒	☐	☐	10
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?	☒	☐	☐	11
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	8.7

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?	☐	☒	☐	

Comments:

Name of the main author of the protocol: Marzyeh Amini

Date: 20/08/2024

Signature: