Study Protocol P2-C3-001

04/10/2023

Version v3.1

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DOCUMENT HISTORY

Version	Date	Description
V1	20/06/2023	**Initial version**
V2	06/07/2023	**Resubmission**
V3	28/06/2023	**Third version**
V3.1	04/10/2023	**Third version EUPAS register number added**

Study Title	DARWIN EU – EHDS Use Case: Natural history of coagulopathy in COVID-19 patients and persons vaccinated against SARS-CoV-2 in the context of the OMICRON variant
Protocol version identifier	V3.1
Date of last version of protocol	04/10/2023
EU PAS register number	EUPAS106679
Active substance	Covid-19 vaccines
Medicinal product	ChAdOx1, bnt162b2, Ad26.COV2.S, mRNA-1273
Research question and objectives	Research question: The aim of the study is to contextualise the risk of venous and arterial thromboembolic events associated with COVID-19, during the Omicron period, and SARS-CoV-2 vaccination. The research objectives which will be addressed incrementally to support the project aim are: 1) To estimate the background incidence rate of venous and arterial thromboembolic events among the general pre-pandemic population. 2) To estimate the incidence rate of venous and arterial thromboembolic events among patients with COVID-19 within 30-, 60-, and 90- and 180-days during the Omicron period, stratified by prior SARS-CoV-2 vaccination and prior infection status. 3) To estimate the incidence rate of venous and arterial thromboembolic events among patients with SARS-CoV-2 vaccination within 30-, 60-, 90- and 180-days, , stratified by prior infection status. 4) To estimate a) the association between clinical risk factors including prior SARS-CoV-2 vaccination on the incidence rate of venous and arterial events among patients with COVID-19 and b) the impact that thromboembolic events have on worsening severity of COVID-19 during the Omicron period. 5) To estimate incidence rate ratios for venous and arterial thromboembolic events among patients with COVID-19 and people vaccinated against SARS-CoV-2, compared to the background

	population using incidence rates estimated in objectives 1 to 3.
Country(-ies) of study	Spain, The UK, Germany, The Netherlands, and Estonian
Author	Xintong Li, Marti Catala-Sabate

LIST OF ABBREVIATIONS

Abbreviation	Name
ATC	Anatomical Therapeutic Chemical Classification
EHDS	European Health Data Space
CDM	Common Data Model
COVID-19	Coronavirus disease-2019
DVT	Deep vein thrombosis
ECMO	Extracorporeal membrane oxygenation
EHR	Electronic Health Record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ICU	Intensive care unit
LPD	Longitudinal Patient Data
MACE	Major cardiovascular events
OMOP	Observational Medical Outcomes Partnership
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
VTE	Venous thromboembolic events
ATE	Arterial thrombotic events
RT-PCR	Reverse transcription polymerase chain reaction
IRR	Incidence rate ratio
SIR	Standardized incidence rate ratio
CPRD	Clinical Practice Research Datalink
IPCI	Integrated Primary Care Information
SIDIAP	The Information System for Research in Primary Care
SNOMED	Systematized Nomenclature of Medicine
HIV/AIDS	Human immunodeficiency virus/ acquired immunodeficiency syndrome

1. TITLE

DARWIN EU – EHDS Use Case: Natural history of coagulopathy in COVID-19 patients and persons vaccinated against SARS-CoV-2 IN the context of the OMICRON variant.

2. RESPONSIBLE PARTIES – STUDY TEAM

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

Study team Role	Names	Organisation
		Organisation will either be members of the DARWIN EU® CC and/or Data Partners
Principal Investigator	Marti Catala-Sabate Xintong Li	*University of Oxford* *University of Oxford*
Data Scientist/Statistician	Marti Catala-Sabate Edward Burn	*University of Oxford* *University of Oxford*
Epidemiologist	Xintong Li Annika Jodicke	*University of Oxford* *University of Oxford*
Clinical Domain Expert	Albert Prats-Uribe	*University of Oxford*

Data partner	Local Study Coordinator/Data Analyst	Organisation
SIDIAP	Talita Duarte Salles	*IDIAP JGOL*
Estonia Biobank	Raivo Kolde	*University of Tartu*
IPCI	Mees Mosseveld	*Erasmus MC*
IQVIA Germany	James Brash	*IQVIA*
CPRD GOLD	Antonella Delmestri	*University of Oxford*

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

Title: DARWIN EU – EHDS Use Case: Natural history of coagulopathy in COVID-19 patients and persons vaccinated against SARS-CoV-2 IN the context of the OMICRON variant

Rationale and background: Coronavirus disease-2019 (COVID-19) patients are at increased risk of venous and arterial thromboembolic events. SARS-CoV-2 variants have evolved during the COVID-19 pandemic with the dominant variant being Omicron now (as of December 2021). Information relating to thromboembolic risk and its impact on COVID-19 largely relates to COVID-19 variants occurring earlier during the pandemic. Therefore, evidence used to contextualize coagulopathy risk in light of vaccination may now differ. There is a need to better understand the risks of thromboembolic events among patients with COVID-19 associated with the Omicron variant, their impact on prognosis, and whether risk factors for such events remain the same, overall and in the context of prior COVID-19 infection, SARS-CoV-2 vaccination and among certain subgroups.
This study is one of the five use cases selected in the pilot project to test and inform HealthData@EU frameworks. HealthData@EU pilot project is the European Health Data Space (EHDS) Pilot project that aims to investigate and establish an infrastructure and data ecosystem for the secondary use of health data to facilitate research, innovation and better policy making; and assess the ability to scale towards a Union-wide infrastructure, as a core component of the EHDS.

Objectives:
1. To estimate the background incidence rate of venous and arterial thromboembolic events among the general population pre-pandemic population.
2. To estimate the incidence rate of venous and arterial thromboembolic events among patients with COVID-19 within 30-, 60-, 90- and 180-days during the Omicron period, stratified by prior SARS-CoV-2 vaccination and prior infection status.
3. To estimate the incidence rate of venous and arterial thromboembolic events among patients with SARS-CoV-2 vaccination within 30-, 60-, 90- and 180-days, stratified by prior infection status.
4. To estimate a) the association between clinical risk factors and prior SARS-CoV-2 vaccination on the incidence rate of venous and arterial events among people with COVID-19 and b) the impact that thromboembolic events have on worsening severity of COVID-19 during the Omicron period.
5. To estimate incidence rate ratios for venous and arterial thromboembolic events among patients with COVID-19 and different SARS-CoV-2 vaccine doses compared to the background population, using incidence rates estimated in objectives 1 to3.

Study type: population-level cohort
Study population:
1) Pre-pandemic cohort to calculate background rates of venous and arterial thromboembolic events in the general population (year 2017-2019).
2) People with COVID-19 during the time when OMICRON was the dominant variant (coded or test positive). All participants are required to be visible in the data source since 1st January 2020 to have full records on infection and vaccination history.
3) People vaccinated against SARS-CoV-2 (+/- during the period when OMICRON was the dominant variant). All participants are required to be visible in the data source since 1st January 2020 to have full records on infection and vaccination history.
For allcohorts, individuals with recent VTE or ATE event (defined as having a diagnosis of VTE or ATE within 183 days prior to index date, with sensitivity analysis of using any time prior and 91-days as wash-out periods.) will be excluded.

Analysis:
Standardized incidence rate ratio (SIR) compared to the background population will be estimated using indirect standardization.
Cohorts will be stratified by prior COVID-19 infection occurrence and prior SARS-CoV-2 vaccination (COVID-19 and vaccine cohorts only), age, sex. All cohorts will additionally be stratified by whether patients are immunocompromised on the index date.

4. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
V3.1	04/10/2023	Document history	Update	EUPAS register number added

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	June 2023
Final Study Protocol	July 2023
Creation of Analytical code	To be confirmed
Execution of Analytical Code on the data	To be confirmed
Interim Study Report (if applicable)	To be confirmed
Draft Study Report	To be confirmed
Final Study Report	To be confirmed

6. RATIONALE AND BACKGROUND

Coronavirus disease-2019 (COVID-19) patients are at increased risk of venous and arterial thromboembolic events. SARS-CoV-2 variants have evolved during the COVID-19 pandemic with the dominant variant being Omicron now (as of December 2021). Information relating to thromboembolic risk and its impact on COVID-19 largely relates to COVID-19 variants occurring earlier during the pandemic. Therefore, evidence used to contextualize coagulopathy risk in light of vaccination may now differ. Therefore, there is a need to better understand the risks of thromboembolic events among patients with COVID-19 associated with the Omicron variant, their impact on prognosis, and whether risk factors for such events remain the same, overall and in the context of prior COVID-19 infection, SARS-CoV-2 vaccination and among certain subgroups.

European Health Data Space

HealthData@EU pilot project is the European Health Data Space (EHDS) Pilot project that aims to investigate and establish an infrastructure and data ecosystem for the secondary use of health data for research, innovation and better policy making. The HealthData@EU pilot project will assess the ability to scale towards a Union-wide infrastructure as a core component of the European Health Data Space. The proposed study is one of the five use cases selected to test and inform HealthData@EU frameworks.

Occurrence of venous and arterial thromboembolic events among people with COVID-19

Coronavirus disease-2019 (COVID-19) may cause both venous and arterial thromboembolic events due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis. [1] A number of observational studies and case series have reported high rates of venous and arterial thromboembolic events among patients hospitalised with COVID-19. In a case series of COVID-19 patients admitted to ICU in

the Netherlands, the incidence of thrombotic complications was found to be 31%, [2] while a similar case series from a hospital in Italy found the incidence of thromboembolic events to be 28%. [3] Meanwhile, the rate of venous thromboembolism was found to be as high as 69% for a case series from two French intensive care units (ICU). [4]

Studies assessing the incidence of thromboembolic events among people with COVID-19 during the early period of the pandemic were conducted in relatively small study populations, partly constrained by data availability at the time, and predominantly focused on hospitalised populations. Consequently, uncertainty remained around the incidence of thromboembolic events among patients with COVID-19. Several larger studies examining coagulopathy risk have since been conducted using routinely collected health data. One study from Sweden demonstrated an increased risk of deep vein thrombosis (DVT) up to 70 days post-COVID-19 diagnosis and an increased risk of pulmonary embolism up to 110 days post-COVID-19 diagnosis. [5] Meanwhile, another study from England reported an increased risk of venous thromboembolism up to 49 weeks post-COVID-19. [6] Studies have also observed that the elevated risk of thromboembolic events associated with COVID-19 infection may be attenuated following SARS-CoV-2 vaccination. [7] SARS-CoV-2 variants have changed over time, with Omicron now widely established as the dominant SARS-CoV-2 variant. On 26 November 2021, the European Centre for Disease Prevention and Control classified the Omicron B.1.1.529 variant as a variant of concern due to concerns regarding immune escape and potentially increased transmissibility compared to the SARS-CoV-2 delta variant. [8] However, existing studies largely examined COVID-19 during the period when Omicron was not the dominant variant. The risk of venous and arterial thromboembolic events with Omicron COVID-19 is therefore less well studied, particularly in the context of exposure to either prior COVID-19 infection or prior SARS-CoV-2 vaccinations.

Thromboembolic events and worsening of COVID-19 during the Omicron period

COVID-19 patients with thromboembolic events are at increased risk of worse outcomes, with a systematic review finding a strong association between cardiovascular and thromboembolic events and poor prognosis among people with COVID-19. [9] However, it has been suggested that the Omicron variant has a milder course and therefore, subsequent coagulopathy risk may differ. This may be further influenced by prior SARs-CoV-2 vaccination. As with measuring the incidence of thromboembolic events themselves, routinely collected data may also be used to describe the risks of worsening among people with COVID-19 during the period when Omicron was the dominant variant.

Risk factors for thromboembolic events among people with COVID-19 during the Omicron period

Various patient factors have been associated with worse outcomes among people with COVID-19 that occurred during the early stages of the pandemic when Omicron was not the dominant variant. Older age, male sex, hypertension, diabetes, and being overweight or obese have all been reported to be associated with an increased risk of hospitalisation and mortality among people with COVID-19. [10–16] Many of these same factors have also previously been seen to predispose individuals to thromboembolic events. [17,18] In one study a set of pre-existing cardiovascular risk factors were associated with increased mortality among people with COVID-19, independent of patients´ age and sex. [19] Whilst the associations between such risk factors and thromboembolic events among patients with SARS-CoV-2 variants has been studied, this largely included data on COVID-19 during the early stages of the pandemic when Omicron was not the dominant variant. Information is limited on whether risk factors for venous and arterial thromboembolic events

remain the same for COVID-19 associated with the Omicron variant, and to what degree this may be influenced by prior SARs-CoV-2 vaccination and the impact of immunosuppression.

Contextualising incidence rates for thromboembolic events with COVID-19 during the Omicron period

Two studies have compared incidence rates of thrombosis and thrombocytopenia after vaccination against SARS-CoV-2 and with COVID-19 using data from the United Kingdom and Spain. These studies calculated incidence rates of thromboembolic events in people vaccinated against SARS-CoV-2 and in people with COVID-19 infection and compared them to pre-pandemic rates in a historic background cohort.[20,21] Compared to pre-pandemic rates, standardised incidence ratios were elevated for venous thromboembolism shortly following both initial vaccination against SARS-CoV-2 and for COVID-19 infection, although to a much greater extent with COVID-19 infection. It is uncertain however to what extent evidence generated by these studies is generalisable to COVID-19 infection during the Omicron period.

7. RESEARCH QUESTION AND OBJECTIVES

The aim of the study is to contextualise the risk of venous and arterial thromboembolic events associated with COVID-19, during the Omicron period and SARS-CoV-2 vaccination. To do so, the research objectives are:

1.To estimate the background incidence rate of venous and arterial thromboembolic events among the general pre-pandemic population.

2. To estimate the incidence rate of venous and arterial thromboembolic events among patients with COVID-19 within 30-, 60-, and 90- and 180-days during the Omicron period, stratified by prior SARS-CoV-2 vaccination and prior infection status.

3. To estimate the incidence rate of venous and arterial thromboembolic events among patients with SARS-CoV-2 vaccination within 30-, 60-, 90- and 180-days, stratified by prior infection status.

4.To estimate a) the association between clinical risk factors, including prior SARS-CoV-2 vaccination, on the incidence rate of venous and arterial events among people with COVID-19 and b) the impact that thromboembolic events have on worsening severity of COVID-19 during the Omicron period.

5. To estimate incidence rate ratios for venous and arterial thromboembolic events among patients with COVID-19 and different SARS-CoV-2 vaccine doses compared to the background population, using incidence rates estimated in objectives 1 to 3.

Table X: Primary and secondary research questions and objective

A. Primary research question and objective

Objective:	1. To estimate the background incidence rate of venous and arterial thromboembolic events among the general pre-pandemic population. 2. To estimate the incidence rate of venous and arterial thromboembolic events among patients with COVID-19 within 30-, 60-, and 90- and 180-days during the Omicron period, stratified by prior SARS-CoV-2 vaccination and prior infection status.

	3. To estimate the incidence rate of venous and arterial thromboembolic events among patients with SARS-CoV-2 vaccination within 30-, 60-, 90- and 180-days, stratified by prior infection status. 4. To estimate a) the association between clinical risk factors, including prior SARS-CoV-2 vaccination, on the incidence rate of venous and arterial events among patients with COVID-19 and b) the impact that thromboembolic events have on worsening severity of COVID-19 during the Omicron period. 5. To estimate incidence rate ratios for venous and arterial thromboembolic events among patients with COVID-19 and different SARS-CoV-2 vaccine doses compared to the background population, using incidence rates estimated in objectives 1 to 3.
Hypothesis:	Objective 1 – 3 are descriptive incidence rate, not applicable. Objective 4: Some factors/ characteristics are associated with a) the incidence of venous and arterial thromboembolic events among patients with COVID-19 and b) worsening of COVID-19 during the period when OMICRON was the dominant variant. Objective 5: Being infected with Omicron variant or being vaccinated may be related to changes in the incidence rates of thromboembolic events.
Population *(mention key inclusion-exclusion criteria):*	Objective 1: General population cohort for pre-pandemic background rates will have: • people included in the database as of 1 January 2017 or when they fulfil 365 days of prior history. • follow-up for this cohort will run up to 31 December 2019. Objective 2: Persons tested positive for SARS-CoV-2 or with a clinical diagnosis of COVID-19 during the Omicron period will: • have either a positive test result for SARS-CoV-2 or a clinical diagnosis of COVID-19 on or after 1st December 2021 (with the index date being whichever date comes first if both occur) • have no positive test result for SARS-CoV-2 or clinical diagnosis of COVID-19 within 3 months prior to the index date. Objective 3: Persons vaccinated against SARS-CoV2 infection: • a vaccination record identified by brand (with the index date the date of vaccination record) and not any other record of vaccine in the prior 21 days. The 21 days was based on the

	shortest dosing schedule for primary vaccination series in the participated databases (SIDIAP in Spain) • whether the vaccination record is 1st, 2nd, 3rd or 4th dose. Objective 4: Persons requiring intensive services during a hospitalisation with COVID-19 during the Omicron period will have: • intensive services initiated during a hospitalisation. Objective 5: same as objective 1-4
Exposure:	Objective 1: N/A Objective 2: SARS-CoV-2 infection Objective 3: Vaccination against SARS-CoV2 infection Objective 4: Incidence VTE or ATE, or worsening severity after SARS-CoV2 infection Objective 5: SARS-CoV2 infection and Covid-19 vaccines
Comparator:	Objective 1 – 3 are descriptive incidence rate, not applicable. Objective 4: No incidence VTE or ATE, or worsening severity after SARS-CoV2 infection Objective 5: background population
Outcome:	1. Venous thromboembolic events In the primary analysis, venous thromboembolic events will be identified by diagnostic codes for pulmonary embolism or deep vein thrombosis. 2. Arterial thromboembolic events In the primary analysis, arterial thromboembolic events will be identified by diagnostic codes for an acute myocardial infarction or acute ischemic stroke.
Time *(when follow up begins and ends):*	Objective 1: follow-up will begin on January 1st 2017 or 365 days of prior history and continue up until the first of: outcome of interest, loss to follow-up, death or December 31st 2019. Objective 2: follow-up will begin on their index date and continue up until the first of: outcome of interest, loss to follow-up, death, or either 30-, 60-, 90- or 180-days after the index date (depending upon the follow-up time period of interest). Objective 3: follow-up will begin on their index date and continue up until the first of: outcome of interest, loss to follow-up, death, or

	either 30-, 60-, 90- or 180-days after the index date (depending upon the follow-up time period of interest).
Setting:	Inpatient and outpatient setting using data from the following datasources: IPCI (NL), SIDIAP (Spain), IQVIA Germany (Germany), Estonian Biobank – via Utartu (Estonia) and CPRD GOLD (UK). Inpatient information is only available in SIDIAP.
Main measure of effect:	The incidence of each study outcome will be estimated during 30-, 60-, and 90- and 180-days following the index date for the general pre-pandemic population cohort, the people with COVID-19 cohort, and the vaccinated cohort with 95% confidence intervals. The 90-day cumulative incidence of study outcomes will be estimated. Incidence rate ratios will be calculated.

B. Secondary research question and objective

Outcome:	For the secondary analysis, we will be looking at the outcomes in the primary analysis separately, with additional outcome events as well. All other contents in the table are the same as the primary. 1. Venous thromboembolic events In a secondary analysis pulmonary embolism and deep vein thrombosis will be assessed separately. We will also assess portal vein thrombosis, splanchnic venous thrombosis (SVT) and cerebral venous sinus thrombosis separately. 2. Arterial thromboembolic events In a secondary analysis acute myocardial infarction and acute ischemic stroke will be assessed separately. We also identify stroke in general, for which we will include both ischemic, haemorrhagic and non-specifically recorded stroke. 3. Cardiovascular events Instances of heart failure, cardiac arrhythmia, and angina will be identified. In addition, major cardiovascular events (MACE) will be identified by heart failure, acute myocardial infarction, or stroke, or the occurrence of sudden cardiac death. As a sensitivity analysis, we will require that events were identified by hospitalisation admission or discharge records.

8. RESEARCH METHODS

8.1 Study type and Study Design

STUDY TYPE	STUDY DESIGN	STUDY CLASSIFICATION
Drug/Vaccine Safety Studies	New User Cohorts	Complex (C3)

8.2 Study Setting and Data Sources

The selection of databases for this study was performed based on data reliability and relevance for the proposed research question among those databases onboarded and available within DARWIN EU. The selected databases fulfil the criteria required for the availability of key information on exposures, outcomes, and covariates, while covering different settings and regions of Europe.

Records on Covid-19 infection and vaccination (needed for objectives 2 to 5) will be available in all purposed databases except Estonia Biobank. We have previously published studies showing that these databases can generate reliable evidence on COVID-19 research. [20–22] Specifically, the availability of covid-19 tests results, and linked vaccination records through national/regional immunization program (SPRD, SIDIAP) increased the reliability of the identified study exposures. Inpatient admission and intensive care use (needed for objective 4) will be available in SIDIAP, which provides primary care records with linked hospitalization information.

Table 1. 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	Feasibility count of exposure (if relevant)	Feasibility count of disease (if relevant)	Data lock for the last update
Spain	SIDIAP	Complete records on SARS-CoV-2 infection, Covid-19 vaccination, and outcome events of interest; Include inpatient admission information. (objectives 1 to 5)	primary care database + linkage to hospital data	EHR	5.8M	Covid-19: 3865976, AstraZeneca :1152432, Janssen :257806, Pfizer :6548545, Moderna :3371395	VTE as example for all databases. 101966	1/6/2022
The UK	CPRD GOLD	Complete records on SARS-CoV-2 infection, Covid-19 vaccination,	primary care	EHR	3M	Covid-19: 360198, AstraZeneca	219844	07/2022

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	Feasibility count of exposure (if relevant)	Feasibility count of disease (if relevant)	Data lock for the last update
		and outcome events of interest (objectives 1 to 5, exclude 4b on worsening covid-19)				:2360815, Janssen :3034, Pfizer :2822947, Moderna :311069		
Germany	IQVIA Germany	Complete records on SARS-CoV-2 infection, Covid-19 vaccination, and outcome events of interest (objectives 1 to 5, exclude 4b on worsening covid-19)	outpatient visits of primary care physicians and a sample of specialists	EHR	8.5M	Covid-19:1723895, AstraZeneca :189261 , Janssen :83771 , Pfizer :2614482 , Moderna :428057	392674	1/9/2022
The Netherlands	IPCI	Complete records on SARS-CoV-2 infection, Covid-19 vaccination, and outcome events of interest (objectives 1 to 5, exclude 4b on worsening covid-19)	Primary care	EHR	1.39M	Covid-19: 941329, AstraZeneca :178192 , Janssen :19645 , Pfizer :1173104 , Moderna :463315	57087	1/12/2022

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	Feasibility count of exposure (if relevant)	Feasibility count of disease (if relevant)	Data lock for the last update
Estonian	Estonian Biobank	Geographic representative (objective 1 only)	Biobank	EHR	0.2M	79411 (Covid-19)	25766	31/3/2021

8.3 Study Period

The study period will start depending upon when the Omicron variant became established in Europe commencing from 1st December 2021.[8] The end of the study period will be the last available date of data collection for each contributing dataset.

8.4 Follow-up

For cohort 1, follow-up will begin on January 1st 2017 and continue up until the first of: outcome of interest, loss to follow-up, death or December 31st 2019. For cohorts 2 to 5, follow-up will begin on their index date and continue up until the first of: outcome of interest, end of observation period, end of data availability, death, or either 30-, 60-, 90- or 180-days after the index date (depending upon the follow-up time period of interest).

Table 2: 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
Background population (cohort 1*)	January 1st 2017 or after when they have 365 days of prior history	Multiple	General population	n/a	n/a	n/a	n/a	n/a	n/a	n/a
SARS-CoV-2 infection cohort (cohort 2*)	Date of test for the positive test result for SARS-CoV-2, or date of clinical diagnosis of COVID-19	Multiple	incident	No covid-19 infection within 3 months prior	OP	SNOMED codes (see appendix)				
hospitalised with COVID-19 cohort (cohort 3*)	Date the date of hospital admission	Multiple	incident	No hospitalization within	IP	SNOMED codes (see appendix)				

				3 months prior						
Intensive care service cohort (cohort 4*)	Date of the following depends on availability in data, descend priority: 1.)Date of intensive care service (mechanical ventilation, tracheostomy, or extracorporeal membrane oxygenation (ECMO)); 2.)Date of ICU admission; 3.)Date of hospital admission.	Multiple	incident	n/a	IP	SNOMED (see appendix)	n/a	Covid-19 hospitalized	n/a	n/a
Vaccinated cohort (cohort 5*)	date of vaccination record	Multiple	n/a	21 days	OP	RxNorm codes (see appendix)				

*Cohorts number as described in 8.5 study population with inclusion and exclusion criteria.

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

Description of the different items from the table can be found below:

Study population name(s): A brief text descriptor naming the study population that is identified for a primary or secondary analysis (e.g. exposed, comparator, pregnant women, patients with diabetes)

Time anchor description: A brief text description of the criterion used to define the time anchor, including at least one entry to define time 0, the point at which the patient enters the cohort (e.g. date of incident dispensation of Drug X, date of heart failure diagnosis, last menstrual period)

Number of entries: Indicate whether patients are allowed to enter the study population only once or multiple times (e.g. single entry, multiple entry)

Type of entry: Indicate whether the criterion for entry to the study population reflects an incident, prevalent, or other condition.

Washout window: If entry to the study population is defined as incident, use bracketed numbers representing time intervals anchored on a primary anchor (usually time 0) to specify the washout window. For example, [-180, -1] would reflect a washout window of 180 days prior to time 0, where the brackets indicate that the window is inclusive of the endpoints.

Care setting: Specify the care setting(s) that are used in the algorithm to define the time 0 (or other primary anchor) criterion. For example, IP = inpatient, ED = emergency department, etc.

Code type: Specify the type(s) of clinical codes that are used to define the time 0 (or other primary anchor) criterion.

Diagnosis position: If the algorithm to define the time 0 (or other primary anchor) criterion used inpatient codes, specify whether the algorithm restricts to primary diagnosis codes (indicating that the code is the primary reason for the encounter) or allows codes in secondary or any position (e.g. primary, secondary, any, n/a)

Incident with respect to: If the type of entry is defined as incident, provide a brief text description of what the patient is required to be incident to. For example, when identifying incident users of Drug X (oral formulation only), the investigator may wish to require that patients be incident with respect to Drug X (oral formulation) as well as Drug X (intravenous formulation) and Drug Y. This would be operationalized as having no record of exposure to any of these drugs during the specified washout period.

Measurement characteristics/validation: If there are measurement characteristics for the outcome algorithm (e.g. PPV, sensitivity, specificity) from publications, or from outcome validation within the study population (e.g., medical record review), provide this information.

Source of algorithm: Specify the source of algorithms to define the time 0 or primary anchor criteria.

The table below further describes the operational definitions with regard to the follow-up start and the follow-up end.

Follow up start	Day 1	Index date
Follow up end[1]	**Select all that apply**	**Specify**
Date of outcome	Yes	
Date of death	Yes	
End of observation in data	Yes	

Day X following index date *(specify day)*	Yes	180 days after index date
End of study period (specify date)	Yes	End of data availability per database
End of exposure *(specify operational details, e.g. stockpiling algorithm, grace period)*	n/a	
Date of add to/switch from exposure *(specify algorithm)*	n/a	
Other date *(specify)*	n/a	

[1] Follow up ends at the first occurrence of any of the selected criteria that end follow up.

8.5 Study Population with inclusion and exclusion criteria

Five non-mutually exclusive study cohorts for the analyses will be defined:

1. **General population cohort for pre-pandemic background rates** will have
    - Individuals will start contributing as of 1st January 2017, or when they have at least 365 days of data availability.
    - follow-up for this cohort will run up to 31 December 2019.
2. **Persons tested positive for SARS-CoV-2 or with a clinical diagnosis of COVID-19 during the Omicron period** will
    - have either a positive test result for SARS-CoV-2 or a clinical diagnosis of COVID-19 on or after 1st December 2021 (with the index date being whichever date comes first if both occur)
    - have no positive test result for SARS-CoV-2 or clinical diagnosis of COVID-19 within 3 months prior to the index date.
    - have at least 365 days of data availability prior to index date
3. **Persons hospitalised with COVID-19 during the Omicron period** will have
    - a hospitalisation on or after 1st December 2021 (with the index date the date of hospital admission),
    - a record of a clinical diagnosis of COVID-19 or a positive test result for SARS-CoV-2 in the period between 3 weeks prior to and up to 3 days following the index date.
    - have no diagnosis of COVID-19 or a positive test result for SARS-CoV-2 between 3 months and 3 weeks prior to index date.
    - have no COVID-19 hospitalisation within 3 weeks prior to the index date.
    - have at least 365 days of data availability prior to index date
4. **Persons requiring intensive services during a hospitalisation with COVID-19 during the Omicron period** will have
    - intensive services initiated during a hospitalisation as described in cohort 3 (with the index date the date at which intensive services were initiated)
    - patients will have had a confirmatory diagnosis or test result of COVID-19 (both as defined above) within a time window from 3 weeks to their index date up to three days following their index date.
    - have at least 365 days of data availability prior to index date

5. **Persons vaccinated against SARS-CoV2 infection**
    - a vaccination record identified by brand (with the index date the date of vaccination record)
    - whether the vaccination record is 1st, 2nd, 3rd or 4th dose. A 21 day gap between two consecutive records of vaccine will be required to avoid repeated records of the same vaccine. The 21-days period was chosen based on the minimal recommended dosing schedule of the primary vaccine course in participated databases (Spain).
    - have at least 365 days of data availability prior to index date

Cohorts 2 to 5 will be stratified by prior COVID-19 infection status and for cohorts 2 to 4 also by prior SARS-CoV-2 vaccination status. All cohorts will additionally be stratified by whether patients are immunocompromised on the index date. People in each of the five cohorts will be required to have at least a year of observed history in the database prior to their index date. This is to ensure a sufficient time period to identify health conditions and medication use prior to individuals´ index dates.

Table 3. 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 of 365day prior entry (all 5 cohorts)	Study participants will be required to have 365 days prior history observed before contributing observation time	before	[-365,0]	n/a	n/a	n/a	All individuals within the selected databases	n/a	n/a
Covid-19 infection (cohort 2)	have either a positive test result for SARS-CoV-2 or a clinical diagnosis of COVID-19 on or after 1st December 2021 (with the index date being whichever date comes first if both occur)	before	n/a	Primary care	SNOMED	n/a	All individuals within the selected databases	n/a	n/a
Covid-19 hospitalized (cohort 3)	a hospitalisation on or after 1st December 2021 (with the index date the date of hospital admission), a record of a clinical diagnosis of COVID-19 or a positive test result for SARS-CoV-2 in the period between 3 weeks prior to and up to 3 days following the index date	before	[-21, 3]	Primary care, secondary care	SNOMED	n/a	All individuals within the selected databases	n/a	n/a

Covid-19 intensive care use (cohort 4)	intensive services initiated during a hospitalisation as described in the "covid-19 hospitalized" criterion	before	During hospitalization	Intensive care	SNOMED	n/a	Individuals who met the "covid-19 hospitalized" criteria	n/a	n/a
Covid-19 vaccinated (cohort 5)	a vaccination record identified by brand (with the index date the date of vaccination record)	before	n/a	Primary care	RxNorm	n/a	All individuals within the 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)

Table 4. Operational Definitions of Exclusion 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
Prior covid-19 (cohort 2-4)	have no positive test result for SARS-CoV-2 or clinical diagnosis of COVID-19 within 3 months prior to the index date.	After	[-91,0]	OP,IP	SNOMED, RxNorm	n/a	SARS-CoV-2 infected, hospitalized (cohorts 2, 3, 4)	n/a	n/a

Hospitalization (cohort 3)	have no diagnosis of COVID-19 or a positive test result for SARS-CoV-2 between 3 months and 3 weeks prior to index date. Have no COVID-19 hospitalisation within 3 weeks prior to the index date.	After	Covid-19 [-91,-21]; Hospitalization [-21,0]	IP	SNOMED	n/a	Covid-19 hospitalized (cohorts 3, 4)	n/a	n/a
Vaccinated (cohort 5)	No vaccine records in the 21 days prior to index vaccine	after	[-21 , 0]	OP	RxNorm	n/a	Vaccinated (cohort 5)	n/a	n/a
Prior outcomes all cohorts)	Exclude people with the outcome of interests during the 183 day prior to index. (primary analysis, different washout period will be applied in sensitivity analysis)		[-183,0]	IP, OP	SNOMED	n/a	(cohorts 1-5)	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)

Criterion: A brief text entry naming the in- and/or exclusion criterion (e.g. age, sex, atrial fibrillation)

Details: An optional brief text description to provide more information about the in- and/or exclusion criterion (e.g. age in years defined by (time 0 – year of birth)/365, baseline enrolment measured by Part A, B, D and no HMO insurance coverage with 30 day gaps allowed), 2 codes required

Order of application: Specify whether the in and exclusion criterion is applied before or after selection of the study entry date. For example, enter "before" if you plan to apply the criterion, identify all possible study entry dates, and then choose one or more. Enter "after" if you select the first possible study entry date and then apply the in- and/or exclusion criterion. If the patient does not meet the criterion, then the patient drops out. These decisions can impact which samples of person-time are included in the study.

Assessment window: Use bracketed numbers representing time intervals anchored on a primary anchor (usually time 0) to specify the window over which to evaluate patient data relevant for the in- and/or exclusion criterion. For example, [-180, 0] would reflect an assessment window of 180 days prior to and including time 0, where the brackets indicate that the window is inclusive of the endpoints.

Care setting: Specify the care setting(s) that are used in the algorithm to define the in- and/or exclusion criterion. For example, IP = inpatient, ED = emergency department, etc.

Code type: Specify the type(s) of clinical codes that are used to define the in- and/or exclusion criterion.

Diagnosis position: If the algorithm to define the in- and/or exclusion criterion used inpatient codes, specify whether the algorithm restricts to primary diagnosis codes (indicating that the code is the primary reason for the encounter) or allows codes in secondary or any position (e.g. primary, secondary, any, n/a)

Applied to study populations: Indicate which study populations the in- and/or exclusion criterion should be applied to (study population names are specified in Table 2).

Measurement characteristics/validation: If there are measurement characteristics for the outcome algorithm (e.g. PPV, sensitivity, specificity) from publications, or from outcome validation within the study population (e.g., medical record review), provide this information.

Source of algorithm: Specify the source of algorithms to define the in- and/or exclusion criterion.

8.6 Variables

8.6.1. Exposures

Positive test result for SARS-CoV-2

RT-PCR tests have high sensitivity and specificity for SARS-CoV-2. However, as a result of changes in the availability of population wide RT-PCR and home self-reported lateral flow tests during the Omicron period, it may not be possible to exclusively use RT-PCR tests when identifying positive test results in all datasets.[23] All positive test results for SARS-CoV-2 observable in the database will therefore be included for the primary analysis, with documentation of what type of test it was to allow sensitivity analysis restricted to RT-PCR diagnosed patients as needed.

Clinical diagnosis of COVID-19

Whilst testing for SARS-CoV-2 was commonly performed in some of the countries that will be represented in this study, clinical diagnoses of COVID-19 were also made for many individuals. Diagnostic codes compatible with COVID-19 will therefore also be identified, with the recorded date being used in the analyses.

Hospitalisation with COVID-19

Patients hospitalised with COVID-19 will be identified based on having a hospitalisation along with a confirmatory diagnosis or test result of COVID-19 (both as defined above) within a time window from 21 days prior to admission up to three days following their admission. This time window has been chosen to include those who had the diagnosis made prior to their hospitalisation and to allow for a delay in test results or diagnoses to be made or recorded, while excluding individuals with hospital-acquired COVID-19.

Intensive care services during a hospitalisation with COVID-19

Patients who received intensive care services during a hospitalisation with COVID-19 will be identified based on having a hospitalisation where they were admitted to the intensive care unit, received mechanical ventilation, tracheostomy, or extracorporeal membrane oxygenation (ECMO). If the date at which the intervention was initiated is observable in the database, this date will be used as the index date. If the date at which the intervention was initiated is not observed (for example, if such interventions are recorded at time of discharge) then the date of ICU admission, or hospital admission if ICU admission is not recorded, will be used as the index date.

Vaccination against SARS-CoV-2

COVID-19 vaccine exposure will be defined as the date of a vaccination record. Vaccination exposures will be defined by dose (1st, 2nd, 3rd, 4th etc.) and brand. The standard concepts used to define vaccine are available in the appendix.

Table 5. Operational Definitions of Exposure

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
Positive test result for SARS-CoV-2	All positive test results for SARS-CoV-2 observable in the database. We will record the test type as well.	3 months	n/a	OP, IP	SNOMED	n/a	All meet observation period criteria	n/a	n/a	n/a
Clinical diagnosis of COVID-19	Diagnostic codes compatible with COVID-19 will therefore also be identified	3 months	n/a	OP, IP	SNOMED	n/a	All meet observation period criteria	n/a	n/a	n/a
Covid-19 hospitalization	having a hospitalisation along with a confirmatory diagnosis or test result of COVID-19 (both as defined above) within a time window from 21 days prior to admission up to three days following their admission.	*3 months*	*n/a*	*IP*	SNOMED		All meet observation period criteria	n/a	n/a	n/a
Covid-19 intensive care services	received intensive care services during a hospitalisation with COVID-19 will be identified based on having a hospitalisation where they were admitted to the intensive care unit, received mechanical ventilation,	*n/a*	*During hospitalization*	*IP*	SNOMED	n/a	*All patient meet the covid-19 hospitalization criteria*	n/a	n/a	n/a

	tracheostomy, or extracorporeal membrane oxygenation (ECMO).									
Vaccination against SARS-CoV-2	COVID-19 vaccine exposure will be defined as the date of a vaccination record. Vaccination exposures will be defined by dose (1st, 2nd, 3rd, 4th etc.) and brand.	*21 days*	*n/a*	*OP*	*SNOMED*	n/a		n/a	n/a	n/a

[1] IP = inpatient, OP = outpatient

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

Criterion: A brief text entry naming the in- and/or exclusion criterion (e.g. age, sex, atrial fibrillation)

Details: An optional brief text description to provide more information about the in- and/or exclusion criterion (e.g. age in years defined by (time 0 – year of birth)/365, baseline enrolment measured by Part A, B, D and no HMO insurance coverage with 30 day gaps allowed), 2 codes required

Order of application: Specify whether the in and exclusion criterion is applied before or after selection of the study entry date. For example, enter "before" if you plan to apply the criterion, identify all possible study entry dates, and then choose one or more. Enter "after" if you select the first possible study entry date and then apply the in- and/or exclusion criterion. If the patient does not meet the criterion, then the patient drops out. These decisions can impact which samples of person-time are included in the study.

Assessment window: Use bracketed numbers representing time intervals anchored on a primary anchor (usually time 0) to specify the window over which to evaluate patient data relevant for the in- and/or exclusion criterion. For example, [-180, 0] would reflect an assessment window of 180 days prior to and including time 0, where the brackets indicate that the window is inclusive of the endpoints.

Care setting: Specify the care setting(s) that are used in the algorithm to define the in- and/or exclusion criterion. For example, IP = inpatient, ED = emergency department, etc.

Code type: Specify the type(s) of clinical codes that are used to define the in- and/or exclusion criterion.

Diagnosis position: If the algorithm to define the in- and/or exclusion criterion used inpatient codes, specify whether the algorithm restricts to primary diagnosis codes (indicating that the code is the primary reason for the encounter) or allows codes in secondary or any position (e.g. primary, secondary, any, n/a)

Applied to study populations: Indicate which study populations the in- and/or exclusion criterion should be applied to (study population names are specified in Table 2).

Measurement characteristics/validation: If there are measurement characteristics for the outcome algorithm (e.g. PPV, sensitivity, specificity) from publications, or from outcome validation within the study population (e.g., medical record review), provide this information.

Source of algorithm: Specify the source of algorithms to define the in- and/or exclusion criterion.

8.6.2. Outcomes

Venous thromboembolic events

In the primary analysis, venous thromboembolic events will be identified by diagnostic codes for pulmonary embolism or deep vein thrombosis. In a secondary analysis pulmonary embolism and deep vein thrombosis will be assessed separately. We will also assess portal vein thrombosis, splanchnic venous thrombosis (SVT) and cerebral venous sinus thrombosis separately.

Arterial thromboembolic events

In the primary analysis, arterial thromboembolic events will be identified by an acute myocardial infarction or acute ischemic stroke. In a secondary analysis acute myocardial infarction and acute ischemic stroke will be assessed separately. We also identify stroke in general, for which we will include both ischemic, haemorrhagic and non-specifically recorded stroke.

Cardiovascular events

Instances of heart failure, cardiac arrhythmia, and angina will be identified. In addition, major cardiovascular events (MACE) will be identified by heart failure, acute myocardial infarction, or stroke, or the occurrence of sudden cardiac death. As a sensitivity analysis, we will require that events were identified by hospitalisation admission or discharge records.

Table 6. Operational Definitions of Outcome

Outcome name	Details	Primary outcome?	Type of outcome	Washout window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study:	Measurement characteristics/ validation	Source of algorithm
Venous thromboembolic events	venous thromboembolic events will be identified by diagnostic codes for pulmonary embolism or deep vein thrombosis	Yes	Binary, time-to-event	[-183,-1]	IP,OP	SNOMED	n/a	All included cohorts	n/a	n/a
Arterial thromboembolic events	arterial thromboembolic events will be identified by an acute myocardial infarction or acute ischemic stroke	Yes	Binary, time-to-event	[-183,-1]	IP,OP	SNOMED	n/a	All included cohorts	n/a	n/a
Cardiovascular events	heart failure, cardiac arrhythmia, and angina will be identified.	No	Binary, time-to-event	[-183,-1]	IP,OP	SNOMED	n/a	All included cohorts	n/a	n/a
major cardiovascular events (MACE)	MACE will be identified by heart failure, acute myocardial infarction, or stroke, or the occurrence of sudden cardiac death.	No	Binary, time-to-event	[-1835,-1]	IP,OP	SNOMED	n/a	All included cohorts	n/a	n/a
pulmonary embolism		No	Binary, time-to-event	[-183,-1]	IP,OP	SNOMED	n/a	All included cohorts	n/a	n/a
deep vein thrombosis		No	Binary, time-to-event	[-183,-1]	IP,OP	SNOMED	n/a	All included cohorts	n/a	n/a
portal vein thrombosis		No	Binary, time-to-event	[-183,-1]	IP,OP	SNOMED	n/a	All included cohorts	n/a	n/a
splanchnic venous		No	Binary, time-to-event	[-183,-1]	IP,OP	SNOMED	n/a	All included cohorts	n/a	n/a

thrombosis (SVT)										
cerebral venous sinus thrombosis		No	Binary, time-to-event	[-183,-1]	IP,OP	SNOMED	n/a	All included cohorts	n/a	n/a
acute myocardial infarction		No	Binary, time-to-event	[-183,-1]	IP,OP	SNOMED	n/a	All included cohorts	n/a	n/a
acute ischemic stroke		No	Binary, time-to-event	[-183,-1]	IP,OP	SNOMED	n/a	All included cohorts	n/a	n/a
stroke in general	stroke in general will include both ischemic, haemorrhagic and non-specifically recorded stroke.	No	Binary, time-to-event	[-183,-1]	IP,OP	SNOMED	n/a	All included cohorts	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)

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

Location at index date

For cohort 2 (Persons tested positive for SARS-CoV-2 or with a clinical diagnosis of COVID-19) and cohort 5 (Persons vaccinated against SARS-CoV2 infection) we will identify whether individuals were currently hospitalised on their index date. All people in the cohort 3 (Persons hospitalised with COVID-19) and cohort 4 (Persons requiring intensive services during a hospitalisation with COVID-19) will be hospitalised on their index date.

Demographics

Patients´ age at index date and sex will be identified. Age groups will also be identified using the following groupings: <20; 20-44; 45-54; 55-64; 65-74; 75-84; ≥85 years. For those databases where such information is available, individual or area level socioeconomic status and whether they are living in the community or were a nursing home resident will also be identified.

Health conditions pre-index date

Individuals´ history of the study outcomes will be identified over three time periods prior to the index date:

1) 30 days prior to one day prior index date,
2) 365 days prior to one day prior index date,
3) all available days observed up to one day prior to index date.

A range of health conditions, including whether a patient was immunocompromised prior to the index date, will be identified using the same time windows. Among these, the following conditions will be identified: antiphospholipid syndrome, asthma, chronic obstructive pulmonary disease, atrial fibrillation, cancer (excluding non-melanoma skin cancers), venous thromboembolism, myocardial infarction, stroke, transient ischaemic attack (TIA), heart failure, diabetes, chronic kidney disease, chronic liver disease , hypertension, rheumatoid arthritis, thrombophilia, inflammatory bowel disease (Crohn's disease or ulcerative colitis), dementia, alcohol or drug substance misuse and obesity. Venous thromboembolism, myocardial infarction and stroke are also outcomes of interest. Therefore, the number of events for venous thromboembolism, myocardial infarction and stroke in the patients history will only represent events identified prior to the washout period used to identify outcomes (section 8.6.2 and Table 6).

Medications pre-index date

Pre-existing medication use will be identified using 2 time windows, defined as 183 days to one day prior to index date, and 30 days to 1 day prior to index date. Medications of interest will be identified on the basis of Anatomical Therapeutic Chemical (ATC) codes, with use of the following medications identified:

- COVID-19 medications (ATC code: J05AB18 molnupiravir, J05AE30 nirmatrelvir ritonavir, J06BD05 sotrovimab)
- non-steroidal anti-inflammatory drugs (ATC group: M01A, with all descendant codes included)
- Cox2 inhibitors (M01AH)
- systemic corticosteroids (H02AB and H02BX), antithrombotic and anticoagulant therapies (B01A)
- lipid modifying agents (C10)
- agents acting on the renin-angiotensin system (C09)
- antineoplastic and immunomodulating agents (L)
- hormonal contraceptives for systemic use (G03A)
- tamoxifen (L02BA01)

- sex hormones and modulators of the genital system (G03).

Immunocompromised at the index date

People who are immunocompromised at the index data will be defined by the recording of certain conditions or certain conditions plus treatments prior to index date. People will be considered immunocompromised if they have one or more of the following conditions recorded within 365 days prior to index date:

- HIV/AIDS,
- Hematological malignancies
- Solid malignancies
- Other intrinsic immune conditions

People will be defined as being immunocompromised if they are treated with antineoplastic and immunomodulating agents between 183 days to one day prior to index date. People will also be defined as being immunocompromised if they are treated with systemic corticosteroids between 183 days to one day prior to index date and have a recording of the following within 365 days prior to index date:

- Organ transplantations
- Rheumatologic/inflammatory conditions (rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematosus)

Smoking status pre-index date

Individuals´ smoking status (current smoker, ex-smoker, or non-smoker) will be identified when available. All available history for an individual will be used to identify records of their smoking status, with the most recent record included in the analysis.

Medications on or post-index date

We will also identify medication use on or after the index date first up to 30-days. For each medication of interest, we will group users into prevalent and new users. The following medications will be identified where available: anticoagulants, anti-platelet drugs, thrombolytic agent, or transfusion with blood products or immunoglobulins, and COVID-19 medications (molnupiravir, nirmatrelvir ritonavir, sotrovimab).

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
Location at index date	The covid-19 hospitalized and the intensive care cohorts need to be identified in hospital setting	Binary	[0]	IP, intensive care	SNOMED	n/a	Covid-19 infected or hospitalized	N/a	n/a
Comorbidity	Check for conditions of interest at start of follow-up	Binary	All history	Primary and secondary care	SNOMED	N/A	All cohort	n/a	n/a
Medication pre-index	Check for medications exposures prior to the index date	binary	[-183,-1] [-31 –1]	Primary and secondary care	ATC, RxNorm	N/A	All cohort	n/a	n/a
Immunocompromised	1.) People will be considered immunocompromised if they have one or more of the following conditions recorded in the 365 days prior to index: • HIV/AIDS, • Hematological malignancies • Solid malignancies	binary	[-365, 0] for condition, [-183,-1] for treatment	Primary and secondary care	SNOMED, ATC, RxNorm	N/A	All cohort	n/a	n/a

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
	• Other intrinsic immune conditions 2.) People will be defined as being immunocompromised if they are treated with antineoplastic and immunomodulating agents between 183 days to one day prior to index date. 3.) People will also be defined as being immunocompromised if they are treated with systemic corticosteroids between 183 days to one day prior to index date and have a recording of the following within 365 days prior to index date: • Organ transplantations • Rheumatologic/inflammatory conditions								

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
Smoking status	Individuals´ smoking status (current smoker, ex-smoker, or non-smoker) will be identified when available.	Binary	All records	Primary care and secondary care	SNOMED and LOINC	N/A	All cohort	n/a	n/a
Measurements	Check for measurements factors prior to the index date	Continuous	[- 12 months, 0]	Primary and secondary care	SNOMED and LOINC	N/A	All cohort	n/a	n/a
Medication during follow-up	The following medications will be identified where available: anticoagulants, anti-platelet drugs, thrombolytic agent, or transfusion with blood products or immunoglobulins, and COVID-19 medications (molnupiravir, nirmatrelvir ritonavir, sotrovimab).	Binary	[0,30]	Primary and secondary care	ATC, RxNorm	N/A	All cohort	n/a	n/a

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

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

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8.7 Study size

For each database, all individuals that satisfy the eligibility criteria for a study cohort will be included.

8.8 Analysis

8.8.1 Descriptive statistics

The observed characteristics of each study population overall, and stratified by age, sex, prior COVID-19 diagnosis, prior SARS-CoV-2 vaccination, whether patients were hospitalised or whether patients were immunocompromised on their index date will be reported. The time at risk observed along with the number of events observed over follow-up will be summarised for each study population overall and by age and sex as well as stratified by whether individuals´ had a prior COVID-19 diagnosis, prior SARS-CoV-2 vaccination, where hospitalised on the index date or where immunocompromised on the index date. The proportion of missing data for a given characteristic, for example relating to smoking status, will also be reported.

8.8.2 Incidence of study outcomes

The incidence of each study outcome described in section 8.6.2 will be estimated during 30-, 60-, and 90- and 180-days following the index date for each cohort of interest with 95% confidence intervals in each database. The 90-day cumulative incidence of study outcomes will be estimated. Given the risk of mortality among patients with COVID-19, particularly among those hospitalised, the competing risk of mortality will be accounted for by estimating cumulative incidence functions. If death is not available, cumulative incidence will be estimated using the Kaplan-Meier approach. As well as estimating the incidence of outcomes for each study cohort as a whole, incidence will also be estimated by age group stratified by sex. Other stratifications by prior COVID-19 diagnosis, prior SARS-CoV-2 vaccination, whether patients were hospitalised on the index date or where immunocompromised on the index date will also be performed.

8.8.3 Assessing the association between risk factors for thromboembolic events and COVID-19 during the Omicron period

To assess the association between potential risk factors on the incidence of venous and arterial thromboembolic events among patients with COVID-19 during the Omicron period, cause-specific Cox models will be used to calculate hazard ratios for the incidence of venous and arterial thromboembolic events for each of the COVID-19 cohorts. Adjusted models will evaluate potential predictors including age, sex, prior COVID-19 infection status, prior vaccination status, cancer, whether patients were immunocompromised on the index date, prior use of antithrombotics, prior use of corticosteroids, and pre-index comorbidities listed in section 8.6.3.

8.8.4 Risks of COVID-19 “worsening” (hospital admission or death) stratified by thromboembolic event occurrence during the Omicron period

[This analysis will only be conducted in the SIDIAP data given the availability of hospital data]

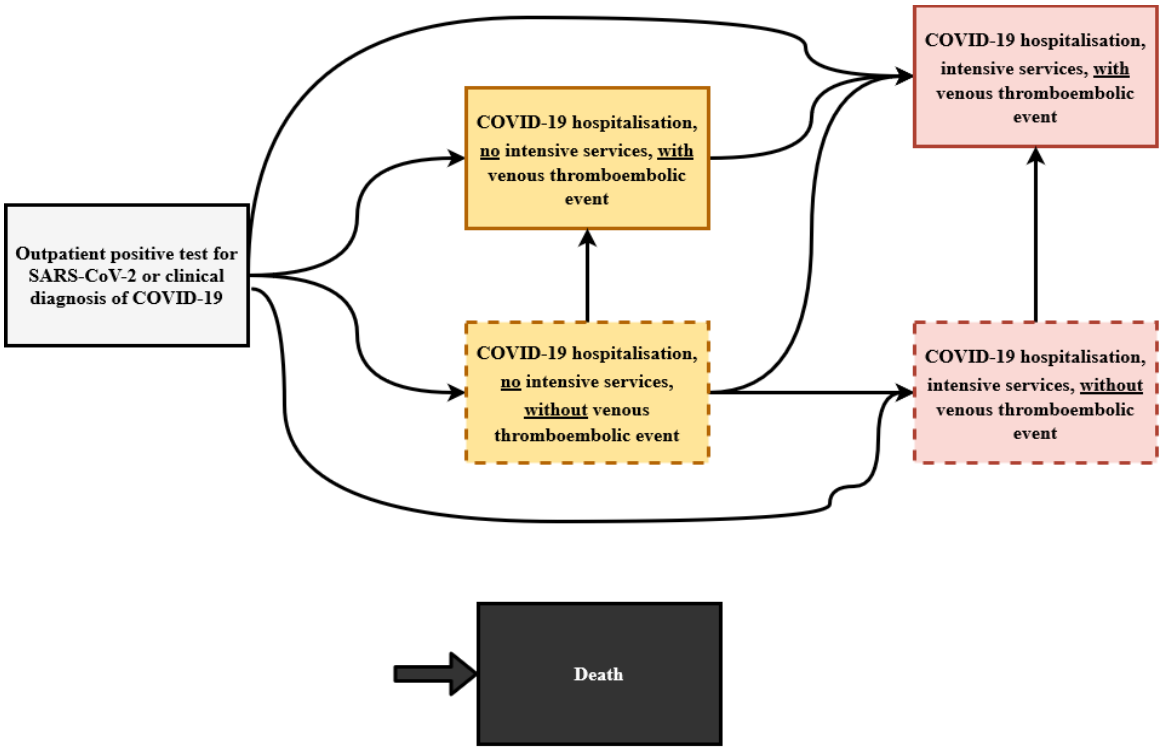
A multistate-type modelling approach will be used to assess risks of COVID-19 worsening during the period when Omicron was the dominant variant, stratified by thromboembolic event occurrence. Multistate models allow for a consideration of individuals progression to multiple events of interest, extending on competing risk models by also describing transitions to intermediate events. [24] In the context of COVID-19, use of intensive care services during a hospitalisation can be considered as key intermediate events between testing positive for SARS-COV-2 or having a clinical diagnosis of COVID-19 in an outpatient setting on the one end to a COVID-19-related death on the other.

Venous thromboembolism and arterial thromboembolism will be assessed separately, as time-dependent exposures for the following transitions:

(1) from outpatient COVID-19 diagnosis or PCR test positive to hospitalised with COVID-19
(2) from outpatient COVID-19 diagnosis or PCR test positive to death (without a COVID-19 hospitalisation in between)
(3) from being hospitalised with COVID-19 to death

Figure 1 shows an exemplar model for assessing COVID-19 worsening stratified by venous thromboembolic event, where individuals would begin by being identified as having a positive test for SARS-CoV-2 or clinical diagnosis of COVID-19 in an outpatient setting and then would progress through the various hospitalisation-related states, and would capture deaths (either after such a hospitalisation or directly after the test, for those individuals who were not hospitalised before their deaths).

Figure 1. Example multi-state model framework to assess COVID-19 worsening stratified by venous thromboembolic event



Cause-specific Cox models within the multistate framework will be used to estimate hazard ratios associated with the risk factors of interest. This approach will allow for the factors of interest to have a different effect by the transition of interest and, where the model includes a state representing deaths, will account for the competing risk of mortality. Models will be adjusted for age and sex.

8.8.5 Contextualising incidence rates for thromboembolic events in COVID-19 during the period when Omicron was the dominant variant

We will calculate crude incidence rate ratios (IRRs) for each event with 95% confidence intervals, for the vaccinated and COVID-19 cohorts compared against the background general population cohort. This will be done both overall and stratified by key factors including age, sex, prior COVID-19 diagnosis, prior vaccination status and whether patients are immunosuppressed. We will estimate the number of events expected among the vaccinated and COVID-19 cohorts using indirect standardisation by age and sex (with 10-year age bands), using the general population cohort as the standard population. We will calculate standardized incidence rate ratios (SIRs) and 95% confidence intervals comparing observed and expected rates. Rates will be reported overall, and by 10-year age bands, by sex, by prior COVID-19 diagnosis, by prior vaccination status and whether patients were immunosuppressed. A standardized incidence rate ratio above 1 will indicate that the observed rate for a specific outcome is higher than what is expected in the general background population.

Table 8: Primary, secondary, and subgroup analysis specification

A. Primary analysis

Hypothesis:	Objective 1 -3: Not applicable, descriptive incidence rate. Objective 4: use of intensive care services during a hospitalisation can be considered as key intermediate events between testing positive for SARS-COV-2 or having a clinical diagnosis of COVID-19 in an outpatient setting on the one end to a COVID-19-related death on the other. Objective 5: Covid-19 infection or vaccination may change the incidence rate of study events in population.
Exposure contrast:	Objective 1 -3: Not applicable, descriptive incidence rate. Objective 4: Not applicable, risk factor analysis Objective 5: Infected or vaccinated vs. the non-infected or non-vaccinated population
Outcome:	Objective 1 -3: Incidence rates of VTE, ATE Objective 4: VTE, ATE, death Objective 5: Incidence rates of VTE, ATE
Analytic software:	R
Model(s): ***(provide details or code)***	Objective 1 -3: We will use Poisson models to estimate incidence rates and 95% confidence interval. Overall, age group, and sex specific rates will be reported. Within each age-sex strata, rates by prior COVID-19 diagnosis, prior vaccination status and brand, and whether patients are immunosuppressed will be reported as well when event number is larger than 5 within the strata. Objective 4a: To assess the association between potential risk factors on the incidence of venous and arterial thromboembolic events among patients with COVID-19 during the Omicron period, cause-specific Cox models will be used to calculate hazard ratios for the incidence of venous and arterial thromboembolic events for each of the COVID-19 cohorts. Adjusted models will evaluate potential predictors including age, sex, prior COVID-19 infection status, prior vaccination status and brand, cancer, whether patients were immunocompromised on the index date, prior use of antithrombotics, prior use of corticosteroids, and pre-index comorbidities. Objective 4b: Cause-specific Cox models within the multistate framework will be used to estimate hazard ratios associated with the risk factors of interest. This approach will allow for the factors of interest to have a different effect by the transition of interest and, where the model includes a state representing deaths, will account for the competing risk of mortality. Models will be adjusted for age and sex. Objective 5: We will calculate crude incidence rate ratios (IRRs) for each event with 95% confidence intervals, for the vaccinated and COVID-19 cohorts compared against the background general population cohort. This will be

	done both overall and stratified by key factors including age, sex, prior COVID-19 diagnosis, prior vaccination status and brand, and whether patients are immunosuppressed. We will estimate the number of events expected among the vaccinated and COVID-19 cohorts using indirect standardisation by age and sex (with 10-year age bands), using the general population cohort as the standard population. We will calculate standardized incidence rate ratios (SIRs) and 95% confidence intervals comparing observed and expected rates. Rates will be reported overall, and by 10-year age bands, by sex, by prior COVID-19 diagnosis, by prior vaccination status and brand, and whether patients were immunosuppressed. A standardized incidence rate ratio above 1 will indicate that the observed rate for a specific outcome is higher than what is expected in the general background population.
Confounding adjustment method	***Name method and provide relevant details, e.g. bivariate, multivariable, propensity score matching (specify matching algorithm ratio and caliper), propensity score weighting (specify weight formula, trimming, truncation), propensity score stratification (specify strata definition), other.***
	For incidence rates, we will estimate the rates with stratification. For incidence rate ration, standardized incidence rate ration (SIRs) will be calculated.
Missing data methods	***Name method and provide relevant details, e.g. missing indicators, complete case, last value carried forward, multiple imputation (specify model/variables), other.***
	For cohort 2-5, we will only include individuals with complete exposure information.
Subgroup Analyses	***List all subgroups***
	All analysis will be stratified by age, sex, prior COVID-19 diagnosis, prior SARS-CoV-2 vaccination, whether patients were hospitalised or whether patients were immunocompromised on their index date will be reported, when sample size allowed.

B. Secondary Analysis 1

The only difference between the primary and secondary analysis is the outcomes of interest. Hence here we only show this item in the table.

Outcome:	1. Venous thromboembolic events

	In a secondary analysis pulmonary embolism and deep vein thrombosis will be assessed separately. We will also assess portal vein thrombosis, splanchnic venous thrombosis (SVT) and cerebral venous sinus thrombosis separately. 2. Arterial thromboembolic events In a secondary analysis acute myocardial infarction and acute ischemic stroke will be assessed separately. We also identify stroke in general, for which we will include both ischemic, haemorrhagic and non-specifically recorded stroke. 3. Cardiovascular events Instances of heart failure, cardiac arrhythmia, and angina will be identified. In addition, major cardiovascular events (MACE) will be identified by heart failure, acute myocardial infarction, or stroke, or the occurrence of sudden cardiac death. As a sensitivity analysis, we will require that events were identified by hospitalisation admission or discharge records.

Table 9 Sensitivity analyses – rationale, strengths and limitations

	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary
Restrict to RT-PCR test	In main analysis, the exposure definition of "Positive test result for SARS-CoV-2" will include all type of test. In the sensitivity analysis, we will restrict to RT-PCR test.	As a result of changes in the availability of population wide RT-PCR and home self-reported lateral flow tests during the Omicron period, it may not be possible to exclusively use RT-PCR tests when identifying positive test results in all datasets.	Increase specificity of exposure definition.	Loss in sensitivity.

Require inpatient cardiovascular events only	In the outcome definition of cardiovascular events, restrict to hospitalisation admission or discharge records	Cardiovascular events are acute and usually lead to inpatient admission	Increase specificity of exposure definition.	Loss in sensitivity.
Washout period for outcome events	In the main analysis, we will exclude patients with VTE or ATE within 183 days prior to the index date. Here, we will do 1.) reduce the period to 91 days. And 2.) exclude people with any VTE or ATE history	The choice of washout period may impact on the included study population, therefore impact on the generalisability of the rate for the vaccine cohort vs the risk of misclassification with prior event recording.	1.) can reduce the risk of survival bias; 2.) increase the specificity of incident event.	1.) may include recurrent events. 2.) increase the risk of survival bias as people need to have no VTE or ATE after prior vaccines to be included in the later vaccine cohorts.

8.9 Evidence synthesis

We will pool the results across databases using random effect meta-analyses, I^2 for heterogeneity will be reported.

9. DATA MANAGEMENT

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

10. QUALITY CONTROL

Note: This section will be automatically generated based on the DARWIN EU® Q/C processes, as detailed in a separate Deliverable 1.3.5.1)

11. LIMITATIONS OF THE RESEARCH METHODS

The study will be informed by routinely collected health care data that is available through existing governance and infrastructure and so data access and quality issues must be considered, and these will be documented to inform the HealthData@EU pilot. For example, cohorts of individuals with COVID-19 will be identified. However, outpatient tested positive cohorts will not capture all those individuals infected, given the variable availability of testing in outpatient settings. The inclusion of a study cohort identified by clinical diagnoses will address some of these limitations.

The included databases will vary in the data elements that they capture and in their current duration of follow-up. Depending on the dataset, not all study populations will be observed. For example, identifying the intensive services cohort will not be possible where inpatient hospital interventions are not observed. Similarly, not all outcomes may be available in all databases e.g. deaths. Some datasets may not capture COVID-19 diagnoses or tests occurring outside of hospital. Only the cohorts and outcomes that can reliably be identified will be assessed in the analyses. Since the vaccination programs changed over time (e.g. the primary vaccine courses targeted the general population, while the 4th dose were offered to more vulnerable people), the characteristics of patients receiving different doses may be differ. However, we will stratify our analysis by prior vaccines whenever the power allows. It will also be assumed that vaccination recording is complete. Due to the availability of more recent data (CPRD is available until July 2022), some databases may have relative short follow-up time for study cohorts, and therefore may impact on the 90-days and 180-days incidence rates. The data elements that each data partner can provide will be detailed. The contextualisation of incidence rates using a historical background period assumes that coding practices and data recording are similar over time. However, this method have been used in previous studies focused on the 1st wave of covid, contracted by the same research group. [20,21] The analysis will calculate crude incidence rates and standardised incidence rates accounting for age and sex only. Differences in other potential confounders factors may exist and the characteristics of each cohort and stratification group will be inspected. No validation of outcomes using case note review will be performed.

12. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

According to the new guideline on good pharmacovigilance practice (EMA/873138/2011 Rev 2*) there is no requirement for expedited reporting of adverse drug reactions from studies with secondary use of data (such as electronic health care databases).

13. GOVERNANCE BOARD ASPECTS

SIDIAP, IPCI, CPRD, EBB will require ethical approvals to perform this study. IQVIA DA Germany will not require any further specific approvals to undertake this study.

14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Dissemination activities to be undertaken will include mainly, although not exclusively, the creation of a final report, scientific publications, and presentations at conferences.

15. OTHER ASPECTS

N/A

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17. ANNEXES

Appendix I: List of Stand-Alone documents (e.g. lists with concept definitions (conditions & drugs))

Appendix II: ENCePP checklist for study protocols

APPENDIX I – PRELIMINARY CONCEPTS FOR STUDY VARIABLES

APPENDIX I, TABLE 1: PRELIMINARY CONCEPTS FOR EXPOSURE

Exposures:

Concept Id	Concept name			domain
3661405	Acute bronchitis caused by SARS-CoV-2	COVID Diagnosis	Exposure	Condition
3655976	Acute hypoxemic respiratory failure due to disease caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Exposure	Condition
3661748	Acute kidney injury due to disease caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Exposure	Condition
3661406	Acute respiratory distress syndrome due to disease caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Exposure	Condition
3662381	Asymptomatic SARS-CoV-2	COVID Diagnosis	Exposure	Condition
756031	Bronchitis caused by COVID-19	COVID Diagnosis	Exposure	Condition
3656667	Cardiomyopathy due to disease caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Exposure	Condition
3656668	Conjunctivitis due to disease caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Exposure	Condition
439676	Coronavirus infection	COVID Diagnosis	Exposure	Condition
37311061	COVID-19	COVID Diagnosis	Exposure	Condition
4100065	Disease due to Coronaviridae	COVID Diagnosis	Exposure	Condition
3656669	Dyspnea caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Exposure	Condition
37310284	Encephalopathy due to disease caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Exposure	Condition
3661885	Fever caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Exposure	Condition
37310283	Gastroenteritis caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2)	COVID Diagnosis	Exposure	Condition
37310286	Infection of upper respiratory tract caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Exposure	Condition
3663281	Lower respiratory infection caused by SARS-CoV-2	COVID Diagnosis	Exposure	Condition
3661631	Lymphocytopenia due to Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Exposure	Condition

37310287	Myocarditis due to disease caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Exposure	Condition
37310254	Otitis media due to disease caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Exposure	Condition
704995	Patient meets COVID-19 clinical diagnostic criteria	COVID Diagnosis	Exposure	Observation
700297	Patient meets COVID-19 laboratory confirmation criterion (detection of specific RNA in a clinical specimen using a molecular amplification detection test)	COVID Diagnosis	Exposure	Observation
704996	Patient meets COVID-19 laboratory diagnostic criteria	COVID Diagnosis	Exposure	Observation
700296	Patient meets COVID-19 presumptive laboratory evidence criteria (detection of specific antigen in a clinical specimen, OR detection of specific antibody in serum, plasma, or whole blood indicative of a new or recent infection)	COVID Diagnosis	Exposure	Observation
37016927	Pneumonia caused by Human coronavirus	COVID Diagnosis	Exposure	Condition
3661408	Pneumonia caused by SARS-CoV-2	COVID Diagnosis	Exposure	Condition
40479642	Pneumonia due to Severe acute respiratory syndrome coronavirus	COVID Diagnosis	Exposure	Condition
756039	Respiratory infection caused by COVID-19	COVID Diagnosis	Exposure	Condition
3655977	Rhabdomyolysis due to disease caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Exposure	Condition
3655975	Sepsis due to disease caused by Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Exposure	Condition
320651	Severe acute respiratory syndrome	COVID Diagnosis	Exposure	Condition
37396171	Severe acute respiratory syndrome of upper respiratory tract	COVID Diagnosis	Exposure	Condition
37311060	Suspected COVID-19	COVID Diagnosis	Exposure	Observation
3661632	Thrombocytopenia due to Severe acute respiratory syndrome coronavirus 2	COVID Diagnosis	Exposure	Condition
45763724	Suspected coronavirus infection	COVID Diagnosis	Exposure	Observation
40218804	2019-ncov coronavirus, sars-cov-2/2019-ncov (covid-19), any technique, multiple types or subtypes (includes all targets), non-cdc	COVID19 positive test	Exposure	Measurement
40218805	Cdc 2019 novel coronavirus (2019-ncov) real-time rt-pcr diagnostic panel	COVID19 positive test	Exposure	Measurement
44789510	Coronavirus nucleic acid detection	COVID19 positive test	Exposure	Measurement

44811805	Coronavirus nucleic acid detection assay	COVID19 positive test	Exposure	Measurement
45770687	Coronavirus RNA (ribonucleic acid) detection assay	COVID19 positive test	Exposure	Measurement
44807536	Coronavirus RNA (ribonucleic acid) measurement by NAAT (nucleic acid amplification test)	COVID19 positive test	Exposure	Measurement
3667069	Detection of ribonucleic acid of Severe acute respiratory syndrome coronavirus 2 using polymerase chain reaction	COVID19 positive test	Exposure	Observation
36660491	Human coronavirus 229E RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection	COVID19 positive test	Exposure	Measurement
36659667	Human coronavirus HKU1 RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection	COVID19 positive test	Exposure	Measurement
36660329	Human coronavirus NL63 RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection	COVID19 positive test	Exposure	Measurement
36660364	Human coronavirus OC43 RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection	COVID19 positive test	Exposure	Measurement
742224	Infectious agent antigen detection by immunoassay technique, qualitative or semiquantitative, multiple-step method; severe acute respiratory syndrome coronavirus (eg, SARS-CoV, SARS-CoV-2 [COVID-19]) (Coronavirus disease [COVID-19])	COVID19 positive test	Exposure	Measurement
700360	Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]), amplified probe technique	COVID19 positive test	Exposure	Measurement
742218	Infectious disease (bacterial or viral respiratory tract infection), pathogen-specific nucleic acid (DNA or RNA), 22 targets including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), qualitative RT-PCR, nasopharyngeal swab	COVID19 positive test	Exposure	Measurement
742219	Infectious disease (bacterial or viral respiratory tract infection), pathogen-specific nucleic acid (DNA or RNA), 22 targets including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), qualitative RT-PCR, nasopharyngeal swab	COVID19 positive test	Exposure	Measurement
36661384	Influenza virus A and B and SARS-CoV-2 (COVID-19) and SARS-related CoV RNA panel - Respiratory specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement

36661375	Influenza virus A and B and SARS-CoV-2 (COVID-19) identified in Respiratory specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
36661376	Influenza virus A and B RNA and SARS-CoV-2 (COVID-19) N gene panel - Respiratory specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
705104	Measurement of Coronavirus (Coronavirinae subfamily species)	COVID19 positive test	Exposure	Measurement
705105	Measurement of Coronavirus (Coronavirinae subfamily species) antigen	COVID19 positive test	Exposure	Measurement
37310257	Measurement of Severe acute respiratory syndrome coronavirus 2 antigen	COVID19 positive test	Exposure	Measurement
756055	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	COVID19 positive test	Exposure	Measurement
586310	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Genetic material using Molecular method	COVID19 positive test	Exposure	Measurement
704991	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Blood	COVID19 positive test	Exposure	Measurement
756029	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Respiratory specimen	COVID19 positive test	Exposure	Measurement
586307	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Saliva	COVID19 positive test	Exposure	Measurement
705107	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Sample from nose	COVID19 positive test	Exposure	Measurement
704976	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Sample from oropharynx	COVID19 positive test	Exposure	Measurement
586309	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Specified specimen	COVID19 positive test	Exposure	Measurement
756065	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Unspecified specimen	COVID19 positive test	Exposure	Measurement
702834	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) specific cell-mediated immune response in Blood	COVID19 positive test	Exposure	Measurement
704992	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Culture method	COVID19 positive test	Exposure	Measurement
705001	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique	COVID19 positive test	Exposure	Measurement

705000	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Blood	COVID19 positive test	Exposure	Measurement
756085	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Respiratory specimen	COVID19 positive test	Exposure	Measurement
586308	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Saliva	COVID19 positive test	Exposure	Measurement
705106	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Sample from nose	COVID19 positive test	Exposure	Measurement
704975	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Sample from oropharynx	COVID19 positive test	Exposure	Measurement
756084	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Unspecified specimen	COVID19 positive test	Exposure	Measurement
704993	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Sequencing	COVID19 positive test	Exposure	Measurement
723477	SARS-CoV-2 (COVID-19) Ag [Presence] in Respiratory specimen by Rapid immunoassay	COVID19 positive test	Exposure	Measurement
706167	SARS-CoV-2 (COVID-19) N gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
706157	SARS-CoV-2 (COVID-19) N gene [Cycle Threshold #] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N1	COVID19 positive test	Exposure	Measurement
706155	SARS-CoV-2 (COVID-19) N gene [Cycle Threshold #] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N2	COVID19 positive test	Exposure	Measurement
715272	SARS-CoV-2 (COVID-19) N gene [Presence] in Nasopharynx by NAA with probe detection	COVID19 positive test	Exposure	Measurement
757678	SARS-CoV-2 (COVID-19) N gene [Presence] in Nose by NAA with probe detection	COVID19 positive test	Exposure	Measurement
706161	SARS-CoV-2 (COVID-19) N gene [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
586524	SARS-CoV-2 (COVID-19) N gene [Presence] in Respiratory specimen by Nucleic acid amplification using CDC primer-probe set N1	COVID19 positive test	Exposure	Measurement

586525	SARS-CoV-2 (COVID-19) N gene [Presence] in Respiratory specimen by Nucleic acid amplification using CDC primer-probe set N2	COVID19 positive test	Exposure	Measurement
36661378	SARS-CoV-2 (COVID-19) N gene [Presence] in Saliva (oral fluid) by NAA with probe detection	COVID19 positive test	Exposure	Measurement
586520	SARS-CoV-2 (COVID-19) N gene [Presence] in Serum or Plasma by NAA with probe detection	COVID19 positive test	Exposure	Measurement
706175	SARS-CoV-2 (COVID-19) N gene [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
706156	SARS-CoV-2 (COVID-19) N gene [Presence] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N1	COVID19 positive test	Exposure	Measurement
706154	SARS-CoV-2 (COVID-19) N gene [Presence] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N2	COVID19 positive test	Exposure	Measurement
723469	SARS-CoV-2 (COVID-19) ORF1ab region [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
706168	SARS-CoV-2 (COVID-19) ORF1ab region [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
723478	SARS-CoV-2 (COVID-19) ORF1ab region [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
723464	SARS-CoV-2 (COVID-19) ORF1ab region [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
586516	SARS-CoV-2 (COVID-19) [Presence] in Unspecified specimen by Organism specific culture	COVID19 positive test	Exposure	Measurement
723471	SARS-CoV-2 (COVID-19) RdRp gene [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
723470	SARS-CoV-2 (COVID-19) RdRp gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
706160	SARS-CoV-2 (COVID-19) RdRp gene [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
706173	SARS-CoV-2 (COVID-19) RdRp gene [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
586528	SARS-CoV-2 (COVID-19) RNA [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
586529	SARS-CoV-2 (COVID-19) RNA [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement

715262	SARS-CoV-2 (COVID-19) RNA [Log #/volume] (viral load) in Unspecified specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
706158	SARS-CoV-2 (COVID-19) RNA panel - Respiratory specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
706169	SARS-CoV-2 (COVID-19) RNA panel - Unspecified specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
723476	SARS-CoV-2 (COVID-19) RNA [Presence] in Nasopharynx by NAA with non-probe detection	COVID19 positive test	Exposure	Measurement
586526	SARS-CoV-2 (COVID-19) RNA [Presence] in Nasopharynx by NAA with probe detection	COVID19 positive test	Exposure	Measurement
757677	SARS-CoV-2 (COVID-19) RNA [Presence] in Nose by NAA with probe detection	COVID19 positive test	Exposure	Measurement
706163	SARS-CoV-2 (COVID-19) RNA [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
36661377	SARS-CoV-2 (COVID-19) RNA [Presence] in Respiratory specimen by Sequencing	COVID19 positive test	Exposure	Measurement
715260	SARS-CoV-2 (COVID-19) RNA [Presence] in Saliva (oral fluid) by NAA with probe detection	COVID19 positive test	Exposure	Measurement
715261	SARS-CoV-2 (COVID-19) RNA [Presence] in Saliva (oral fluid) by Sequencing	COVID19 positive test	Exposure	Measurement
723463	SARS-CoV-2 (COVID-19) RNA [Presence] in Serum or Plasma by NAA with probe detection	COVID19 positive test	Exposure	Measurement
706170	SARS-CoV-2 (COVID-19) RNA [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
723467	SARS-CoV-2 (COVID-19) S gene [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
723468	SARS-CoV-2 (COVID-19) S gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
723465	SARS-CoV-2 (COVID-19) S gene [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
586519	SARS-CoV-2 (COVID-19) S gene [Presence] in Serum or Plasma by NAA with probe detection	COVID19 positive test	Exposure	Measurement
723466	SARS-CoV-2 (COVID-19) S gene [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement

586517	SARS-CoV-2 (COVID-19) whole genome [Nucleotide sequence] in Isolate by Sequencing	COVID19 positive test	Exposure	Measurement
757685	SARS-CoV+SARS-CoV-2 (COVID-19) Ag [Presence] in Respiratory specimen by Rapid immunoassay	COVID19 positive test	Exposure	Measurement
706172	SARS-like coronavirus N gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
706171	SARS-like coronavirus N gene [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
706166	SARS-related coronavirus E gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
586523	SARS-related coronavirus E gene [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
586518	SARS-related coronavirus E gene [Presence] in Serum or Plasma by NAA with probe detection	COVID19 positive test	Exposure	Measurement
706174	SARS-related coronavirus E gene [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
706159	SARS-related coronavirus+MERS coronavirus RNA [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
706165	SARS-related coronavirus RNA [Presence] in Respiratory specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
723472	SARS-related coronavirus RNA [Presence] in Unspecified specimen by NAA with probe detection	COVID19 positive test	Exposure	Measurement
739902	SARS-COV-2 (COVID-19) vaccine, vector non-replicating	covid-19 vaccine	Exposure	drug
739903	SARS-COV-2 (COVID-19) vaccine, vector - Ad26 100000000000 UNT/ML	covid-19 vaccine	Exposure	drug
739905	SARS-COV-2 (COVID-19) vaccine, vector non-replicating Injectable Suspension	covid-19 vaccine	Exposure	drug
739906	SARS-COV-2 (COVID-19) vaccine, vector - Ad26 100000000000 UNT/ML Injectable Suspension	covid-19 vaccine	Exposure	drug
37003432	SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein	covid-19 vaccine	Exposure	drug
37003433	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML	covid-19 vaccine	Exposure	drug
37003435	SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein Injectable Suspension	covid-19 vaccine	Exposure	drug
37003517	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML	covid-19 vaccine	Exposure	drug

37003518	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML Injectable Suspension	covid-19 vaccine	Exposure	drug
37003436	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension	covid-19 vaccine	Exposure	drug
35894915	COVID-19 vaccine	covid-19 vaccine	Exposure	drug
35897994	COVID-19 vaccine Injectable Solution	covid-19 vaccine	Exposure	drug
36118948	COVID-19 vaccine, whole virus, inactivated, adjuvanted with Alum and CpG 1018	covid-19 vaccine	Exposure	drug
36118949	COVID-19 vaccine, recombinant, full-length nanoparticle spike (S) protein, adjuvanted with Matrix-M	covid-19 vaccine	Exposure	drug
36119720	COVID-19 vaccine, whole virus, inactivated, adjuvanted with Alum and CpG 1018 Injectable Suspension	covid-19 vaccine	Exposure	drug
36119721	COVID-19 vaccine, recombinant, full-length nanoparticle spike (S) protein, adjuvanted with Matrix-M Injectable Suspension	covid-19 vaccine	Exposure	drug
36119722	COVID-19 vaccine, recombinant, plant-derived Virus-Like Particle (VLP) spike (S) protein, adjuvanted with AS03 Injectable Suspension	covid-19 vaccine	Exposure	drug
36126197	COVID-19 vaccine, recombinant, plant-derived Virus-Like Particle (VLP) spike (S) protein, adjuvanted with AS03	covid-19 vaccine	Exposure	drug
724905	SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-ChAdOx1, preservative free, 0.5 mL	covid-19 vaccine	Exposure	drug
724904	SARS-COV-2 (COVID-19) vaccine, UNSPECIFIED	covid-19 vaccine	Exposure	drug

APPENDIX I, TABLE 2: PRELIMINARY CONCEPTS FOR OUTCOMES

Concept ID	Concept name
Outcome	**Cerebral venous sinus thrombosis (CVST)**
4102202	Cerebral venous sinus thrombosis
4048786	Cerebral venous thrombosis of sigmoid sinus
4043735	Cerebral venous thrombosis of straight sinus
4111713	Non-pyogenic venous sinus thrombosis
314667	Nonpyogenic thrombosis of intracranial venous sinus
4116206	Septic thrombophlebitis of cavernous sinus
4121335	Septic thrombophlebitis of lateral sinus
4119136	Septic thrombophlebitis of sagittal sinus
4041680	Septic thrombophlebitis of sigmoid sinus
4100225	Thrombophlebitis lateral venous sinus
4217471	Thrombophlebitis of basilar sinus

4104695	Thrombophlebitis of cavernous sinus
4167985	Thrombophlebitis of inferior sagittal sinus
764714	Thrombophlebitis of sigmoid sinus
4100224	Thrombophlebitis of superior longitudinal venous sinus
4098706	Thrombophlebitis of superior sagittal sinus
4277833	Thrombophlebitis of torcular Herophili
764710	Thrombophlebitis of transverse sinus
4228209	Thrombosis of basilar sinus
4234264	Thrombosis of cavernous venous sinus
4048890	Thrombosis of inferior sagittal sinus
4057329	Thrombosis of lateral venous sinus
4102203	Thrombosis of superior longitudinal sinus
4290940	Thrombosis of superior sagittal sinus
4079905	Thrombosis of torcular Herophili
4105338	Thrombosis transverse sinus
Outcome	**DVT-narrow**
762047	Acute bilateral thrombosis of subclavian veins
762148	Acute deep vein thrombosis of bilateral iliac veins
761444	Acute deep vein thrombosis of bilateral lower limbs following coronary artery bypass graft
35616028	Acute deep vein thrombosis of left iliac vein
35615035	Acute deep vein thrombosis of left lower limb following procedure
761416	Acute deep vein thrombosis of left upper limb following coronary artery bypass graft
35615031	Acute deep vein thrombosis of left upper limb following procedure
43531681	Acute deep vein thrombosis of lower limb
35616027	Acute deep vein thrombosis of right iliac vein
35615034	Acute deep vein thrombosis of right lower limb following procedure
761415	Acute deep vein thrombosis of right upper limb following coronary artery bypass graft
35615030	Acute deep vein thrombosis of right upper limb following procedure
44782746	Acute deep venous thrombosis
44782751	Acute deep venous thrombosis of axillary vein
762008	Acute deep venous thrombosis of bilateral axillary veins
760875	Acute deep venous thrombosis of bilateral calves
765155	Acute deep venous thrombosis of bilateral ileofemoral veins
762017	Acute deep venous thrombosis of bilateral internal jugular veins
762417	Acute deep venous thrombosis of bilateral legs
762020	Acute deep venous thrombosis of bilateral popliteal veins
765546	Acute deep venous thrombosis of bilateral tibial veins
762004	Acute deep venous thrombosis of both upper extremities
44782742	Acute deep venous thrombosis of calf

44782747	Acute deep venous thrombosis of femoral vein
762015	Acute deep venous thrombosis of ileofemoral vein of left leg
765541	Acute deep venous thrombosis of ileofemoral vein of right lower extremity
44782748	Acute deep venous thrombosis of iliofemoral vein
44782752	Acute deep venous thrombosis of internal jugular vein
762009	Acute deep venous thrombosis of left axillary vein
760876	Acute deep venous thrombosis of left calf
765540	Acute deep venous thrombosis of left femoral vein
765922	Acute deep venous thrombosis of left internal jugular vein
762418	Acute deep venous thrombosis of left lower extremity
765537	Acute deep venous thrombosis of left upper extremity
44782767	Acute deep venous thrombosis of lower extremity as complication of procedure
46270071	Acute deep venous thrombosis of lower limb due to coronary artery bypass grafting
762022	Acute deep venous thrombosis of politeal vein of right leg
44782743	Acute deep venous thrombosis of popliteal vein
762021	Acute deep venous thrombosis of popliteal vein of left leg
762010	Acute deep venous thrombosis of right axillary vein
760877	Acute deep venous thrombosis of right calf
762013	Acute deep venous thrombosis of right femoral vein
762018	Acute deep venous thrombosis of right internal jugular vein
762419	Acute deep venous thrombosis of right lower extremity
762005	Acute deep venous thrombosis of right upper extremity
44782745	Acute deep venous thrombosis of thigh
44782744	Acute deep venous thrombosis of tibial vein
762026	Acute deep venous thrombosis of tibial vein of left leg
765156	Acute deep venous thrombosis of tibial vein of right leg
44782421	Acute deep venous thrombosis of upper extremity
764016	Acute deep venous thrombosis of upper extremity after coronary artery bypass graft
44782766	Acute deep venous thrombosis of upper extremity as complication of procedure
762048	Acute thrombosis of left subclavian vein
45757410	Acute thrombosis of mesenteric vein
762049	Acute thrombosis of right subclavian vein
36712892	Acute thrombosis of splenic vein
44782762	Acute thrombosis of subclavian vein
37109253	Bilateral acute deep vein thrombosis of femoral veins
40478951	Bilateral deep vein thrombosis of lower extremities
4046884	Deep vein thrombosis of leg related to air travel
4133004	Deep venous thrombosis
4181315	Deep venous thrombosis associated with coronary artery bypass graft

45773536	Deep venous thrombosis of femoropopliteal vein
763942	Deep venous thrombosis of left lower extremity
761980	Deep venous thrombosis of left upper extremity
443537	Deep venous thrombosis of lower extremity
4133975	Deep venous thrombosis of pelvic vein
40480555	Deep venous thrombosis of peroneal vein
4322565	Deep venous thrombosis of profunda femoris vein
763941	Deep venous thrombosis of right lower extremity
761928	Deep venous thrombosis of right upper extremity
4207899	Deep venous thrombosis of tibial vein
4028057	Deep venous thrombosis of upper extremity
193512	Embolism and thrombosis of the renal vein
435565	Embolism and thrombosis of the vena cava
4119760	Iliofemoral deep vein thrombosis
4124856	Inferior mesenteric vein thrombosis
4281689	Phlegmasia alba dolens
4284538	Phlegmasia cerulea dolens
4309333	Postoperative deep vein thrombosis
46285905	Provoked deep vein thrombosis
4033521	Splenic vein thrombosis
4055089	Superior mesenteric vein thrombosis
42538533	Thrombosis of iliac vein
44811347	Thrombosis of internal jugular vein
765049	Thrombosis of left peroneal vein
4317289	Thrombosis of mesenteric vein
4203836	Thrombosis of subclavian vein
4175649	Thrombosis of the popliteal vein
4153353	Traumatic thrombosis of axillary vein
46285904	Unprovoked deep vein thrombosis
4221821	Thrombophlebitis of deep veins of lower extremity
46271900	Recurrent deep vein thrombosis
4189004	Deep vein thrombosis of leg related to intravenous drug use
Outcome	**SVT**
4033521	Splenic vein thrombosis
36712892	Acute thrombosis of splenic vein
4033521	Splenic vein thrombosis
196715	Budd-Chiari syndrome
199837	Portal vein thrombosis
4317289	Thrombosis of mesenteric vein
4092406	Portal thrombophlebitis
36712892	Acute thrombosis of splenic vein

4173167	Mesenteric embolus
4144032	Mesenteric thrombus and/or embolus
45757410	Acute thrombosis of mesenteric vein
45757409	Chronic thrombosis of mesenteric vein
4318407	Thrombophlebitis of mesenteric vein
4124856	Inferior mesenteric vein thrombosis
4055089	Superior mesenteric vein thrombosis
199837	Portal vein thrombosis
36717492	Acute occlusion of mesenteric vein
45757410	Acute thrombosis of mesenteric vein
4124856	Inferior mesenteric vein thrombosis
4055089	Superior mesenteric vein thrombosis
4317289	Thrombosis of mesenteric vein
45757409	Chronic thrombosis of mesenteric vein
4318407	Thrombophlebitis of mesenteric vein
4173167	Mesenteric embolus
4144032	Mesenteric thrombus and/or embolus
36717492	Acute occlusion of mesenteric vein
36712892	Acute thrombosis of splenic vein
196715	Budd-Chiari syndrome
35624285	Complete obstruction of hepatic portal vein
4301208	Hepatic vein thrombosis
37110194	Hepatic veno-occlusive disease with immunodeficiency syndrome
37109927	Obstruction of visceral vein
4238060	Portal vein obstruction
4033521	Splenic vein thrombosis
4277276	Veno-occlusive disease of the liver
37111372	Visceral venous thrombosis
36712891	Chronic thrombosis of splenic vein
Outcome	**Pulmonary embolism**
4120091	Acute massive pulmonary embolism
45768439	Acute pulmonary embolism
45768888	Acute pulmonary thromboembolism
4309039	Hemorrhagic pulmonary infarction
762808	Infarction of lung due to embolus
40480461	Infarction of lung due to iatrogenic pulmonary embolism
4108681	Postoperative pulmonary embolus
4091708	Pulmonary air embolism
440417	Pulmonary embolism
37109911	Pulmonary embolism due to and following acute myocardial infarction
37016922	Pulmonary embolism on long-term anticoagulation therapy

43530605	Pulmonary embolism with pulmonary infarction
4119608	Pulmonary fat embolism
254662	Pulmonary infarction
4253796	Pulmonary microemboli
45766471	Pulmonary oil microembolism
4121618	Pulmonary thromboembolism
4119610	Pulmonary tumor embolism
4119607	Subacute massive pulmonary embolism
4119609	Subacute pulmonary fat embolism
4236271	Recurrent pulmonary embolism
Outcome	**Ischemic stroke**
4045735	Anterior cerebral circulation infarction
4031045	Anterior choroidal artery syndrome
761110	Bilateral cerebral infarction due to precererbral arterial occlusion
4110189	Cerebral infarct due to thrombosis of precerebral arteries
443454	Cerebral infarction
762951	Cerebral infarction due to anterior cerebral artery occlusion
765515	Cerebral infarction due to basilar artery stenosis
43530683	Cerebral infarction due to carotid artery occlusion
762933	Cerebral infarction due to cerebral artery occlusion
762937	Cerebral infarction due to cerebral venous thrombosis
4111714	Cerebral infarction due to cerebral venous thrombosis, non-pyogenic
4108356	Cerebral infarction due to embolism of cerebral arteries
45772786	Cerebral infarction due to embolism of middle cerebral artery
4110190	Cerebral infarction due to embolism of precerebral arteries
762935	Cerebral infarction due to internal carotid artery occlusion
763015	Cerebral infarction due to middle cerebral artery occlusion
46273649	Cerebral infarction due to occlusion of basilar artery
35610084	Cerebral infarction due to occlusion of cerebral artery
46270031	Cerebral infarction due to occlusion of precerebral artery
762934	Cerebral infarction due to posterior cerebral artery occlusion
43531607	Cerebral infarction due to stenosis of carotid artery
35610085	Cerebral infarction due to stenosis of cerebral artery
46270381	Cerebral infarction due to stenosis of precerebral artery
4110192	Cerebral infarction due to thrombosis of cerebral arteries
45767658	Cerebral infarction due to thrombosis of middle cerebral artery
44782773	Cerebral infarction due to vertebral artery occlusion
46270380	Cerebral infarction due to vertebral artery stenosis
37110678	Cerebral ischemic stroke due to occlusion of extracranial large artery
37110679	Cerebral ischemic stroke due to stenosis of extracranial large artery
4043731	Infarction - precerebral

4131383	Infarction of basal ganglia
4046237	Infarction of optic radiation
4119140	Infarction of visual cortex
4141405	Left sided cerebral infarction
37116473	Multifocal cerebral infarction due to and following procedure on cardiovascular system
4077086	Occipital cerebral infarction
4046359	Partial anterior cerebral circulation infarction
4319146	Pituitary infarction
4146185	Right sided cerebral infarction
36717605	Silent cerebral infarct
4142739	Thalamic infarction
4046358	Total anterior cerebral circulation infarction
372924	Cerebral artery occlusion
Outcome	**Myocardial infarction**
4119457	Acute Q wave infarction - anterolateral
4119943	Acute Q wave infarction - anteroseptal
4121464	Acute Q wave infarction - inferior
4121465	Acute Q wave infarction - inferolateral
4124684	Acute Q wave infarction - lateral
4119948	Acute Q wave infarction - widespread
4126801	Acute Q wave myocardial infarction
4296653	Acute ST segment elevation myocardial infarction
46270162	Acute ST segment elevation myocardial infarction due to left coronary artery occlusion
761737	Acute ST segment elevation myocardial infarction due to occlusion of circumflex coronary artery
46270163	Acute ST segment elevation myocardial infarction due to right coronary artery occlusion
43020460	Acute ST segment elevation myocardial infarction involving left anterior descending coronary artery
45766076	Acute ST segment elevation myocardial infarction of anterior wall involving right ventricle
761736	Acute ST segment elevation myocardial infarction of anteroapical wall
46270159	Acute ST segment elevation myocardial infarction of anterolateral wall
46270160	Acute ST segment elevation myocardial infarction of anteroseptal wall
45766116	Acute ST segment elevation myocardial infarction of inferior wall
45766151	Acute ST segment elevation myocardial infarction of inferior wall involving right ventricle
35611570	Acute ST segment elevation myocardial infarction of inferolateral wall
35611571	Acute ST segment elevation myocardial infarction of inferoposterior wall
46274044	Acute ST segment elevation myocardial infarction of lateral wall
46270161	Acute ST segment elevation myocardial infarction of posterior wall
46273495	Acute ST segment elevation myocardial infarction of posterobasal wall

46270158	Acute ST segment elevation myocardial infarction of posterolateral wall
46270164	Acute ST segment elevation myocardial infarction of septum
45766075	Acute anterior ST segment elevation myocardial infarction
4178129	Acute anteroapical myocardial infarction
4267568	Acute anteroseptal myocardial infarction
312327	Acute myocardial infarction
44782769	Acute myocardial infarction due to left coronary artery occlusion
44782712	Acute myocardial infarction due to right coronary artery occlusion
45766115	Acute myocardial infarction during procedure
434376	Acute myocardial infarction of anterior wall
45766150	Acute myocardial infarction of anterior wall involving right ventricle
438438	Acute myocardial infarction of anterolateral wall
4243372	Acute myocardial infarction of apical-lateral wall
4108669	Acute myocardial infarction of atrium
4151046	Acute myocardial infarction of basal-lateral wall
4275436	Acute myocardial infarction of high lateral wall
438170	Acute myocardial infarction of inferior wall
45771322	Acute myocardial infarction of inferior wall involving right ventricle
438447	Acute myocardial infarction of inferolateral wall
441579	Acute myocardial infarction of inferoposterior wall
436706	Acute myocardial infarction of lateral wall
4324413	Acute myocardial infarction of posterobasal wall
4051874	Acute myocardial infarction of posterolateral wall
4303359	Acute myocardial infarction of septum
4147223	Acute myocardial infarction with rupture of ventricle
4145721	Acute non-Q wave infarction
4119944	Acute non-Q wave infarction - anterolateral
4119456	Acute non-Q wave infarction - anteroseptal
4119945	Acute non-Q wave infarction - inferior
4119946	Acute non-Q wave infarction - inferolateral
4121466	Acute non-Q wave infarction - lateral
4124685	Acute non-Q wave infarction - widespread
4270024	Acute non-ST segment elevation myocardial infarction
35610091	Acute nontransmural myocardial infarction
319039	Acute posterior myocardial infarction
444406	Acute subendocardial infarction
35610093	Acute transmural myocardial infarction
4119947	Acute widespread myocardial infarction
37109912	Arrhythmia due to and following acute myocardial infarction
438172	Atrial septal defect due to and following acute myocardial infarction
4124687	Cardiac rupture due to and following acute myocardial infarction

4215259	First myocardial infarction
4108678	Hemopericardium due to and following acute myocardial infarction
4173632	Microinfarct of heart
45771327	Mitral valve regurgitation due to acute myocardial infarction with papillary muscle and chordal rupture
45766214	Mitral valve regurgitation due to acute myocardial infarction without papillary muscle and chordal rupture
45766212	Mitral valve regurgitation due to and following acute myocardial infarction
4323202	Mixed myocardial ischemia and infarction
4329847	Myocardial infarction
37309626	Myocardial infarction due to demand ischemia
4170094	Myocardial infarction in recovery phase
4200113	Non-Q wave myocardial infarction
4030582	Postoperative myocardial infarction
35610087	Postoperative nontransmural myocardial infarction
4206867	Postoperative subendocardial myocardial infarction
35610089	Postoperative transmural myocardial infarction
4207921	Postoperative transmural myocardial infarction of anterior wall
4209541	Postoperative transmural myocardial infarction of inferior wall
37109911	Pulmonary embolism due to and following acute myocardial infarction
4108679	Rupture of cardiac wall without hemopericardium as current complication following acute myocardial infarction
4108219	Rupture of chordae tendinae due to and following acute myocardial infarction
4124686	Silent myocardial infarction
765132	Subendocardial myocardial infarction
45766114	Subsequent ST segment elevation myocardial infarction
45766113	Subsequent ST segment elevation myocardial infarction of anterior wall
45773170	Subsequent ST segment elevation myocardial infarction of inferior wall
4108217	Subsequent myocardial infarction
4108677	Subsequent myocardial infarction of anterior wall
4108218	Subsequent myocardial infarction of inferior wall
45766241	Subsequent non-ST segment elevation myocardial infarction
4108680	Thrombosis of atrium, auricular appendage, and ventricle due to and following acute myocardial infarction
439693	True posterior myocardial infarction
37109910	Ventricular aneurysm due to and following acute myocardial infarction
Outcome	**Intestinal infarction**
4195665	Gastrointestinal tract vascular insufficiency
4148299	Ischemic colitis
4173167	Mesenteric embolus
4317289	Thrombosis of mesenteric vein
4319280	Acute bowel infarction
4144032	Mesenteric thrombus and/or embolus

45757410	Acute thrombosis of mesenteric vein
45757409	Chronic thrombosis of mesenteric vein
44811741	Acute ischaemia of large intestine
44811740	Acute ischaemia of small intestine
37117790	Insufficiency of mesenteric artery
37016198	Epiploic appendagitis
35622081	Nongangrenous ischemic colitis
35622080	Gangrenous ischemic colitis
4345926	Abdominal angina
4342767	Transient ischemic colitis
4341648	Hemorrhagic infarction of intestine
4341646	Occlusive mesenteric ischemia
4340939	Non-occlusive mesenteric ischemia
4340378	Transmural infarction of intestine
4340375	Focal segmental ischemia of small intestine
4318537	Large bowel gangrene
4318407	Thrombophlebitis of mesenteric vein
4240850	Acute ischemic enterocolitis
4239942	Embolic mesenteric infarction
4237654	Ischemic enterocolitis
4215949	Nonocclusive intestinal infarction
4214720	Thrombotic mesenteric infarction
4192856	Acute ischemic colitis
4188336	Chronic ischemic enterocolitis
4174014	Inferior mesenteric artery embolus
4149013	Mesenteric infarction
4148257	Chronic gastrointestinal tract vascular insufficiency
4148256	Acute GIT vascular insufficiency
4124856	Inferior mesenteric vein thrombosis
4055089	Superior mesenteric vein thrombosis
4055025	Superior mesenteric artery embolus
4045408	Ischemic stricture of intestine
201894	Acute vascular insufficiency of intestine
192673	Vascular insufficiency of intestine

APPENDIX I, TABLE 3: PRELIMINARY CONCEPTS FOR OTHER OUTCOMES

Concept id	Concept name	group		domain

4306655	Death	Death	Outcome	Observation
9201	Inpatient Visit	IP/ER	Outcome	Visit
262	Emergency Room and Inpatient Visit	IP/ER	Outcome	Visit
9203	Emergency Room Visit	IP/ER	Outcome	Visit

APPENDIX I, TABLE 4: LIST WITH CONCEPT DEFINITIONS FOR COVARIATES

Condition	Inclusion, incl. descendants	Exclusion, incl. descendants
Infections	132736, 256451, 432250, 42597240, 4280729, 37395594, 255848, 132797, 4270490	437474
Asthma	317009, 4293734, 4308356, 46287068, 4279553	4029337, 4312524
COLD	255573, 256448, 36685451, 36685452, 36685453, 36685454, 36685455, 36685456, 36685457, 36685458, 44782563, 44788819	
Bronchiectasis	256449	
Pulmonary fibrosis	4197819	
Lung cancer	443388, 35610239, 4201621	
Upper respiratory tract infection	4110027, 4181583	
Lower respiratory tract infection	255848, 256451, 4270490	
Cardiovascular comorbidity	134057, 4131484, 40488442, 4071689, 4103183, 4353966, 4115558, 4277352, 4021774, 4353840, 4147185, 4031892, 136237, 4322000, 134057, 4311860, 4236414, 4308201, 4086525, 42593070, 40487084, 44788314, 4190527, 4264330, 4161988, 4103193, 4182004, 37110754, 4116966, 4152505, 4115415, 443251, 4011467, 4353957	
Gastrointestinal comorbidity	4000610	443568, 4244495, 36715498
Hepatic comorbidity	4093333	4115573, 36545521, 42593076, 4243887, 36538946, 4246127, 4130519
Renal comorbidity	4091056	4217308, 196653, 4243885
Neurological comorbidity	376337	4157331

Condition	Inclusion, incl. descendants	Exclusion, incl. descendants
Musculoskeletal comorbidity	135930	
Endocrine comorbidity	31821	
Metabolic comorbidity	436670	
Haematological comorbidity	317248	
Psychiatric comorbidity	432586	4244690
Cancer	443392	4112752, 4111921, 4116082
Anaphylaxis	441202	
Tuberculosis	434557	
HIV-infection	439727, 4013106, 4083350, 4186235, 4221489, 4298853, 40484507, 44783623	
Acute liver disease	201343, 4049298, 37396531, 4184847, 4243475, 36715006, 36676901, 4058676, 4250743, 4331678, 196455	
Hepatitis B	200031, 439673, 4013553, 4014007, 4244873, 4247369, 4281232, 42537336, 44792587, 45772057, 46286608	
Hepatitis C	197494, 439672, 4132902, 4153375, 4196134, 4227247, 4340380, 43531723, 44789328, 44792611, 44806379, 44813294, 45757360, 45757396, 46273598, 46286609	
Arterial hypertension	316866	4071202
Severe asthma exacerbations	4152913	
Gastro-oesophageal reflux disease	36717641, 36713494, 4175650, 318800, 30437	
Atopic dermatitis	133834	
Nasal polyposis	42537251	
Chronic sinusitis	257012	
Chronic idiopathic urticaria	4199697	
Rhinitis	257007	

Condition	Inclusion, incl. descendants	Exclusion, incl. descendants
Diabetes mellitus	201820, 442793, 604741, 760977, 760978, 760979, 760980, 760989, 761050, 761063, 765375, 4019513, 4034961, 4055679, 4060085, 4065354, 4129379, 4130165, 4144221, 4146514, 4175440, 4182243, 4219466, 4220981, 4242853, 4305491, 4307799, 37018224, 40482801, 40484648, 40484649, 40485020, 42536400, 42689695, 43020791, 45766963, 45768456	
Osteoporosis	80502, 36716194, 4109181, 44783850, 37204244	
Smoking (current or past)	619068, 437264	
Alcohol abuse	436607, 4322643, 4030588, 195300, 4106575, 378421, 4214950, 4302744, 4176651, 4202330, 46269816, 46269817, 37016176, 45757494, 318773, 36714559, 619608, 45757783, 35610532, 46269818, 3655834, 44782445	
Drug abuse	606210, 436954, 4127868, 4022666, 40480941, 40482269, 4295481	
Drug abuse	42529475, 4168205, 4239438, 4206984, 4219142, 3022196, 36031658, 36031249, 4017177, 4229859, 42529480, 4036792, 4038240, 4037138, 42539778, 1616455	
Alcohol abuse	4116983, 4053784, 45766930, 4080065, 36674487, 45772695, 44793164, 37206970, 4207141, 44792459, 3036878, 762596, 4145860, 4042872, 4027638, 44786671, 432456, 44786700, 40481082, 4038704, 3027199, 608490, 44812667	
Smoking (current or past)	44788975, 44788976, 762499, 3012697, 4052948, 600776, 44786669, 762498, 4131520, 37395605, 1616974, 42528924, 44804450, 4206526, 4203874, 4046886, 4141787, 44809281	

Concept IDs include descendants unless highlighted as being excluded. By OMOP standards descendants automatically include the ancestor.

Before finalizing the concept sets, CohortDiagnostics will run on cohorts created using the initial concept sets to check code counts and patient characteristics which might give indications to adjust the concept sets.

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

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: DARWIN EU – EHDS Use Case: Natural history of coagulopathy in COVID-19 patients and persons vaccinated against SARS-CoV-2 IN the context of the OMICRON variant

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

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

Comments:

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

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

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1 Study type and Study Design
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.2 Study Setting and Data Sources
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.8 Analysis
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))	☒	☐	☐	8.8 Analysis
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?	☒	☐	☐	8.5 Study Population
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	8.3 Study Period
4.2.2 Age and sex	☒	☐	☐	8.6.3. Other covariates
4.2.3 Country of origin	☒	☐	☐	8.2 Study Setting and Data Sources
4.2.4 Disease/indication	☒	☐	☐	8.6.1. Exposures

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.5 Duration of follow-up	☒	☐	☐	8.4 Follow-up
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.5 Study Population with inclusion and exclusion criteria

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. Exposures
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?	☒	☐	☐	8.6.1. Exposures
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	8.6.1. Exposures
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. Outcomes
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.6.2. Outcomes, Appendix I
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 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)	☐	☐	☒	

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)	☒	☐	☐	8.8 Analysis

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)	☒	☐	☐	8.6.1. Exposures and Appendix I
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.6.2. Outcomes, Appendix I
9.1.3 Covariates and other characteristics?	☒	☐	☐	8.6.3. Other covariates
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)	☒	☐	☐	8.2 Study Setting and Data Sources
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.2 Study Setting and Data Sources
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.2 Study Setting and Data Sources
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.6.1. Exposures and Appendix I
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.6.2. Outcomes, Appendix I
9.3.3 Covariates and other characteristics?	☒	☐	☐	8.6.3. Other covariates
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 Analysis
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	8.8.1 Descriptive statistics
10.4 Are stratified analyses included?	☒	☐	☐	8.8 Analysis
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 Analysis

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. DATA MANAGEMENT
11.2 Are methods of quality assurance described?	☒	☐	☐	
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:				11. LIMITATIONS OF THE RESEARCH METHODS
12.1.1 Selection bias?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	
12.1.3 Residual/unmeasured confounding?	☒	☐	☐	
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).				
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☐	☒	

Comments:

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

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. AMENDMENTS AND UPDATES

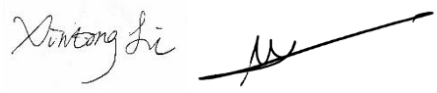
Comments:

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. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	14. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Comments:

Name of the main author of the protocol: Xintong Li, Marti Catala-Sabate

Date: 20/06/2023

Signature: 

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