ASSOCIATION BETWEEN THROMBOSIS WITH THROMBOCYTOPENIA SYNDROME (TTS) OR THROMBOEMBOLIC EVENTS, AND COVID-19 VACCINES

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2 List of abbreviations

Abbreviation	Name
ATE	Arterial thromboembolism
ASMD	Absolute standardised mean difference
ATC	Anatomical Therapeutic Chemical Classification
CDM	Common Data Model
COVID-19	Coronavirus disease-2019
CPRD	Clinical Practice Research Datalink
CVST	Cerebral venous sinus thrombosis
DA	Disease Analyzer
DVT	Deep vein thrombosis
ECMO	Extracorporeal membrane oxygenation
EHR	Electronic Health Record
HES APC	Hospital Episode Statistics Admitted Patient Care
HM	Hospital de Madrid
IPCI	Integrated Primary Care Information
IRR	Incidence Rate Ratio
LPD	Longitudinal Patient Data
MACE	MAjor Cardiovascular Events
MDRR	Minimum Detectable Relative Risk
OMOP	Observational Medical Outcomes Partnership
OR	Odd Ratio
PE	Pulmonary Embolism
PS	Propensity Score
RR	Relative Risk
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SIDIAP	Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària
SVVT	Splanchnic and Visceral Vein Thrombosis
TTS	Thrombosis with Thrombocytopenia Syndrome/s
TE	Thromboembolic Events
VTE	Venous ThromboEmbolism

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4 Abstract

Association between thrombosis with thrombocytopenia syndrome (TTS) or thromboembolic events, and COVID-19 vaccines

Version and Date: Version 1.0, XXMMM 2021

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Rationale and background:

Thrombosis alone or with thrombocytopenia syndrome (TTS) are being investigated as potential adverse effects of some COVID-19 vaccines. Published case series suggested unusual thrombosis with raised antibodies against platelet factor 4 were presented in very small number of people following vaccination with viral vector-based vaccines, called vaccine-induced immune thrombotic thrombocytopenia. Several European countries restricted the use of viral vector-based vaccines in younger age groups as a pre-cautionary measure. There have been some attempts to compare the incidence of adverse outcomes before and after vaccination, however, they are subject to limited vaccine brands covered, small sample size, and residual confounding. Insight to the magnitude of TTS risk related to COVID-19 vaccination is urgently needed.

Research question and objectives

The proposed study objectives are:
1a) To quantify the association between the administration of a COVID-19 vaccine and the occurrence of **thrombosis with thrombocytopenia syndrome/s (TTS)** within pre-specified risk periods, stratified by vaccine type/brand, age and gender, while controlling for relevant confounding factors; 1b) To quantify the **comparative association** of developing **TTS** between the administration of different COVID-19 vaccine brands, while controlling for relevant confounding factors; 2a) To quantify the association of the administration of a COVID-19 vaccine and the occurrence of **thromboembolic events (TE)** within pre-specified risk periods, stratified by vaccine type/brand, age and gender, while controlling for relevant confounding factors; 2b) To quantify the comparative association between the occurrence of TE and the administration of different COVID-19 vaccine brands, while controlling for relevant confounding factors; 3) To study the **association** between potential **risk factors and TTS/TE** in people receiving COVID-19 vaccine/s; 4) To characterize the **treatments** used in vaccinated patients with **TTS/TE**, including the use of anticoagulants and other therapeutic products.

Study design

We will perform a European international network cohort study using data mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM).

Population

The following study cohorts will be defined: 1) 1st, 2nd dose of vaccination and unvaccinated cohorts will be identified with the use of time-varying exposure of vaccination (Objective 1a and 2a); 2) Different brands of COVID-19 vaccines where the sample size allows will be identified for Objective 1b and 2b. Feasibility counts showed sufficient power for the comparative analyses between Vaxzervria and Comirnaty in UK and Spanish databases. 3) heterologous cohort where people had viral vector-based vaccine as the 1st dose followed by mRNA as the 2nd dose, will be compared to a homologous cohort where both doses are viral vector-based for Objective 1b and 2b. These cohorts will be only built in Spanish, French, and German databases where heterologous vaccine schedule is recommended. Finally, three post vaccination TTS/venous thromboembolism (VTE)/Arterial thromboembolic events (ATE) cohorts will be used for Objective 3 and 4.

Variables

Vaccination status, patient demographics, health conditions and medication use will be extracted.

TTS will be defined based on the Brighton collaboration and encompasses of one of five TE events, including cerebral venous sinus thrombosis (CVST), deep vein thrombosis (DVT), pulmonary embolism (PE), splanchnic and visceral vein thrombosis (SVVT) and stroke, with concurrent thrombocytopenia within 10 days before/after the TE date. TE events of interests consist of two broad classes namely VTE and ATE. In addition, mortality will be also identified for the study populations. For each outcome, its occurrence within 14, 21 and 28 days following the index date will be identified. Risk factors including COVID-19 history, health conditions at any time prior and medication use within 365 days prior will be identified. Specific medication use including e.g. non-steroidal anti-inflammatory drugs, Cox2 inhibitors, systemic corticosteroids, in patients with post-vaccination TTS, VTE or ATE will be identified during the inpatient stay as well anytime post in the outpatient records.

Data sources

Five European primary care, two outpatient and one inpatient databases across six countries in Europe will be analysed. In addition, one US claims and one large US hospital databases will be accessed to maximise sample size and exposure to vaccines that are currently under-represented in European data, e.g. Janssen and Moderna.

Study size

From the contributing databases, all the individuals satisfying the eligibility criteria for the study will be included.

Data analysis

The study period will cover from Dec 2020 (first vaccine users) until the latest data release available in each of the contributing databases. For objective 1a-2b, we will use propensity-score-matching to select comparable people in each two cohorts. We will report incidence rates of TTS or TE in the 14, 21 and 28 days following the index date in each PS matched cohort. Incidence Rate ratio (IRR) will be used to quantify the risk of developing TTS (Objective 1) or TE (Objective 2) via Poisson models. RRs will be stratified by 10-year age bands, sex, and vaccine type/brand (only for Objective 1a and 2a). Logistic regression will be used to identify risk factors associated with TTS/VTE/ATE among people vaccinated against SARS-CoV-2. Post-TTS/VTE/ATE treatment pathways will be examined using Sunburst and Sankey diagrams.

5 Amendments and updates

There have been no formal amendments to the protocol so far.

Number	Date	Amendment or update	Reason
…			

6 Milestones

Milestone	**Planned date**
Approval Study Protocol by EMA	Aug 2021
<Registration in the EU PAS register>	Aug 2021
Start of data collection	No data collection is required.
End of data collection	No data collection is required.
Draft report	Dec 2021
Final study report accepted by EMA	Feb 2022
Manuscript to be provided to EMA	Feb 2022

7 Rationale and background

7.1 Thrombosis with thrombocytopenia syndrome (TTS) pharmacovigilance signals following COVID-19 vaccines

As of May 2021, four different COVID-19 vaccines were granted conditional marketing authorisation by the European Medicines Agency (EMA) after showing high efficacy and safety in phase-3 clinical trials [1-3]. These vaccines are classified into either viral vector-based including Vaxzevria (previously AstraZeneca or ChAdOx1) and COVID-19 Vaccine Janssen, or mRNA including Comirnaty (previously BNT162b2) and Spikevax (previously Moderna). After millions of vaccine doses were administered in large-scale immunization campaigns, spontaneous case reports of **thrombosis with thrombocytopenia syndrome (TTS)** usually within 2 weeks following the first dose of **viral vector-based vaccines** emerged [4-6]. As of 7th July 2021, 405 reports of major thromboembolic events with concurrent thrombocytopenia had been documented following 44.3 million first doses and 33.9 million second doses of the Vaxzevria vaccine in the UK[7]. Although fewer concerns have been raised about safety signals for Comirnaty (mRNA COVID-19 vaccine), instances of immune thrombocytopenia have also been observed among recipients of this vaccine[8].

Causal relationship was considered possible by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), leading to an update of the respective product information to include TTS as a **very rare** side effect [link]. As these unusual blood clots in combination with low thrombocyte counts were reported pre-dominantly among women aged <60 years, several European countries restricted the use of viral vector-based vaccines in younger age groups as a pre-cautionary measure. While the pathogenesis is not yet fully understood, an immune response leading to the development of pathologic platelet-activating antibodies is suggested (vaccine-induced immune thrombotic thrombocytopenia)[6, 9]. Although these events are very rare, based on the worldwide roll-out of these vaccines absolute numbers of affected patients may accumulate fast.

To further monitor COVID-19 vaccine safety and complement pharmacovigilance measures, multi-national observational studies have been requested by the EMA: Incidences of patient-reported side effects after COVID-19 vaccination [10] and adverse events of special interest [11, 12] are closely being monitored. The Covid-Vaccine-Monitor [13] project will facilitate the rapid signal assessment of emerging safety concerns. While these studies are designed to identify a broad range of new potential safety signals, one ongoing EMA project already focusses on cardiovascular and thromboembolic risk in both COVID-19 patients and COVID-19 vaccinated people [14]. The study is assessing incidences of thromboembolic events and their consequences, as well as risk factors for thromboembolism in COVID-19 patients and vaccinated people. Background incidence rates of five TTSs of special interest [15] were calculated based on records from over 20 million people in 6 European countries, ranging from 0.1 events per 100,000 person-years for cerebral venous sinus thrombosis/thrombocytopenia to 0.2-4.4 events per 100,000 person-years for stroke/thrombocytopenia. The study found TTS in unvaccinated people to be more common in men and older age groups, which differs from characteristics of the patient group reporting vaccine-related TTS. Preliminary findings from this study also showed larger than expected VTE (predominated by PE) in the 28 days following vaccination with either Vaxzevria or Comirnaty in UK and Spain; increasing rate of thrombocytopenia was seen among people vaccinated with Vaxzevria. In another

study based on Danish and Norwegian data, increasing rates of VTE, PE and CVST were also found [16]. These studies provide important data on the incidence of adverse outcomes reported after vaccination and on potential risk factors for thromboembolic events in COVID-19 vaccinated patients. They will not, however, quantify the association between COVID-19 vaccines and the occurrence of these events taking into account possible risk factors. More recently, a nested case-control study from Scotland has suggested no increasing risk of VTE with either vaccines [17]. However, case-control analyses have been recently criticized for increasing bias and incapability of controlling for confounding [18]. In the light of important public-health decisions being based on TTS-risk for COVID-19 vaccines in different countries, insight to the magnitude of TTS risk related to COVID-19 vaccination at a large scale is urgently needed. Therefore, the EMA recently launched an invitation to tender under EMA/2017/09/PE Lot 3 – "Association between thrombosis with thrombocytopenia syndrome (TTS) or thromboembolic events, and COVID-19 vaccines", which was the basis for this protocol.

8 Research question and objectives

The proposed study objectives are:

1a) To quantify the association between the administration of a COVID-19 vaccine and the occurrence of **TTS** within pre-specified risk periods, stratified by vaccine type/brand, age and gender, while controlling for relevant confounding factors.

1b) To quantify the comparative association of developing TTS among people vaccinated with different COVID-19 vaccine brands (where possible/applicable), while controlling for relevant confounding factors.

2a) To quantify the association between the administration of a COVID-19 vaccine and the occurrence of **venous or arterial thromboembolic events (VTE or ATE)** within pre-specified risk periods, stratified by vaccine type/brand, age and gender, while controlling for relevant confounding factors.

2b) To quantify the comparative association of developing VTE/ATE among people vaccinated with different COVID-19 vaccine brands (where possible/applicable), while controlling for relevant confounding factors.

3) To study the **association** between potential **risk factors and VTE, ATE or TTS** in people receiving COVID-19 vaccine/s

4) To characterize the **treatments** used in patients with **VTE, ATE or TTS post-vaccination**, including the use of anticoagulants and other therapeutic products

9 Research methods

9.1 Study design

We will conduct a network cohort study using routinely collected health care data mapped to the OMOP CDM.

9.2 Setting

9.2.1 Countries

Datasets from France, Germany, Netherlands, Spain, United States and United Kingdom will inform the analyses (see section 9.4 Data Sources below for more details).

9.2.2 Study period

The study period to identify exposure and outcomes will cover from Dec 2020 (first vaccine users) until the latest data release available in each of the contributing databases.

For each objective and data source the study period will be unique and will go from cohort-specific index date to the latest data available. Cohort-specific index dates are:

- For vaccinated people (and matched unvaccinated) [*Objectives* 1a-2a, 3, 5.2 and 5.3]: date of first dose vaccine (and same date for matched unvaccinated)
- For comparative cohorts [Objective 1b and 2b]: date of first dose of the corresponding vaccine brand
- For TE and TTS cohorts [*Objective 4*]: date of TE/TTS diagnosis

Specific time windows for each of the objectives is specified in Section 9.2.4.

9.2.3 Study cohorts

All adult persons (aged >=18 at the index date- defined in Section 9.2.4) registered in any of the contributing databases within the study period and with at least one year of database history before the index date will be included in the target population. This is to ensure a sufficient period to identify health conditions and medication use prior to individuals´ index dates.

- **Study population for Objectives 1a and 2a**: Of people in the target population, those with at least one exposure to any COVID-19 vaccine in the study period will be included in the 'exposed' cohort/s, with 1st and 2nd dose vaccine date as time-varying exposure. Unexposed matched participants will be pooled from the target population (as specified in Section 9.2.4).
- **Study populations for Objective 1b and 2b**: Those with exposure to COVID-19 vaccine brand will be included in the exposed group/s and those with exposure to another COVID-19 vaccine in the active comparator group/s. Such comparison is only feasible for

Vaxzevria vs Comirnaty based on the UK (CPRD AURUM, CPRD GOLD, Oxford-RCGP RSC) and Spanish data (SIDIAP), as explained in detail in Section 9.5.1. Therefore, those with Vaxzevria vaccine will be included in the exposed group and those with Comirnaty as the active comparator in the vaccine brand comparative safety analyses.

We hope to quantify the safety association between people vaccinated with Janssen and Spikevax as well as Janssen and Comirnaty in the US open claims data if feasibility power permits.

In addition, heterologous cohort where people had viral vector-based vaccine as the 1st dose followed by mRNA as the 2nd dose, will be compared to a homologous cohort where both doses are viral vector-based for Objective 1b and 2b. These cohorts will be only built in Spanish, French, and German databases where heterologous vaccine schedule is recommended.

- **Study population for Objective 3**: Those with at least one exposure to any COVID-19 vaccine in the study period will be included in this cohort for the analysis of risk factors of post-vaccine VTE, ATE or TTS.

- **Study population for Objectives 4:** Those with a VTE, ATE or TTS event in the up to 28 days post vaccination of 1st dose will be included as 'VTE cases', 'ATE cases' or 'TTS cases', with VTE/ATE/TTS date as index date. etails on the definition/s of vaccine exposure/s are provided in Section 9.3.1, whilst VTE/ATE and TTS definitions are provided in Section 9.3.2.

9.2.4 Follow-up

9.2.4.1 TE and TTS outcome at risk time (Objective 1a-2b)

For **Objectives 1a and 2a**, we use time-varying exposures to minimize immortal time bias. This means that vaccinated persons have multiple index dates depending on the change in the vaccination status during the study period. Persons will be followed up to 28 days or the earliest of the following dates (the last available date or the date of vaccination exposure status change) post each index date. Figure 1 shows an illustrative example of time-varying exposure and follow-up time for each index date using four patients: PatID1 was vaccinated in Mar 2021 with the 1st, had an event 20-days post 1st vaccination, and in June with the 2nd dose, PatID2 was not vaccinated before deceased, PatID3 was vaccinated in Dec 2020 and Mar 2021 with the 1st and 2nd dose, and PatID4 remained unvaccinated throughout the whole study period. In this graph, the outcome at risk time window (28 days) is shown with solid bars and the time outside the outcome at risk window are shown by bars with diagonal stripes.

For vaccinated people, like PatID1 and PatID3, the follow-up time in the 'first dose vaccinated cohort' and in the 'second dose vaccinated cohort' for VTE/ATE/TTS started from the date of 1st and 2nd vaccination respectively, and ended with either the earliest of the 28-day or last available date or the 2nd vaccination date (only for 1st vaccination), as illustrated with solid yellow (1st vaccination) and solid red (2nd vaccination) bars for PatID1 and PatID3. The dates of 1st and 2nd vaccination were their index dates.

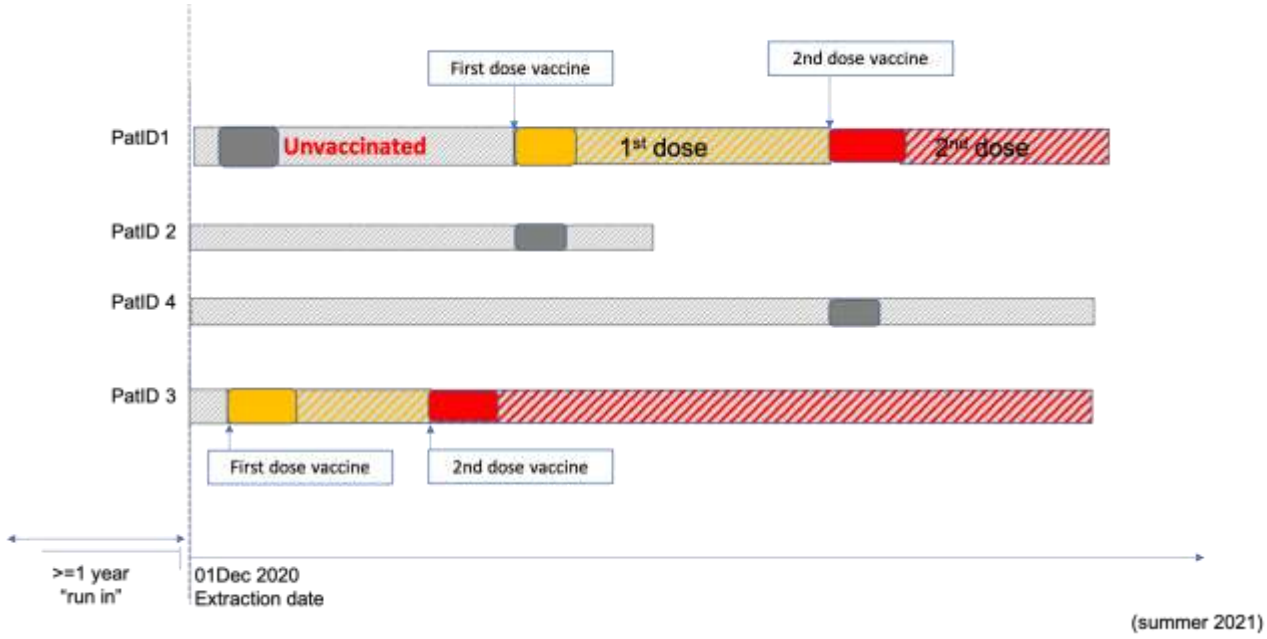
PatID-2 was unvaccinated before deceased though had similar baseline characteristics at the date of first vaccination of PatID1, indicating similar probability of vaccination within the given calendar period to PatID1. Through the propensity-score-matching exercise for the comparison between unvaccinated vs vaccinated, PatID2 was propensity score-matched to PatID1. To avoid surveillance bias, PatID2's follow-up started with the index date of the matched 'vaccinated' counterpart PatID1 and ended 28 days later, as shown by the solid grey bar. Likewise, in the same propensity-score-matched exercise, PatID1's unvaccinated time was propensity-score-matched to PatID3 who was vaccinated earlier and therefore, was assigned to the index date of PatID3's 1st vaccination date and was followed up 28 days following that index date, as shown by grey bars for PatID1.

In another propensity-score-matching exercise for the comparison between 2nd vaccination vs unvaccinated, PatID4 was propensity-score-matched to PatID1 and the follow-up for that analysis was 28 days from PatID1's second vaccination date.

Note: there would be another follow-up time for PatID4 for the unvaccinated vs vaccinated comparison if s/he was propensity-score-matched to another patient not illustrated in Figure 1.

In our study design, people contribute to unvaccinated time if either they are never vaccinated or temporarily unvaccinated (meaning they are vaccinated later).

Figure 1. Diagram of study follow-up for Objective 1a-2b

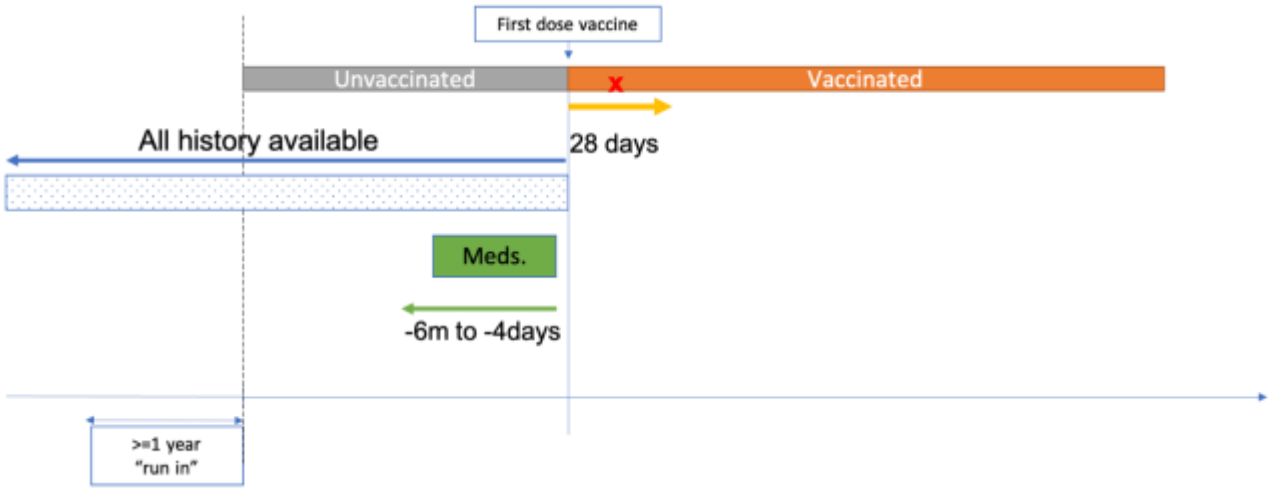


Follow-up for **Objectives 1b and 2b** starts from the index date of 1st vaccination date and lasts up to 28 days and only considers vaccinated people.
As secondary analyses for Objectives 1a to 2b, we will use 14- and 21-day (instead of 28-day) periods for outcome ascertainment.

9.2.4.2 Risk factors time window (Objective 3)

For Objective 3, only vaccinated people are included, and studied for the identification of potential risk factors prior to the 1st dose date. Vaccinated people are then followed for the outcome of interest, either TTS, VTE, or ATE, ascertainment for up to 28 days or to the date of the 2nd vaccination, if this happens prior to 28 days (Figure 2). All available history in the pre-vaccination time window is used to identify pre-vaccination risk factors, as illustrated in blue dotted bar with the exception of medication use where the medication ascertainment time goes from 6 months prior to 4 days prior to the 1st vaccination date, as illustrated in the green solid bar.

Figure 2. Follow-up periods for risk factor and outcome ascertainment in vaccinated people.

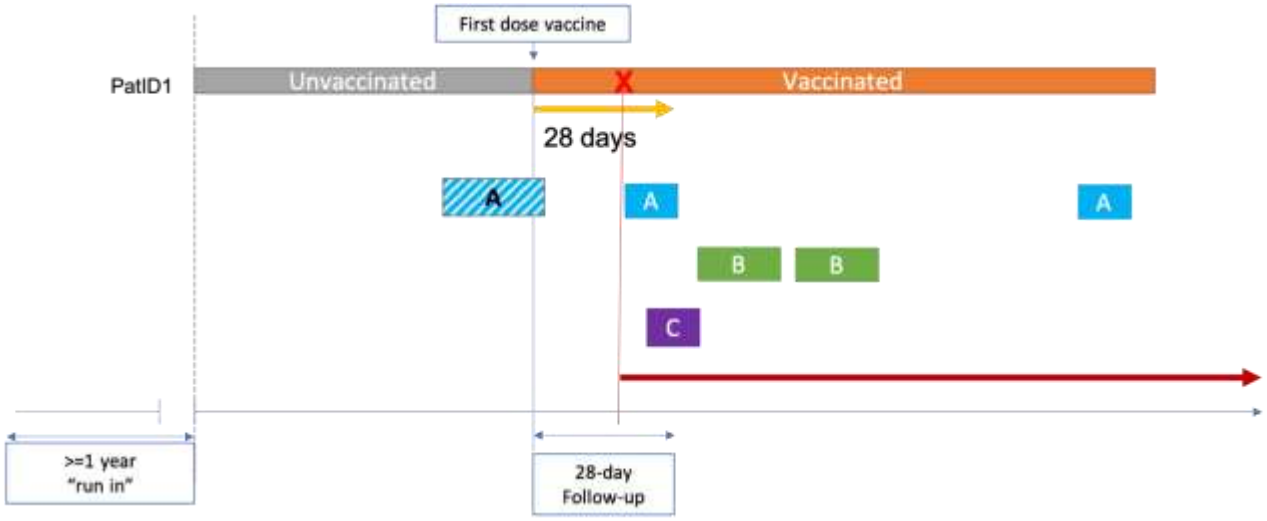


Meds: medications; m: month

9.2.4.3 Inpatient and outpatient treatments follow-up time for TE or TTS for vaccinated people

For **Objective 4** only people with VTE, ATE or TTS occurring in the 28-day post-vaccination and prior to 2nd vaccination are included. They are required to have at least 1 day post event of interest in the database for this analysis. They will be followed up until the last available date in the respective database. No fixed follow-up would allow us to explore all possible treatment pathways in the databases. Inpatient and outpatient treatment/s are explored by different databases (described in Section 9.4) as there is no single database with both data available. See Figure 3 shows treatment history examples for PatID-1 of A (in blue bar), B (in green bar), and C (in purple bar) drugs in the database. An event of interest, marked with X, occurred in day 20 post vaccination. It means, only some treatments of this patient will be included in the treatment ascertainment, as illustrated in solid bars, because we are interested in newly started treatment following the event.

Figure 3. Depiction of patient follow-up for Objective 4



9.3 Variables

9.3.1 Exposures-vaccination against SARS-CoV-2

We will identify individuals who received a vaccination against SARS-CoV-2, with the 1st dose an individual received being used as the index event for one cohort and the 2nd dose for another cohort. We will also define exposure based on vaccine type, viral vector (Vaxzevria/Janssen) vs mRNA (Comirnaty/Spikevax) as well as brand where possible.

9.3.2 Study outcomes

9.3.2.1 Thromboembolism (TE)

The following thromboembolic events (TE) of interest, preliminary code list shown in Annex 4, will be studied:

- Deep vein thrombosis (DVT)
- Pulmonary embolism (PE)
- Venous thromboembolism (VTE) as a composite of DVT or PE
- Cerebral venous sinus thrombosis (CVST)
- Splanchnic and visceral vein thrombosis (SVT)
- Ischemic stroke
- Myocardial infarction
- Arterial thromboembolism (ATE) as a composite of the two above and other rare arterial thromboembolisms defined in Annex 4.

VTE and ATE will be assessed separately for Objectives 2, 3, and 4.

9.3.2.2 TE and thrombosis with thrombocytopenia syndrome (TTS)

Our definition of TTS, the primary outcome for Objective 1a, 1b and 3, is based on the one proposed by the Brighton collaboration (**link**), and encompasses the occurrence of one of the TE of interest above (9.3.2.1) with concurrent thrombocytopenia within 10 days before/after the thromboembolic event date after the vaccination.

Thrombocytopenia will be identified either by a diagnostic code or a measurement of <150,000 platelets per microliter of blood as proposed by the Brighton collaboration, observed over a time window post vaccination starting ten days prior to the event of interest and up to ten days afterwards. This definition has been implemented in the OMOP CDM as part of our ongoing study [19] and can be seen in Annex 4.

The following additional definitions will be used for sensitivity analyses in Objective 1a, 1b and 3:

- TTS with recent/closer thrombocytopenia: by reducing the time window to 5 days before/after thrombosis post vaccination
- TTS with severe thrombocytopenia: by reducing the threshold to <100,000 platelets per microliter for the definition of thrombocytopenia based on laboratory data

We will explore additional time window and threshold for thrombocytopenia according to the latest evidence and guideline.

9.3.2.3 Risk factors for TTS

Here is a preliminary list of medications and health conditions of interest, based on an ongoing study[19]. We will also conduct a data-driven approach to explore additional medications. Details of this approach is described in Section 9.7.2.

9.3.2.3.1 Medications of interest

The following medications will be identified based on the WHO's Anatomical Therapeutic Chemical (ATC) classification codes:

- Non-steroidal anti-inflammatory drugs (M01A)
- Cox2 inhibitors (M01AH)
- Systemic corticosteroids (H02AB and H02BX)
- Antithrombotic and anticoagulant therapies (B01A)
- Heparins (B01AB)
- Lipid modifying agents (C10)
- Agents acting on the renin-angiotensin system (C09)
- Antineoplastic and immunomodulating agents (L)
- Tamoxifen (L02BA01)
- Sex hormones and modulators of the genital system (G03)
- Hormonal contraceptives for systemic use (G03A)
- Selective estrogen receptor modulators(G03XC)

9.3.2.3.2 Health conditions of interest

- History (anytime prior) of cardiovascular or thromboembolic risk factors: obesity, smoking status, alcohol drinking status, hypercholesterolemia, diabetes mellitus, end stage chronic kidney disease, heart failure; history of previous cardiovascular or thromboembolic events, and atherosclerosis.
- History (anytime prior) of medical conditions related to vaccination/priorities guidelines: cancer, organ transplantation, severe lung/respiratory conditions, pregnancy, immune deficiency, sickle cell disease, and Down's syndrome.
- Secondary causes of TTS/TE (any time prior): arterial/venous malformation, atrial fibrillation, polycythaemia, thrombophilia, antiphospholipid antibody syndrome, and systemic lupus erythematosus (where available).
- COVID-19 history including a diagnosis of COVID-19 or a positive test recorded before the first vaccine dose or index date.

9.3.2.4 Medications of interest for treating TTS

Medications of interest used for Objective 4 will be specified later and will be based on clinical guidelines. Here are the preliminary medications based on the COVID-19 vaccine-induced immune thrombocytopenia and thrombosis guideline produced by the British Society for Haematology[20].

- Systemic corticosteroids (H02AB and H02BX)
- Antithrombotic and anticoagulant therapies (B01A)
- Heparins (B01AB)
- Rituximab (L01XC)
- Fibrinogen (B02BB)
- IV immunoglobulin (J06B)
- Plasma exchange (B05AX)
- Platelet transfusion (B05AX)

9.3.3 Characteristics of study participants for Objective 1-2

Data-driven inclusion of characteristics included will be used. It means all demographics, diagnoses, procedures/medications will be explored if it is predictive of the treatment assignment through large-scale regularized regression. Below shows preliminary lists.

9.3.3.1 Demographics

Patients´ age at index date, sex, index month (the month of vaccination), socio-economic status (where available), ethnicity (where available) and community vs nursing home residence (where available) will be identified.

9.3.3.2 Diagnoses pre index date

The health conditions used are described in Section 9.3.2.3.1.

9.3.3.3 Medications/procedure use pre index date

The medications/procedures use described in Section 9.3.2.3.2 will be identified in the time period from 6 months prior to 4 days prior to the index date.

9.4 Data sources

Data will be obtained from five primary care, two outpatient, and one inpatient databases across six countries in Europe. In addition, one US claims and one large US hospital database will be accessed to maximise sample size and exposure to vaccines currently under-represented in European data e.g. Janssen and Spikevax. A summary of key features of the proposed data sources are reported in Table 1.

Table 1. Participanting databases

Database	Country	Active Size (2021)	Objective/s contributing	Key data available				
				COVID vaccine/s	Hospital treatments	Hospital outcome/s	Outpatient treatments	Plate-let counts
Primary care databases								
CPRD GOLD linked HES	UK	3.2m 360k with HES)[22]	1b,2b,3,4	I	No	Yes (HES linkage)	Yes	Yes
CPRD AURUM linked HES	UK	13m (almost all with HES)[23]	1a,1b,2a,2b,3,4	C	No	Yes (HES linkage)	Yes	Yes
RCGP RSC	UK	17m	1a,1b,2a,2b,3,4	C	No	I	Yes	Yes
SIDIAP with CMBD	ES	6m	1a,1b,1,2a,2b,3,4	C	No	Yes (CMBD linkage)	Yes	Yes
IPCI	NL	2m	1b*,2b*,3,4	I	No	I	Yes	Yes
Outpatient databases including primary care and ambulatory specialist data								
LPD France	FR	2.3m	3,4	I	No	I	Yes	Yes
DA Germany	DE	8.5m	1b*,2b*,3,4	I	No	I	Yes	Yes
Health claims database								
OpenClaims	US	187m	1b*,2b*,3,4	I	I	I	Yes	Yes
Hospital electronic medical records								
Hospital CDM	US	30m	3,4, 1b*,2b*	I	Yes	Yes	I	I
Parc Salut Mar	ES	1m	3,4	I	Yes	Yes	No	No

CPRD=Clinical Practice Research Datalink; HES= Hospital Episode Statistics; RCGP RSC = Oxford-Royal College of General Practitioners Research and Surveillance Centre; m = million; I = Incomplete coverage; C = Expected complete coverage; DA= Disease Analyzer; IPCI= Integrated Primary Care Information Project; SIDIAP = Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària; LPD = Longitudinal Patient Data; DA = Disease Analyzer; * on the condition that the database has sufficient power to detect minimal dateable relative risk (MDRR) <=5 for the relative risk estimation;

Specifically, for the countries where general practitioners act as gatekeepers to the system, primary care databases are best positioned to identify COVID-19 vaccines, and will include CPRD GOLD (UK), CPRD AURUM (UK), RCGP RSC (UK), IPCI (NL) and SIDIAP (ES). For countries where general practitioners do not act as gatekeepers to the system (France and Germany), outpatient records

(IQVIA DA France and Germany) including general practice and ambulatory specialist data will be used to identify vaccine exposure, outcomes and risk factors.

Vaccine exposure is complete (fully recorded) in **CPRD AURUM, RCGP, and SIDIAP**, and these will therefore be the primary sources of data for **Objectives 1a &2a** to minimise exposure misclassification in the 'unvaccinated'. In all other data sources, exposure to vaccines is incomplete because vaccine exposure information is not embedded into the system but can be obtained through a linkage to the databases, often with a delay in timing manner. This means lack of vaccine records does not imply unvaccinated status. However, the presence of a vaccine record is equivalent to vaccine administration. Therefore, these data sources will only contribute to the analysis of comparative safety (Objectives 1b and 2b).

LPD France data are excluded from these analyses due to challenges with the coding of venous thromboembolism (VTE) in this data source previously reported as part of our ongoing study[15].

Some databases have a subset linked to hospital data, providing richer information in the identification of these outcomes. In CPRD GOLD and AURUM, 11.3% and 99% of participants will have linked information from the Hospital Episode Statistics Admitted Patient Care (HES APC) database respectively; the whole SIDIAP has been linked to CMBD (*Conjunt Minim Basic de Dades a l'Alta Hospitalaria*), equivalent to HES APC, for this study. Currently, there is delay to link hospital data in CPRD; for example, the coverage of the latest HES APC data release only covers the data up to 30/Oct/2020, prior to the start date (01/Dec/2020) of our study time. SIDIAP currently has hospital data up to 30/Jun/2021.

In the scenario where there is the next HES data release in the next 3 months, we will be able to additionally conduct all the CPRD analyses in this linked subset. The sample size of this linked subset will be smaller and as well likely to have a shorter follow-up due to the differences in the coverage dates between CPRD and HES, however, it would have richer inpatients information to identify TTS, VTE and ATE.

All primary care, outpatient records databases (including LPD France) and US claim data will be used to define risk factors of post-vaccine TTS (**Objective 3).** Various data sources are required in order to identify comprehensive risk factors associated to post-vaccine TTS/VTE/ATE. LPD France is considered here despite of its low rates of TTS/VTE/ATE because of data from ambulatory specialist care on risk factors.

Inpatient hospital medical records obtained from Parc Salut Mar (ES) and Hospital CDM (US) will also be used for the study of inpatient treatments (Objective 4). Outpatient therapies for TTS/VTE/ATE will be obtained from US claims, primary care, and all other outpatient datasets (LPD France and DA Germany).

9.5 Study size

9.5.1. Power considerations for Objective 1 and 2

Figure 4 depicts the necessary sample size (Y axis) for different scenarios of effect size (RR) ranging from 2 to 5 (X axis for TTS) and from 1.1 to 2 (X axis for VTE&ATE), assuming 5% of alpha, at least 80% of power and 1:1 matching ratio (the worst-case scenario). The left figure provides the number of participants per arm needed for Objective 1 (TTS), with an expected background rate of 2.1/100,000 person-years, whilst the right figure provides the number per arm necessary for Objective 2 (VTE /ATE), with an expected background rate of 167/100,000 person-years. These rates have been obtained from our recent analyses [24]. We assume that the rates of TTS and VTE/ATE for persons vaccinated with Comirnaty will be same as the background rates in pre-COVID-19 time.

Figure 4. Necessary sample size (Y axis) according to expected RR (X axis) for the study of the association between vaccination and TTS (left) and VTE/ATE (right)

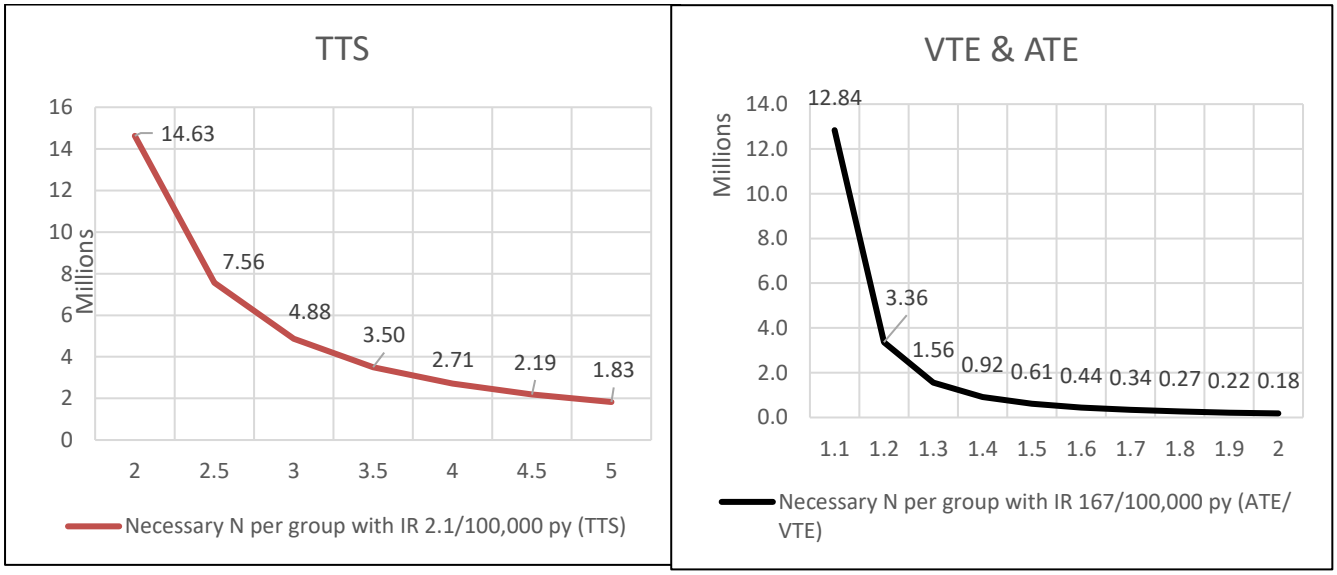


Table 2 shows the minimum detectable RR (MDRR) as significant by the sample size available for each comparison by database. We focus on primary analyses of any vaccine vs no vaccine (Objectives 1a and 2a) and of COVID-19 vaccine brand pairwise comparison (Objectives 1b and 2b). The text below provides further detail and justification.

Table 2 Minimum detectable RR (MDRR) for TTS and VTE/ATE, stratified by cohort and database

	Expected sample size for each analysis	PS cohort sample size (per group)	MDRR for TTS (Objective 1)	MDRR for VTE/ATE (Objective 2)
CPRD AURUM				
Vaccinated vs unvaccinated	9.1m vs 11.2m	9m	2.4	1.12
Fully vaccinated vs unvaccinated	4.6m vs 11.2m	4m	3.3	1.19
Vaxzevria vs Comirnaty	5.9m vs 3.2m	4.5m	3.1	1.18
CPRD GOLD				
Viral vector-based vs mRNA	975,000 vs 525,000	800,000	>5	1.45
ORCHID RCGP				
Vaccinated vs unvaccinated	5.4m vs 5.19m	5m	3.1	1.13
Fully vaccinated vs unvaccinated	2.7m vs 5.19m	2.5m	4.2	1.24
Vaxzevria vs Comirnaty	3.51m vs 1.89m	2m	4.8	1.27
SIDIAP				
Vaccinated vs unvaccinated	4m vs 4.9m	3.5	3.5	1.2
Fully vaccinated vs unvaccinated	4m vs 4.9m	3.5	3.5	1.2
Vaxzevria vs Comirnaty	750,000 vs 3.25m	750,000	>5	1.45
Open Claim				
Janseen vs Comirnaty	1.2m vs 8m	1.2m	>5	1.35
Janseen vs Spikevax	1.2m vs 5.7m	1.2m	>5	1.35

Note: at least 80% power and 5% alpha

CPRD AURUM includes over 13 million active patients and represents 20% of the current UK population. Our ongoing analyses show that 4.8million persons were exposed to any COVID-19 vaccine until end of March. By July (expected data extraction) we expect a 90% vaccine uptake in

the adult population, equivalent to a total of **9.1 million people exposed to at least one dose of any COVID-19 vaccine for Objectives 1, 2, and 3.** By using time-varying exposures, we estimate that >=80% of the vaccinated persons will also contribute (although for a short time) to the unvaccinated group (see Figure 2), in addition to those never vaccinated in the study period, making a total of **11.2 million in the unvaccinated group**. We assume about 9 million people will be propensity score matched per group.

The latest MHRA safety update report indicates a 16% and 84% of all vaccines administrated to be Comirnaty and Vaxzevria vaccines respectively[7]. We expect that by end of July, the proportion will change to 34:65 given recent restrictions in the vaccination of people <40 who are currently the focus of the vaccination campaign in the UK, making an estimated **3.1 and 5.9 million persons vaccinated with** Comirnaty **and** Vaxzevria **vaccines respectively**. Of whom, 4 million persons each group are assumed to be propensity score matched in the comparative safety analyses in Objectives 1b and 2b. The ONS vaccine statistics reports show that 1 in 3 doses given until April was a second dose. We assume that the number of persons fully vaccinated by July will increase to >50%, resulting in a total expected 4.6 million persons fully exposed to COVID-19 vaccines. We therefore assume that 4 million fully vaccinated people will be PS-matched to unvaccinated participants.

CPRD GOLD will be used for secondary analyses of comparative safety, but not for the primary, given the incompleteness of vaccine data in this database. Our feasibility counts indicate that 925,000 persons were exposed to any COVID-19 vaccine until May. We expect that the total number of vaccinated persons in CPRD GOLD will increase to 1.5m by July, of whom, **975,000 and 525,000 persons vaccinated with Vaxzevria and Comirnaty vaccines** respectively.

OXFORD-RCGP RSC contains primary care records for a total of 17 million people in England. Over 3 million people have been vaccinated until May, and about **5.4 million** are expected to be vaccinated by the date of data extraction, with vaccine brand exposure 65% viral **vector-based vaccines (3.51 million) and 35% mRNA (1.89 million)** as well as 50% **fully vaccinated (2.7 million)**.

SIDIAP contains records covering about 5.6 million adult residents in Catalonia, Spain. It is estimated that 70% of adults in Spain will be vaccinated by the study execution date in summer 2021. This is equivalent to **4 million vaccinated and 1.5 million unvaccinated people** available for analyses. By using time-varying exposure and assuming 85% of vaccinated persons we will be able to analyse a total of **4.9 million** (at least temporarily) unvaccinated persons. Based on conversations with regional authorities of Catalonia (Prof DPA is part of the vaccination campaign advisory committee of the Generalitat de Catalunya) we expect about **3.25 million and 750,000 people** will be identified as recipients of at least 1 dose of **Comirnaty and Vaxzevria vaccines** in SIDIAP, respectively. It is estimated that given the proposed vaccination regimens in Spain, most of the participants will be fully vaccinated by the time of study execution. Interestingly, younger Vaxzevria recipients (age <55) have recently been offered a heterologous regimen, with a second dose of Comirnaty vaccine. This will be of interest as a secondary analysis (see Exposure section – heterologous vaccination), but will only provide sufficient power for VTE/ATE (Objective 2), as only 250,000 people are expected in this group.

US open claim will be used for secondary analyses of comparative safety, but not for the primary, given the incompleteness of vaccine data in this database. It contains claims from a total of 187m persons. Over 14.3m persons who have received at least one dose of mRNA COVID-19 vaccine to date. We expect that the number of vaccinated persons will be increased to over 30 million. An estimated 56:40:4 ratio of Comirnaty, Spikevax and Janssen COVID-19 vaccines [25] we expect about 8million, 5.7million and 1.2 million persons receiving Comirnaty, Spikevax and Janssen vaccines, respectively.

No formal power calculation is available at this stage for the other data sources as uncertainty on number of vaccines available is still too high due to a lag in the coding of such vaccines in electronic medical records. Feasibility counts will be specified in the statistical analysis plan.

9.6 Data management

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

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

9.7 Data analysis

All analyses will be conducted in each of the databases that have sufficient power. In CPRD, analyses will be conducted separately in the entire database and in the subset with hospital linkage, as linked data is smaller in sample size and shorter in follow-up due to lags in hospital linkage availability.

9.7.1. Objectives 1 & 2- association between COVID-19 vaccines and TTS (1) and VTE/ATE (2)

Objectives 1a&2a will be addressed using two exposed cohorts in each of CPRD AURUM, RCGP, and SIDIAP databases: 1) vaccinated (1st vaccination); 2) fully vaccinated (2nd vaccination) which both will be matched to unvaccinated cohorts.

Unvaccinated includes both person-time contributed by those later vaccinated (i.e. temporarily unvaccinated) as well as those who - despite being comparable to vaccinated participants - did not receive the vaccine, as represented by PatID1, PatID2, PatID3 and PatID4 in Figure 1 (repeated on the next page).

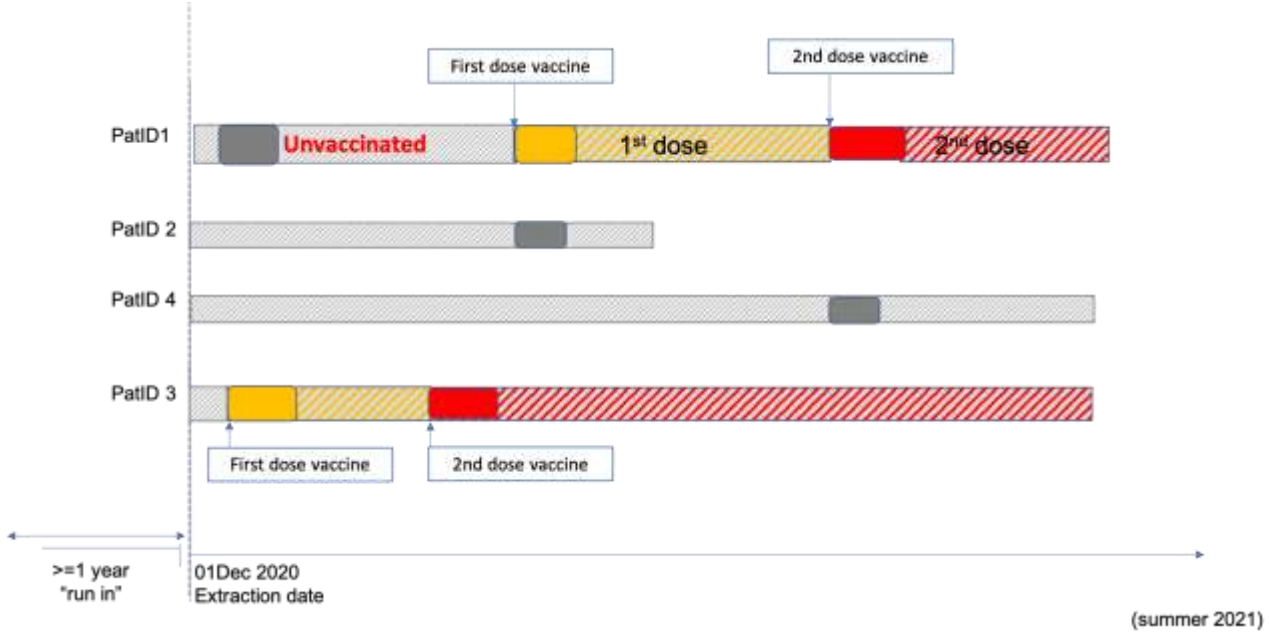
Objective 1b&2b (comparative safety) will be addressed by other cohorts in each of the database with sufficient power for a MDRR<=5: 1) pairs of vaccine brands; As shown in Table 2, we expect to have sufficient power to compare Vaxzevria vs Comirnaty vaccine in some databases such as CPRD AURUM, GOLD, RCGP and SIDIAP. In addition, we expect to compare Janssen vs Spikevax as well as Janssen vs Comirnaty in the US Open claim database if power permits. 2) heterologous (viral vector-based vaccine as 1st dose and mRNA as the 2nd dose) vs homologous (viral vector-based for both doses). These cohorts will be only built in Spanish, French, and German databases where heterologous vaccine schedule is recommended.

9.7.1.1 Propensity score analysis

For each person in a cohort, we will calculate propensity scores (PS) equivalent to their probability of being exposed to any vaccine or a particular vaccine brand, conditional on their baseline covariates using large-scale regularized regression[21].

In the primary cohorts (vaccinated vs unvaccinated), exposed people will be matched to unexposed ones at 1:*n* ratio without replacement based on the greedy PS with a maximum caliper of 0.2 SD_{ps}. As explained in Section 9.2.4.1and Figure 1 (repeated below), follow-up starts for vaccinated and unvaccinated peers on the same calendar date.

(Repeated) Figure 1. Diagram of study follow-up for Objective 1a-2b



9.7.1.2 Incidence rates

All the previously listed outcomes will be reported separately as n (%) and 95% confidence intervals amongst study participants in each of the proposed exposure groups and data sources described in Section9.4, and in -three time windows:

- In the 14 days following the index date
- In the 21 days following the index date
- In the 28 days following the index date

All incidence rates will be stratified by sex, 10-year age band, calendar month, and vaccine type/brand (only for Objective 1a and 2a where applicable).

9.7.1.3 Association between vaccine exposure and TTS (Objective 1) and VTE/ATE (Objective 2) risks

In each PS matched cohort, incidence rate ratio (IRR) (with 95% confidence interval) of each outcome listed above will be estimated using Poisson models. IRR will be the measure for relative risk (RR). We will also report IRR stratified by vaccine types, sex and 10-year age categories. For cohorts with 1st vaccination and 2nd vaccination, analyses will also be stratified by individual vaccine brand, regardless of whether subgroups have sufficient power for a MDRR of 5 and below. We will test for multiplicative interactions with COVID-19 history, and with relevant risk factors identified in Objective 3. Stratified RR will be reported if the interaction term has a p-value less than $p<0.1$.

Further stratification by brands will also be conducted as it will provide a vaccine brand specific RR regardless of whether or not power permitted. Stratified RR means that covariates differences between different vaccine brands are not taken into account. Therefore, formal comparative safety analyses (Objective 1b and 2b) will be conducted in some pairwise brand comparation with power permitted.

9.7.1.4 Accounting for unobserved (residual) confounding

Propensity scores account for measured confounders, but allegedly can fail to adjust for unmeasured (not registered) ones. Hence, we will use negative control outcomes, that are events not caused by the exposure of interest, to detect residual confounding. If there are more than 20% of negative control outcomes have statistically significant RR with an exposure, we will not report estimate from that cohort because it indicates we fail to account for residual confounding in that cohort.
If there are less than 20% of negative control outcomes with significant RRs with an exposure, we will attenuate residual confounding using the empirical calibration to estimate the true association with the outcomes of interests [26].If there are less than 20% of negative control outcomes with significant RRs with an exposure, we will attenuate residual confounding using the empirical calibration to estimate the true association with the outcomes of interests [26].

We have previously developed a list of 93 negative control outcomes not previously identified as safety signals for any known vaccine, and have used these for research on vaccine safety methods [27]. Appendix 5 shows the preliminary code list of these negative control outcomes.[27].

9.7.1.5 Obtaining an overall estimate of association/s with TTS (Objective 1) and VTE/ATE (Objective 2)

We will use a random effects meta-analysis to pool database-specific RRs. Where heterogeneity is high, defined as $I^2>40\%$, we will report database-specific effect estimates without meta-analysis.

9.7.1.6 Sensitivity analyses

Analyses will be repeated using different definitions as specified in the Section 9.3.1 & 9.3.2.

9.7.2 Objective 3.- Identification of key risk factors of VTE/ATE/TTS

In addition to the preliminary pre-specified list described in Section 9.3.3 with the exception of age, sex and calendar month, we will use large-scale regularized regression [21] to select additional potential risk factors. It means all diagnoses, drugs, measurements and medical procedures will be included in a large-scale regularized regression, and only characteristics that are predictive of the outcome, shown by having a beta >0, will be considered as risk factors.

Finally, Logistic regression models adjusted for age, sex and calendar month will be fitted to estimate the association between each of the pre-identified/data driven risk factors and 28-day VTE, ATE or TTS occurrence in the following proposed cohorts, stratified by database:

1. Persons who received at least one dose of vaccine (any brand).
2. Persons who completed full doses of vaccine (any brand).
3. Persons who received at least one dose of viral vector-based vaccines.
4. Persons who received at least one dose of mRNA vaccine.
5. Persons who completed full doses of viral vector-based vaccines.
6. Persons who completed full doses of mRNA vaccine.

Adjusted Odds Ratios (OR) and 95% Confidence Intervals will be reported for each of these models.

Note: no other risk factors will be included in the derivation of the adjusted OR for a risk factor apart from age, sex and calendar month because of statistical power concerns. However, we will explore the interaction between each of the risk factors and COVID-19 vaccine type in the risk factor-specific logistic regression.

9.7.2.1 Obtaining a pooled estimate of association

We will use a meta-analysis random effect model to pool individual ORs together. In the scenario where between-cohort heterogeneity is high, defined as I2>40%, we will report cohort-specific risk factor estimates separately.

9.7.2.2 Power considerations

Based on the rule of thumb of 1 (event):10 (variable), a minimum of 30 TTS events is required in a logistic regression with three covariates. Based on an approximate rate of 1 TTS event in 28 days per 100,000 vaccinees with Vaxzevria, we expect that only CPRD AURUM, Open Claim, SIDIAP, and ORCHID RCGP will have 30 or more events in the database and can contribute to risk identification for TTS. But, we expect all of the contributing databases specified in Section 9.4 will be able to contribute to VTE/ATE pre-vaccinated risk identification.

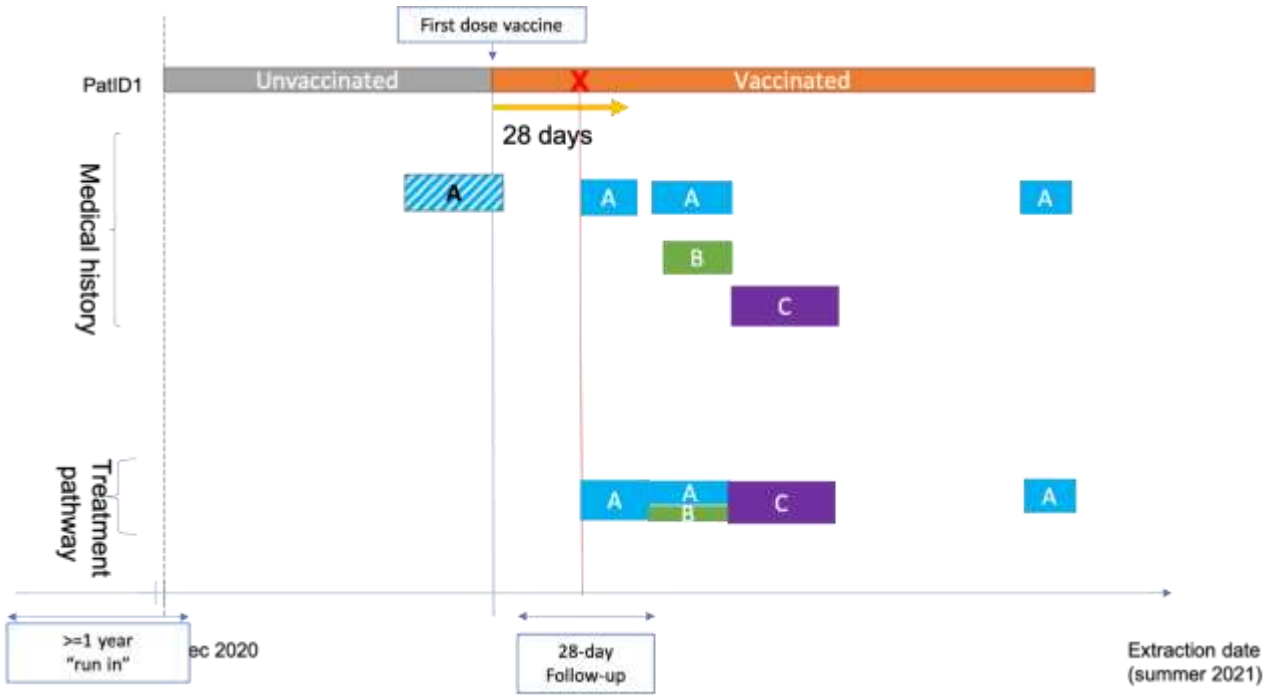
9.7.3 Objective 4.- Drug utilisation in patients with post-vaccine VTE/ATE/TTS

This objective will be addressed using primary care, outpatient databases and hospital electronic medical records separately.

We will use an existing analytical R tool (the R package of "TreatmentPatterns": https://github.com/mi-erasmusmc/TreatmentPatterns) to describe the treatment pathways among medications specified in Section 9.3.2.3 of patients diagnosed with VTE, ATE or TTS within 28 days of post-vaccination. Figure 4 below shows an example how a simple example patient's treatment history for drug A (blue bar), B (green bar), and C (purple bar) is constructed to a treatment pathway for this patient. PatID-1 first had drug A after the event of interest diagnosis for x days and moved to a combination of drug A and B for x days. This patient received drug C for x days. In X days, he restarted drug A.

Definitions of overlap for different treatments, multiple episodes of the same treatments as a continuous treatment will be defined in the statistical analysis plan.

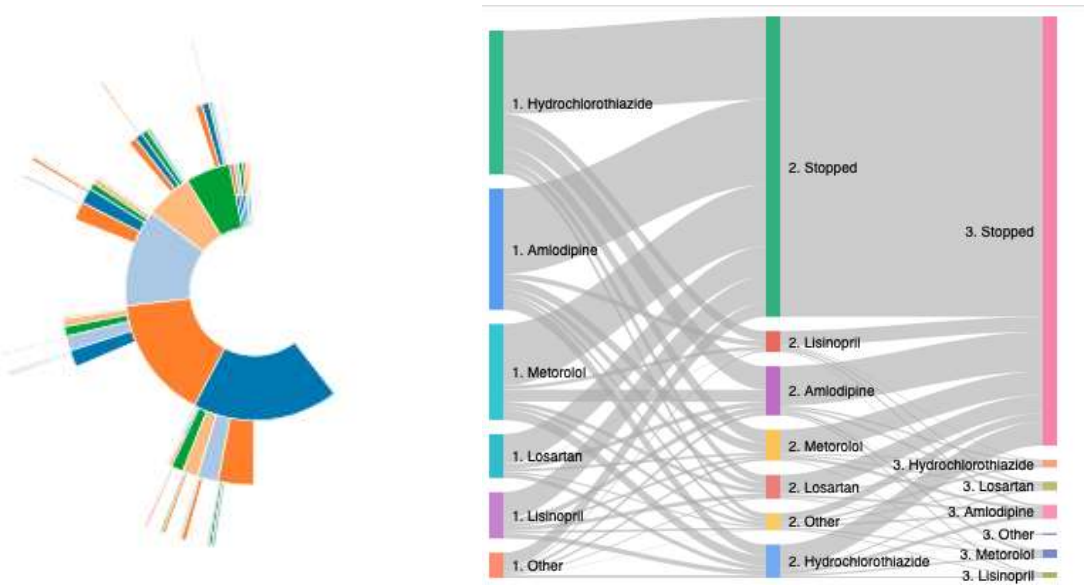
Figure 4. An illustrated example of medication histories for drug A, B and C and a treatment pathway for a patient.



All individual patients' treatment pathways will be visualised in the form of sunburst plots and Sankey diagrams. Figure 5 below shows an example of a sunburst plot (left) and a Sankey diagram (right). Sunburst plot shows the most prevalent therapies used in first (inner circle), second- and higher line (outer layers) treatments, defined in chronological order from the event of interest

diagnosis. The empty area in the circle indicates the proportion of patients with any treatment of interest. Sankey diagram shows that common treatment pathways for each of the 1st line therapy.

Figure 5- An example of Sunburst plot (left) and Sankey diagram (right) for 6 drugs.



If there are enough events of interest, >1000 counts, analyses will also be stratified by vaccine type/brand.

9.8 Quality control

9.8.1 General database quality control

A number of open-source quality control mechanisms for the OMOP CDM have been developed (see Chapter 15 of The Book of OHDSI http://book.ohdsi.org/DataQuality.html). In particular, it is expected that data partners will have run the OHDSI Data Quality Dashboard tool (https://github.com/OHDSI/DataQualityDashboard) . This tool provides a number of checks relating to the conformance, completeness and plausibility of the mapped data. Conformance focuses on checks that describe the compliance of the representation of data against internal or external formatting, relational, or computational definitions, completeness in the sense of data quality is solely focused on quantifying missingness, or the absence of data, while plausibility seeks to determine the believability or truthfulness of data values.[21] Each of these categories has one or more subcategories and are evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

9.8.2 Study-specific quality control

Each of the contributing databases will first run an OHDSI cohort diagnostics package (https://github.com/OHDSI/CohortDiagnostics) to identify the exposure cohorts described above. The results will include a summary of codes from the concept sets that are observed in the database and a summary of the concepts that led to entry into particular study cohorts. It also includes a check for ´orphan concepts´, concepts observed in the database that are not included in a concept set of a cohort but perhaps should have been. This will help to inform a consideration of the validity of the exposure cohorts in each of the databases. Subsequently, a cohort diagnostics package will be run to assess the identification of outcomes and patient features in an analogous manner.

In addition, we will use the following diagnostics for Objectives 1a, 1b, 2a and 2b. Failing in any of these will preclude the reporting of the associated treatment effect estimate:

1. Statistical power: No analyses will be conducted where the minimum detectable rate ratio (MDRR) is >5. In such cases, incidence rates will be reported, but no treatment effect estimate, relative risk, will be provided.
2. Covariate balance: as outlined above, we will explore all covariates before vs post-PS matching. Any covariates with an ASMD>0.1 after matching will be inspected and if considered a confounder, analyses not reported. This is to make sure two groups are comparable in terms of observed confounders.
3. Negative control outcomes: as detailed in previous sections, a large number of negative control outcomes will be analysed, and their association with vaccine/type reported. We will not report treatment effect estimates where >20% of the negative control outcomes remain associated with the exposure of interest after propensity score matching. Where <20% are associated, we will use empirical calibration to minimise the impact of residual confounding due to unobserved variables.

The analytic study package will then be run against each database. This package will be developed using best practices described in Chapter 17 of The Book of OHDSI (http://book.ohdsi.org/SoftwareValidity.html) and will be made publicly available via GitHub.

9.9 Limitations of the research methods

The main limitation of the proposed studies is the potential for confounding in the association studies in Objectives 1 and 2. We will use large-scale propensity scores and robust diagnostics to minimise the risk of residual confounding. Additionally, negative control outcomes and empirical calibration will be used to identify and -if necessary- account for unobserved confounding. Self-

controlled methods, usually preferred to minimise time-fixed confounding, were considered but are not proposed due to 3 reasons: 1. the events under interest are related to high mortality, that violates a SCCS assumption -exposure cannot increase the probability of death, 2. it is highly unlikely that occurrence of ATE/VTE/TTS after first dose will lead to second dose, as this is now a formal contraindication for the Vaxzevria vaccine, and 3. our preliminary characterisation work suggests that historical (pre-vaccine) TTS is a completely different clinical phenomenon compared to post-vaccine TTS (also known as vaccine-induced thrombosis with thrombocytopenia aka VITT).

A second limitation is related to information bias due to incompleteness of recording of exposure, risk factors and study events. We will conduct harmonization exercises and use data quality dashboards to minimize these issues in the contributing data sources. A number of sensitivity and secondary analyses are proposed to minimise the impact of such bias.
Practices that contribute to CPRD AURUM might also contribute to OXFORD-RCGP RSC (the percentage of overlapping is unknown).

In most analyses except for those conducted in CPRD AURUM and OXFORD-RCGP RSC, statistical power is limited for the analysis of TTS (Objective 1). A meta-analysis that combines estimates from different databases is deemed to improve statistical power and precision of the obtained estimates.

9.10 Other aspects

Not applicable

10 Protection of human subjects

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

All the databases used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to.

In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate non-identifiable aggregate summary results.

Regulatory and ethical compliance

Where required, Institutional Review Boards of the respective databases and ethics committees will review the protocol of the study.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology, the relevant guideline, for example, STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) and RECORD-PE (Reporting of studies Conducted using Observational Routinely collected health, specific to PharmacoEpidemiological research), and with the ethical principles laid down in the Declaration of Helsinki.

This study follows the ‘European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct’.

11 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).

12 Plans for disseminating and communicating study results

All timelines for the deliverables are proposed based on the tender specification document.

12.1 Deliverable 1- Study Plan

A study plan will be prepared in the first month of the project (July 2021), to include:

- A study outline including a preliminary study protocol for all the proposed objectives

12.2 Deliverable 2 - Protocol Development

The draft study protocol will be written by the principal investigators following the Guidelines on Good Pharmacovigilance Practices [28] and using the format described in GVP Module VIII In addition to the standard sections requested in section VIII.B.3.1, detail will be provided on:[28]

1. Minimum detectable RR (MDRR) available for each of the Objectives.
2. Minimum set of required variables of interest and types of stratified analyses;
3. Detailed statistical analysis plan, including sensitivity analyses, use of matching variables, proposed algorithms for propensity score estimation. Again, preliminary plans are outlined in previous sections of this application, to be refined based on feasibility figures and input from EMA scientists.
4. Proposal for approaches to mitigate study limitations, including sensitivity analyses and plans to detect and minimise residual confounding. Although already outlined in previous sections, this will be detailed further based on the information available in the proposed databases.
5. A bespoke section detailing the plans for the proposed proof-of concept study (Objective 5).

The draft protocol will be reviewed by the whole study team including database stewards. The resulting study protocol will be sent to EMA for review and feedback during the second month of the study (August 2021). Changes as suggested by EMA will be incorporated and the principal investigators will register the protocol in the EU PAS register[5] and in the EMA database of COVID-19 observational studies.

12.3 Deliverable 3 – Statistical Analysis Plan (SAP)

A bespoke SAP will be prepared by the senior statisticians and epidemiologists in the team, to include details on the proposed analyses and table shells and proposed figures to appear in the study report and/or manuscript/s. The SAP will be submitted by the third month of the study (September 2021).

12.4 Deliverable 4 – Final Report

The final study report will be prepared in accordance with the Guidelines on Good Pharmacovigilance Practice – Module 8. All analytical code related to the generation of tables and figures for this report will be available to the agency in an open repository (eg GitHub). A data steward will be named for each contributing institution, with access to the harmonised data used for

the analyses. Both the analytical code and analysed data will be available to the Agency upon request as per ENCePP guidance on data access (link).

The draft study report will first be reviewed by the study team and updated if needed. This updated draft study report will then be sent to EMA during month 6 (December 2021). Feedback from EMA will be incorporated in the final study report. Upon finalisation, the final study report will also be uploaded to the ENCePP EU-PAS registry.

12.5 Deliverable 5 – Proof-of-Concept Study Report

The results from Objective 5.1, 5.2, and 5.3 will be detailed in a bespoke report. This report will have a format as similar as possible to that proposed for the main study Final Report (Deliverable 4). Deliverable 5 will be sent to EMA during month 7 (January 2022) and once approved uploaded to the EU PAS Registry.

12.6 Deliverable 6 – Manuscript

The Principal Investigators and dedicated clinical epidemiologists will be responsible for drafting the manuscript according to STROBE and RECORD-PE guidelines. The study team will review the draft manuscript, and guidelines as adopted by the International Committee of Medical Journal Editors will be applied to decide on authorship.

A draft manuscript will be submitted to EMA during month 8 (February 2022) for review and feedback. The manuscript will be amended, finalised and submitted to a top-ranked Open Access journal. While awaiting feedback from peer reviewers, the manuscript will also be uploaded to MedRXiv

13 References

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Annex 1. List of stand-alone documents

None

Annex 2. ENCePP checklist for study protocols

Annex 3. Concept set for persons vaccinated against SARS-CoV-2

Please note, these concept sets will be updated as and when the OHDSI vocabularies are updated. Excluded indicates that the related codes will not be used in the definition, while descendants indicates whether terms below the code in the hierarchy will be included in the definition. (Please see https://ohdsi.github.io/TheBookOfOhdsi/Cohorts.html#conceptSets for more details on how these concept sets are operationalised).

Sub concept sets for each type as well as brand of COVID-19 vaccine will be created from the relevant concept ID below.

Concept ID	Name	Vocabulary
59267100003	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension	NDC
59267100002	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension	NDC
592671000	bnt162b2 .23mg/1.8mL INTRAMUSCULAR INJECTION, SUSPENSION	NDC
80777027310	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML Injectable Suspension	NDC
2470234	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML Injectable Suspension	RxNorm
2470233	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML	RxNorm
2470232	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273	RxNorm
2468235	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension	RxNorm
2468234	SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein Injectable Suspension	RxNorm
2468233	SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein Injectable Product	RxNorm
2468232	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML	RxNorm
2468231	SARS-CoV-2 (COVID-19) vaccine, mRNA spike protein	RxNorm
2468230	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2	RxNorm
80777027399	SARS-CoV-2 (COVID-19) vaccine, mRNA-1273 0.2 MG/ML Injectable Suspension	NDC
807770273	cx-024414 .2mg/mL INTRAMUSCULAR INJECTION, SUSPENSION	NDC
39214411000001100	Generic COVID-19 mRNA Vaccine BNT162b2 30micrograms/0.3ml dose concentrate for suspension for injection multidose vials (Pfizer-BioNTech) 1170 dose	dm+d
39326611000001100	Generic COVID-19 mRNA (nucleoside modified) Vaccine Moderna 0.1mg/0.5mL dose dispersion for injection multidose vials 100 dose	dm+d
39326811000001100	Generic COVID-19 mRNA (nucleoside modified) Vaccine Moderna 0.1mg/0.5mL dose dispersion for injection multidose vials	dm+d

Concept ID	Name	Vocabulary
39214511000001100	COVID-19 mRNA Vaccine BNT162b2 30micrograms/0.3ml dose concentrate for suspension for injection multidose vials (Pfizer-BioNTech) (Pfizer-BioNTech) 1170 dose 195 x 6 dose vials	dm+d
39327011000001100	COVID-19 mRNA (nucleoside modified) Vaccine Moderna 0.1mg/0.5mL dose dispersion for injection multidose vials (Moderna, Inc) 100 dose 10 x 10 dose vials	dm+d
39326911000001100	COVID-19 mRNA (nucleoside modified) Vaccine Moderna 0.1mg/0.5mL dose dispersion for injection multidose vials	dm+d
39115611000001100	COVID-19 mRNA Vaccine BNT162b2 30micrograms/0.3ml dose concentrate for suspension for injection multidose vials (Pfizer-BioNTech)	dm+d
39115311000001100	Generic COVID-19 mRNA Vaccine BNT162b2 30micrograms/0.3ml dose concentrate for suspension for injection multidose vials (Pfizer-BioNTech) 6 dose	dm+d
39115711000001100	COVID-19 mRNA Vaccine BNT162b2 30micrograms/0.3ml dose concentrate for suspension for injection multidose vials (Pfizer-BioNTech) (Pfizer-BioNTech) 6 dose	dm+d
39116111000001100	Generic COVID-19 mRNA Vaccine BNT162b2 30micrograms/0.3ml dose concentrate for suspension for injection multidose vials (Pfizer-BioNTech)	dm+d
59676058005	Janssen COVID-19 vaccine, DNA, spike protein, adenovirus type 26 (Ad26) vector, preservative free, 5x1010 viral particles/0.5mL dosage, for intramuscular use	NDC
310122210	AZD1222 Astrazeneca COVID-19 vaccine, DNA, spike protein, chimpanzee adenovirus Oxford 1 (ChAdOx1) vector, preservative free, 5x1010 viral particles/0.5mL dosage, for intramuscular use	NDC
310122215	azd1222 50000000000[VP]/.5mL INTRAMUSCULAR INJECTION, SUSPENSION	NDC
59267100001	SARS-CoV-2 (COVID-19) vaccine, mRNA-BNT162b2 0.1 MG/ML Injectable Suspension	NDC
91303	Janssen Covid-19 Vaccine	CPT4
91302	AstraZeneca Covid-19 Vaccine	CPT4
91301	Moderna Covid-19 Vaccine	CPT4
91300	Pfizer-Biontech Covid-19 Vaccine	CPT4
0022A	AstraZeneca Covid-19 Vaccine Administration - Second Dose	CPT4
0021A	AstraZeneca Covid-19 Vaccine Administration - First Dose	CPT4
0031A	Janssen Covid-19 Vaccine Administration	CPT4
0012A	Moderna Covid-19 Vaccine Administration - Second Dose	CPT4
0011A	Moderna Covid-19 Vaccine Administration - First Dose	CPT4
0002A	Pfizer-Biontech Covid-19 Vaccine Administration - Second Dose	CPT4
0001A	Pfizer-Biontech Covid-19 Vaccine Administration - First Dose	CPT4
208	SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 30 mcg/0.3mL dose	CVX
207	SARS-COV-2 (COVID-19) vaccine, mRNA, spike protein, LNP, preservative free, 100 mcg/0.5mL dose	CVX

Concept ID	Name	Vocabulary
210	SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-ChAdOx1, preservative free, 0.5 mL	CVX
212	SARS-COV-2 (COVID-19) vaccine, vector non-replicating, recombinant spike protein-Ad26, preservative free, 0.5 mL	CVX

Annex 4. Preliminary lists of included concepts for study outcomes

Please note, these concept set will be updated as and when the OHDSI vocabularies are updated. Excluded indicates that the related codes will not be used in the definition, while descendants indicates whether terms below the code in the hierarchy will be included in the definition. (Please see https://ohdsi.github.io/TheBookOfOhdsi/Cohorts.html#conceptSets for more details on how these concept sets are operationalised).

A4.1. Cerebral venous sinus thrombosis (CVST)

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4102202	Cerebral venous sinus thrombosis	SNOMED	FALSE	FALSE
4048786	Cerebral venous thrombosis of sigmoid sinus	SNOMED	FALSE	FALSE
4043735	Cerebral venous thrombosis of straight sinus	SNOMED	FALSE	FALSE
4111713	Non-pyogenic venous sinus thrombosis	SNOMED	FALSE	FALSE
314667	Nonpyogenic thrombosis of intracranial venous sinus	SNOMED	FALSE	FALSE
4116206	Septic thrombophlebitis of cavernous sinus	SNOMED	FALSE	FALSE
4121335	Septic thrombophlebitis of lateral sinus	SNOMED	FALSE	FALSE
4119136	Septic thrombophlebitis of sagittal sinus	SNOMED	FALSE	FALSE
4041680	Septic thrombophlebitis of sigmoid sinus	SNOMED	FALSE	FALSE
4100225	Thrombophlebitis lateral venous sinus	SNOMED	FALSE	FALSE
4217471	Thrombophlebitis of basilar sinus	SNOMED	FALSE	FALSE
4104695	Thrombophlebitis of cavernous sinus	SNOMED	FALSE	FALSE
4167985	Thrombophlebitis of inferior sagittal sinus	SNOMED	FALSE	FALSE
764714	Thrombophlebitis of sigmoid sinus	SNOMED	FALSE	FALSE
4100224	Thrombophlebitis of superior longitudinal venous sinus	SNOMED	FALSE	FALSE
4098706	Thrombophlebitis of superior sagittal sinus	SNOMED	FALSE	FALSE
4277833	Thrombophlebitis of torcular Herophili	SNOMED	FALSE	FALSE
764710	Thrombophlebitis of transverse sinus	SNOMED	FALSE	FALSE
4228209	Thrombosis of basilar sinus	SNOMED	FALSE	FALSE
4234264	Thrombosis of cavernous venous sinus	SNOMED	FALSE	FALSE
4048890	Thrombosis of inferior sagittal sinus	SNOMED	FALSE	FALSE
4057329	Thrombosis of lateral venous sinus	SNOMED	FALSE	FALSE
4102203	Thrombosis of superior longitudinal sinus	SNOMED	FALSE	FALSE
4290940	Thrombosis of superior sagittal sinus	SNOMED	FALSE	FALSE
4079905	Thrombosis of torcular Herophili	SNOMED	FALSE	FALSE

4105338	Thrombosis transverse sinus	SNOMED	FALSE	FALSE

A4.2. Deep vein thrombosis – narrow

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
762047	Acute bilateral thrombosis of subclavian veins	SNOMED	FALSE	FALSE
762148	Acute deep vein thrombosis of bilateral iliac veins	SNOMED	FALSE	FALSE
761444	Acute deep vein thrombosis of bilateral lower limbs following coronary artery bypass graft	SNOMED	FALSE	FALSE
35616028	Acute deep vein thrombosis of left iliac vein	SNOMED	FALSE	FALSE
35615035	Acute deep vein thrombosis of left lower limb following procedure	SNOMED	FALSE	FALSE
761416	Acute deep vein thrombosis of left upper limb following coronary artery bypass graft	SNOMED	FALSE	FALSE
35615031	Acute deep vein thrombosis of left upper limb following procedure	SNOMED	FALSE	FALSE
43531681	Acute deep vein thrombosis of lower limb	SNOMED	FALSE	FALSE
35616027	Acute deep vein thrombosis of right iliac vein	SNOMED	FALSE	FALSE
35615034	Acute deep vein thrombosis of right lower limb following procedure	SNOMED	FALSE	FALSE
761415	Acute deep vein thrombosis of right upper limb following coronary artery bypass graft	SNOMED	FALSE	FALSE
35615030	Acute deep vein thrombosis of right upper limb following procedure	SNOMED	FALSE	FALSE
44782746	Acute deep venous thrombosis	SNOMED	FALSE	FALSE
44782751	Acute deep venous thrombosis of axillary vein	SNOMED	FALSE	FALSE
762008	Acute deep venous thrombosis of bilateral axillary veins	SNOMED	FALSE	FALSE
760875	Acute deep venous thrombosis of bilateral calves	SNOMED	FALSE	FALSE
765155	Acute deep venous thrombosis of bilateral ileofemoral veins	SNOMED	FALSE	FALSE
762017	Acute deep venous thrombosis of bilateral internal jugular veins	SNOMED	FALSE	FALSE
762417	Acute deep venous thrombosis of bilateral legs	SNOMED	FALSE	FALSE
762020	Acute deep venous thrombosis of bilateral popliteal veins	SNOMED	FALSE	FALSE
765546	Acute deep venous thrombosis of bilateral tibial veins	SNOMED	FALSE	FALSE
762004	Acute deep venous thrombosis of both upper extremities	SNOMED	FALSE	FALSE
44782742	Acute deep venous thrombosis of calf	SNOMED	FALSE	FALSE
44782747	Acute deep venous thrombosis of femoral vein	SNOMED	FALSE	FALSE
762015	Acute deep venous thrombosis of ileofemoral vein of left leg	SNOMED	FALSE	FALSE
765541	Acute deep venous thrombosis of ileofemoral vein of right lower extremity	SNOMED	FALSE	FALSE
44782748	Acute deep venous thrombosis of iliofemoral vein	SNOMED	FALSE	FALSE
44782752	Acute deep venous thrombosis of internal jugular vein	SNOMED	FALSE	FALSE
762009	Acute deep venous thrombosis of left axillary vein	SNOMED	FALSE	FALSE
760876	Acute deep venous thrombosis of left calf	SNOMED	FALSE	FALSE
765540	Acute deep venous thrombosis of left femoral vein	SNOMED	FALSE	FALSE
765922	Acute deep venous thrombosis of left internal jugular vein	SNOMED	FALSE	FALSE
762418	Acute deep venous thrombosis of left lower extremity	SNOMED	FALSE	FALSE

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
765537	Acute deep venous thrombosis of left upper extremity	SNOMED	FALSE	FALSE
44782767	Acute deep venous thrombosis of lower extremity as complication of procedure	SNOMED	FALSE	FALSE
46270071	Acute deep venous thrombosis of lower limb due to coronary artery bypass grafting	SNOMED	FALSE	FALSE
762022	Acute deep venous thrombosis of politeal vein of right leg	SNOMED	FALSE	FALSE
44782743	Acute deep venous thrombosis of popliteal vein	SNOMED	FALSE	FALSE
762021	Acute deep venous thrombosis of popliteal vein of left leg	SNOMED	FALSE	FALSE
762010	Acute deep venous thrombosis of right axillary vein	SNOMED	FALSE	FALSE
760877	Acute deep venous thrombosis of right calf	SNOMED	FALSE	FALSE
762013	Acute deep venous thrombosis of right femoral vein	SNOMED	FALSE	FALSE
762018	Acute deep venous thrombosis of right internal jugular vein	SNOMED	FALSE	FALSE
762419	Acute deep venous thrombosis of right lower extremity	SNOMED	FALSE	FALSE
762005	Acute deep venous thrombosis of right upper extremity	SNOMED	FALSE	FALSE
44782745	Acute deep venous thrombosis of thigh	SNOMED	FALSE	FALSE
44782744	Acute deep venous thrombosis of tibial vein	SNOMED	FALSE	FALSE
762026	Acute deep venous thrombosis of tibial vein of left leg	SNOMED	FALSE	FALSE
765156	Acute deep venous thrombosis of tibial vein of right leg	SNOMED	FALSE	FALSE
44782421	Acute deep venous thrombosis of upper extremity	SNOMED	FALSE	FALSE
764016	Acute deep venous thrombosis of upper extremity after coronary artery bypass graft	SNOMED	FALSE	FALSE
44782766	Acute deep venous thrombosis of upper extremity as complication of procedure	SNOMED	FALSE	FALSE
762048	Acute thrombosis of left subclavian vein	SNOMED	FALSE	FALSE
45757410	Acute thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
762049	Acute thrombosis of right subclavian vein	SNOMED	FALSE	FALSE
36712892	Acute thrombosis of splenic vein	SNOMED	FALSE	FALSE
44782762	Acute thrombosis of subclavian vein	SNOMED	FALSE	FALSE
37109253	Bilateral acute deep vein thrombosis of femoral veins	SNOMED	FALSE	FALSE
40478951	Bilateral deep vein thrombosis of lower extremities	SNOMED	FALSE	FALSE
4046884	Deep vein thrombosis of leg related to air travel	SNOMED	FALSE	FALSE
4133004	Deep venous thrombosis	SNOMED	FALSE	FALSE
4181315	Deep venous thrombosis associated with coronary artery bypass graft	SNOMED	FALSE	FALSE
45773536	Deep venous thrombosis of femoropopliteal vein	SNOMED	FALSE	FALSE
763942	Deep venous thrombosis of left lower extremity	SNOMED	FALSE	FALSE
761980	Deep venous thrombosis of left upper extremity	SNOMED	FALSE	FALSE
443537	Deep venous thrombosis of lower extremity	SNOMED	FALSE	FALSE
4133975	Deep venous thrombosis of pelvic vein	SNOMED	FALSE	FALSE
40480555	Deep venous thrombosis of peroneal vein	SNOMED	FALSE	FALSE
4322565	Deep venous thrombosis of profunda femoris vein	SNOMED	FALSE	FALSE
763941	Deep venous thrombosis of right lower extremity	SNOMED	FALSE	FALSE
761928	Deep venous thrombosis of right upper extremity	SNOMED	FALSE	FALSE

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4207899	Deep venous thrombosis of tibial vein	SNOMED	FALSE	FALSE
4028057	Deep venous thrombosis of upper extremity	SNOMED	FALSE	FALSE
193512	Embolism and thrombosis of the renal vein	SNOMED	FALSE	FALSE
435565	Embolism and thrombosis of the vena cava	SNOMED	FALSE	FALSE
4119760	Iliofemoral deep vein thrombosis	SNOMED	FALSE	FALSE
4124856	Inferior mesenteric vein thrombosis	SNOMED	FALSE	FALSE
4281689	Phlegmasia alba dolens	SNOMED	FALSE	FALSE
4284538	Phlegmasia cerulea dolens	SNOMED	FALSE	FALSE
4309333	Postoperative deep vein thrombosis	SNOMED	FALSE	FALSE
46285905	Provoked deep vein thrombosis	SNOMED	FALSE	FALSE
4033521	Splenic vein thrombosis	SNOMED	FALSE	FALSE
4055089	Superior mesenteric vein thrombosis	SNOMED	FALSE	FALSE
42538533	Thrombosis of iliac vein	SNOMED	FALSE	FALSE
44811347	Thrombosis of internal jugular vein	SNOMED	FALSE	FALSE
765049	Thrombosis of left peroneal vein	SNOMED	FALSE	FALSE
4317289	Thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
4203836	Thrombosis of subclavian vein	SNOMED	FALSE	FALSE
4175649	Thrombosis of the popliteal vein	SNOMED	FALSE	FALSE
4153353	Traumatic thrombosis of axillary vein	SNOMED	FALSE	FALSE
46285904	Unprovoked deep vein thrombosis	SNOMED	FALSE	FALSE
4221821	Thrombophlebitis of deep veins of lower extremity	SNOMED	FALSE	FALSE
46271900	Recurrent deep vein thrombosis	SNOMED	FALSE	FALSE
4189004	Deep vein thrombosis of leg related to intravenous drug use	SNOMED	FALSE	FALSE

A4.3. SVT

- **Splenic vein thrombosis**

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4033521	Splenic vein thrombosis	SNOMED	FALSE	FALSE
36712892	Acute thrombosis of splenic vein	SNOMED	FALSE	FALSE

- **Splanchnic Vein Thrombosis**

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4033521	Splenic vein thrombosis	SNOMED	FALSE	FALSE

196715	Budd-Chiari syndrome	SNOMED	FALSE	FALSE
199837	Portal vein thrombosis	SNOMED	FALSE	FALSE
4317289	Thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
4092406	Portal thrombophlebitis	SNOMED	FALSE	FALSE
36712892	Acute thrombosis of splenic vein	SNOMED	FALSE	FALSE
4173167	Mesenteric embolus	SNOMED	FALSE	FALSE
4144032	Mesenteric thrombus and/or embolus	SNOMED	FALSE	FALSE
45757410	Acute thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
45757409	Chronic thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
4318407	Thrombophlebitis of mesenteric vein	SNOMED	FALSE	FALSE
4124856	Inferior mesenteric vein thrombosis	SNOMED	FALSE	FALSE
4055089	Superior mesenteric vein thrombosis	SNOMED	FALSE	FALSE

- **Portal vein thrombosis**

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
199837	Portal vein thrombosis	SNOMED	FALSE	FALSE

- **Mesenteric vein thrombosis**

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
36717492	Acute occlusion of mesenteric vein	SNOMED	FALSE	FALSE
45757410	Acute thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
4124856	Inferior mesenteric vein thrombosis	SNOMED	FALSE	FALSE
4055089	Superior mesenteric vein thrombosis	SNOMED	FALSE	FALSE
4317289	Thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
45757409	Chronic thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
4318407	Thrombophlebitis of mesenteric vein	SNOMED	FALSE	FALSE
4173167	Mesenteric embolus	SNOMED	FALSE	FALSE
4144032	Mesenteric thrombus and/or embolus	SNOMED	FALSE	FALSE

- **Visceral venous thrombosis or obstruction**

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
36717492	Acute occlusion of mesenteric vein	SNOMED	FALSE	FALSE
36712892	Acute thrombosis of splenic vein	SNOMED	FALSE	FALSE
196715	Budd-Chiari syndrome	SNOMED	FALSE	FALSE
35624285	Complete obstruction of hepatic portal vein	SNOMED	FALSE	FALSE
4301208	Hepatic vein thrombosis	SNOMED	FALSE	FALSE
37110194	Hepatic veno-occlusive disease with immunodeficiency syndrome	SNOMED	FALSE	FALSE
37109927	Obstruction of visceral vein	SNOMED	FALSE	FALSE
4238060	Portal vein obstruction	SNOMED	FALSE	FALSE
4033521	Splenic vein thrombosis	SNOMED	FALSE	FALSE
4277276	Veno-occlusive disease of the liver	SNOMED	FALSE	FALSE
37111372	Visceral venous thrombosis	SNOMED	FALSE	FALSE
36712891	Chronic thrombosis of splenic vein	SNOMED	FALSE	FALSE

A4.4. Pulmonary embolism

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4120091	Acute massive pulmonary embolism	SNOMED	FALSE	FALSE
45768439	Acute pulmonary embolism	SNOMED	FALSE	FALSE
45768888	Acute pulmonary thromboembolism	SNOMED	FALSE	FALSE
4309039	Hemorrhagic pulmonary infarction	SNOMED	FALSE	FALSE
762808	Infarction of lung due to embolus	SNOMED	FALSE	FALSE
40480461	Infarction of lung due to iatrogenic pulmonary embolism	SNOMED	FALSE	FALSE
4108681	Postoperative pulmonary embolus	SNOMED	FALSE	FALSE
4091708	Pulmonary air embolism	SNOMED	FALSE	FALSE
440417	Pulmonary embolism	SNOMED	FALSE	FALSE
37109911	Pulmonary embolism due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
37016922	Pulmonary embolism on long-term anticoagulation therapy	SNOMED	FALSE	FALSE
43530605	Pulmonary embolism with pulmonary infarction	SNOMED	FALSE	FALSE
4119608	Pulmonary fat embolism	SNOMED	FALSE	FALSE
254662	Pulmonary infarction	SNOMED	FALSE	FALSE
4253796	Pulmonary microemboli	SNOMED	FALSE	FALSE
45766471	Pulmonary oil microembolism	SNOMED	FALSE	FALSE
4121618	Pulmonary thromboembolism	SNOMED	FALSE	FALSE
4119610	Pulmonary tumor embolism	SNOMED	FALSE	FALSE
4119607	Subacute massive pulmonary embolism	SNOMED	FALSE	FALSE
4119609	Subacute pulmonary fat embolism	SNOMED	FALSE	FALSE
4236271	Recurrent pulmonary embolism	SNOMED	FALSE	FALSE

A4.5. Thrombocytopenia

- Platelet measurement

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
3007461	Platelets [#/volume] in Blood	LOINC	FALSE	TRUE
3031586	Platelets [#/volume] in Blood by Estimate	LOINC	FALSE	TRUE
3024929	Platelets [#/volume] in Blood by Automated count	LOINC	FALSE	TRUE
3039827	Platelets [#/volume] in Body fluid by Automated count	LOINC	FALSE	TRUE
3024386	Platelet mean volume [Entitic volume] in Blood by Rees-Ecker	LOINC	FALSE	TRUE
4267147	Platelet count	SNOMED	FALSE	TRUE
37393863	Platelet count	SNOMED	FALSE	TRUE

- Thrombocytopenia diagnosis

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
37397537	Beta thalassemia X-linked thrombocytopenia syndrome	SNOMED	FALSE	FALSE
432870	Thrombocytopenic disorder	SNOMED	FALSE	FALSE
46272950	Thrombocytopathy, asplenia and miosis	SNOMED	FALSE	FALSE
44782445	Thrombocytopenia due to alcohol	SNOMED	FALSE	FALSE
42536958	Pancytopenia caused by medication	SNOMED	FALSE	FALSE
40321716	Secondary thrombocytopenia	SNOMED	FALSE	FALSE
37312165	Atypical hemolytic uremic syndrome	SNOMED	FALSE	FALSE
37209558	Pancytopenia caused by immunosuppressant	SNOMED	FALSE	FALSE
37204551	Hereditary isolated aplastic anemia	SNOMED	FALSE	FALSE
37204548	Hereditary thrombocytopenia with normal platelets	SNOMED	FALSE	FALSE
37204520	Bleeding diathesis due to thromboxane synthesis deficiency	SNOMED	FALSE	FALSE
37204478	Pancytopenia due to IKZF1 mutations	SNOMED	FALSE	FALSE
37117164	Revesz syndrome	SNOMED	FALSE	FALSE
37116398	Thyrocerebrorenal syndrome	SNOMED	FALSE	FALSE
37110394	Isolated thrombocytopenia	SNOMED	FALSE	FALSE
37019055	Aplastic anemia co-occurrent with human immunodeficiency virus infection	SNOMED	FALSE	FALSE
37018663	Thrombocytopenia co-occurrent and due to alcoholism	SNOMED	FALSE	FALSE
37017607	Antibody mediated acquired pure red cell aplasia caused by erythropoiesis stimulating agent	SNOMED	FALSE	FALSE
37017165	GATA binding protein 1 related thrombocytopenia with dyserythropoiesis	SNOMED	FALSE	FALSE
37016797	MYH9 related disease	SNOMED	FALSE	FALSE
37016151	Aplastic anemia caused by antineoplastic agent	SNOMED	FALSE	FALSE
36717326	DK phocomelia syndrome	SNOMED	FALSE	FALSE
36716406	Severe fever with thrombocytopenia syndrome virus	SNOMED	FALSE	FALSE
36716047	Radioulnar synostosis with amegakaryocytic thrombocytopenia syndrome	SNOMED	FALSE	FALSE
36715586	Refractory thrombocytopenia	SNOMED	FALSE	FALSE
36715053	Autosomal dominant macrothrombocytopenia	SNOMED	FALSE	FALSE
36713970	WT limb blood syndrome	SNOMED	FALSE	FALSE
36713443	MYH9 macrothrombocytopenia syndrome	SNOMED	FALSE	FALSE
36713112	Pancytopenia due to antineoplastic chemotherapy	SNOMED	FALSE	FALSE
36674972	Macrothrombocytopenia with mitral valve insufficiency	SNOMED	FALSE	FALSE
36674474	Pancytopenia with developmental delay syndrome	SNOMED	FALSE	FALSE
35625536	Ataxia pancytopenia syndrome	SNOMED	FALSE	FALSE
35623407	Adult pure red cell aplasia	SNOMED	FALSE	FALSE
4345236	Parvoviral aplastic crisis	SNOMED	FALSE	FALSE
4338386	Thrombocytopenia due to non-immune destruction	SNOMED	FALSE	FALSE
4316372	HELLP syndrome	SNOMED	FALSE	FALSE

4314802	Kasabach-Merritt syndrome	SNOMED	FALSE	FALSE
4311682	Radial aplasia-thrombocytopenia syndrome	SNOMED	FALSE	FALSE
4305588	Doan-Wright syndrome	SNOMED	FALSE	FALSE
4301602	Thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4301128	Thrombocytopenia due to diminished platelet production	SNOMED	FALSE	FALSE
4300464	Wiskott-Aldrich autosomal dominant variant syndrome	SNOMED	FALSE	FALSE
4299560	Thrombocytopenic purpura due to defective platelet production	SNOMED	FALSE	FALSE
4298690	Immunologic aplastic anemia	SNOMED	FALSE	FALSE
4292531	Thrombocytopenic purpura due to platelet consumption	SNOMED	FALSE	FALSE
4292425	Sex-linked thrombocytopenia	SNOMED	FALSE	FALSE
4272928	Thrombocytopenia due to hypersplenism	SNOMED	FALSE	FALSE
4264464	Mediterranean macrothrombocytopenia	SNOMED	FALSE	FALSE
4258261	Drug induced thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4247776	Posttransfusion purpura	SNOMED	FALSE	FALSE
4239484	Acquired pancytopenia	SNOMED	FALSE	FALSE
4235220	Hereditary thrombocytopenic disorder	SNOMED	FALSE	FALSE
4234973	Chronic acquired pure red cell aplasia	SNOMED	FALSE	FALSE
4233407	Megakaryocytic aplasia	SNOMED	FALSE	FALSE
4230266	Autoimmune thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4226905	Thrombocytopenia associated with AIDS	SNOMED	FALSE	FALSE
4225810	Aplastic anemia associated with AIDS	SNOMED	FALSE	FALSE
4219476	Thrombocytopenia due to defective platelet production	SNOMED	FALSE	FALSE
4218171	Uremic thrombocytopenia	SNOMED	FALSE	FALSE
4214947	Thrombocytopenic purpura associated with metabolic disorder	SNOMED	FALSE	FALSE
4211348	Aplastic anemia associated with pancreatitis	SNOMED	FALSE	FALSE
4204900	Acquired thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4197574	Dilutional thrombocytopenia	SNOMED	FALSE	FALSE
4188208	Estren-Dameshek anemia	SNOMED	FALSE	FALSE
4186108	Aplastic anemia associated with metabolic alteration	SNOMED	FALSE	FALSE
4185078	Bernard Soulier syndrome	SNOMED	FALSE	FALSE
4184758	Acquired aplastic anemia	SNOMED	FALSE	FALSE
4184200	Secondary aplastic anemia	SNOMED	FALSE	FALSE
4177177	Cellular immunologic aplastic anemia	SNOMED	FALSE	FALSE
4173278	Thrombocytopenia due to blood loss	SNOMED	FALSE	FALSE
4172008	Cyclic thrombocytopenia	SNOMED	FALSE	FALSE
4166754	Perinatal thrombocytopenia	SNOMED	FALSE	FALSE
4159966	Upshaw-Schulman syndrome	SNOMED	FALSE	FALSE
4159749	Idiopathic maternal thrombocytopenia	SNOMED	FALSE	FALSE
4159736	Radiation thrombocytopenia	SNOMED	FALSE	FALSE
4156233	Thrombocytopenia due to sequestration	SNOMED	FALSE	FALSE

4148471	Fanconi’s anemia	SNOMED	FALSE	FALSE
4147049	Thrombocytopenia due to extracorporeal circulation	SNOMED	FALSE	FALSE
4146088	Aplastic anemia due to drugs	SNOMED	FALSE	FALSE
4146086	Constitutional aplastic anemia with malformation	SNOMED	FALSE	FALSE
4145458	Thrombocytopenia due to hypothermia	SNOMED	FALSE	FALSE
4140545	Post infectious thrombocytopenic purpura	SNOMED	FALSE	FALSE
4139555	Thrombocytopenia due to massive blood transfusion	SNOMED	FALSE	FALSE
4137430	Idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4133984	Alloimmune thrombocytopenia	SNOMED	FALSE	FALSE
4133983	Secondary autoimmune thrombocytopenia	SNOMED	FALSE	FALSE
4133981	Benign gestational thrombocytopenia	SNOMED	FALSE	FALSE
4125496	Pure red cell aplasia, acquired	SNOMED	FALSE	FALSE
4125494	Pancytopenia with pancreatitis	SNOMED	FALSE	FALSE
4123076	Montreal platelet syndrome	SNOMED	FALSE	FALSE
4123075	May-Hegglin anomaly	SNOMED	FALSE	FALSE
4123074	Megakaryocytic thrombocytopenia	SNOMED	FALSE	FALSE
4121265	Mediterranean thrombocytopenia	SNOMED	FALSE	FALSE
4121264	Epstein syndrome	SNOMED	FALSE	FALSE
4120620	Amegakaryocytic thrombocytopenia	SNOMED	FALSE	FALSE
4119134	Thrombocytopenic purpura	SNOMED	FALSE	FALSE
4103532	Immune thrombocytopenia	SNOMED	FALSE	FALSE
4102469	Acute idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4101603	Thrombocytopenia due to extracorporeal circulation of blood	SNOMED	FALSE	FALSE
4101583	Aplastic anemia due to infection	SNOMED	FALSE	FALSE
4101582	Aplastic anemia due to chronic disease	SNOMED	FALSE	FALSE
4100998	Aplastic anemia due to toxic cause	SNOMED	FALSE	FALSE
4098148	Thrombocytopenia due to drugs	SNOMED	FALSE	FALSE
4098145	Idiopathic aplastic anemia	SNOMED	FALSE	FALSE
4098028	Transient acquired pure red cell aplasia	SNOMED	FALSE	FALSE
4098027	Aplastic anemia due to radiation	SNOMED	FALSE	FALSE
4082738	Autoimmune pancytopenia	SNOMED	FALSE	FALSE
4077348	Pancytopenia-dysmelia	SNOMED	FALSE	FALSE
4031699	Humoral immunologic aplastic anemia	SNOMED	FALSE	FALSE
4028065	Autoimmune thrombocytopenia	SNOMED	FALSE	FALSE
4027374	Alloimmune platelet transfusion refractoriness	SNOMED	FALSE	FALSE
4009307	Heparin-induced thrombocytopenia with thrombosis	SNOMED	FALSE	FALSE
4000065	Drug-induced immune thrombocytopenia	SNOMED	FALSE	FALSE
441264	Primary thrombocytopenia	SNOMED	FALSE	FALSE
440982	Wiskott-Aldrich syndrome	SNOMED	FALSE	FALSE
440372	Acquired thrombocytopenia	SNOMED	FALSE	FALSE

436956	Evans syndrome	SNOMED	FALSE	FALSE
433749	Heparin-induced thrombocytopenia	SNOMED	FALSE	FALSE
432881	Pancytopenia	SNOMED	FALSE	FALSE
318397	Chronic idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
140681	Constitutional aplastic anemia	SNOMED	FALSE	FALSE
138723	Acquired red cell aplasia	SNOMED	FALSE	FALSE
137829	Aplastic anemia	SNOMED	FALSE	FALSE

- Thrombocytopenic purpura

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4119134	Thrombocytopenic purpura	SNOMED	FALSE	FALSE
4301602	Thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4299560	Thrombocytopenic purpura due to defective platelet production	SNOMED	FALSE	FALSE
4292531	Thrombocytopenic purpura due to platelet consumption	SNOMED	FALSE	FALSE
4258261	Drug induced thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4247776	Posttransfusion purpura	SNOMED	FALSE	FALSE
4230266	Autoimmune thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4214947	Thrombocytopenic purpura associated with metabolic disorder	SNOMED	FALSE	FALSE
4204900	Acquired thrombotic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4159966	Upshaw-Schulman syndrome	SNOMED	FALSE	FALSE
4140545	Post infectious thrombocytopenic purpura	SNOMED	FALSE	FALSE
4137430	Idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4102469	Acute idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
318397	Chronic idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
313800	Thrombotic microangiopathy	SNOMED	FALSE	FALSE

- Immune thrombocytopenia

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4103532	Immune thrombocytopenia	SNOMED	FALSE	FALSE
4137430	Idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4133984	Alloimmune thrombocytopenia	SNOMED	FALSE	FALSE
4133983	Secondary autoimmune thrombocytopenia	SNOMED	FALSE	FALSE
4102469	Acute idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE
4028065	Autoimmune thrombocytopenia	SNOMED	FALSE	FALSE
4027374	Alloimmune platelet transfusion refractoriness	SNOMED	FALSE	FALSE
4009307	Heparin-induced thrombocytopenia with thrombosis	SNOMED	FALSE	FALSE

4000065	Drug-induced immune thrombocytopenia	SNOMED	FALSE	FALSE
436956	Evans syndrome	SNOMED	FALSE	FALSE
433749	Heparin-induced thrombocytopenia	SNOMED	FALSE	FALSE
318397	Chronic idiopathic thrombocytopenic purpura	SNOMED	FALSE	FALSE

A4.6. Ischemic stroke

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4045735	Anterior cerebral circulation infarction	SNOMED	FALSE	FALSE
4031045	Anterior choroidal artery syndrome	SNOMED	FALSE	FALSE
761110	Bilateral cerebral infarction due to precererbral arterial occlusion	SNOMED	FALSE	FALSE
4110189	Cerebral infarct due to thrombosis of precerebral arteries	SNOMED	FALSE	FALSE
443454	Cerebral infarction	SNOMED	FALSE	FALSE
762951	Cerebral infarction due to anterior cerebral artery occlusion	SNOMED	FALSE	FALSE
765515	Cerebral infarction due to basilar artery stenosis	SNOMED	FALSE	FALSE
43530683	Cerebral infarction due to carotid artery occlusion	SNOMED	FALSE	FALSE
762933	Cerebral infarction due to cerebral artery occlusion	SNOMED	FALSE	FALSE
762937	Cerebral infarction due to cerebral venous thrombosis	SNOMED	FALSE	FALSE
4111714	Cerebral infarction due to cerebral venous thrombosis, non-pyogenic	SNOMED	FALSE	FALSE
4108356	Cerebral infarction due to embolism of cerebral arteries	SNOMED	FALSE	FALSE
45772786	Cerebral infarction due to embolism of middle cerebral artery	SNOMED	FALSE	FALSE
4110190	Cerebral infarction due to embolism of precerebral arteries	SNOMED	FALSE	FALSE
762935	Cerebral infarction due to internal carotid artery occlusion	SNOMED	FALSE	FALSE
763015	Cerebral infarction due to middle cerebral artery occlusion	SNOMED	FALSE	FALSE
46273649	Cerebral infarction due to occlusion of basilar artery	SNOMED	FALSE	FALSE
35610084	Cerebral infarction due to occlusion of cerebral artery	SNOMED	FALSE	FALSE
46270031	Cerebral infarction due to occlusion of precerebral artery	SNOMED	FALSE	FALSE
762934	Cerebral infarction due to posterior cerebral artery occlusion	SNOMED	FALSE	FALSE
43531607	Cerebral infarction due to stenosis of carotid artery	SNOMED	FALSE	FALSE
35610085	Cerebral infarction due to stenosis of cerebral artery	SNOMED	FALSE	FALSE
46270381	Cerebral infarction due to stenosis of precerebral artery	SNOMED	FALSE	FALSE
4110192	Cerebral infarction due to thrombosis of cerebral arteries	SNOMED	FALSE	FALSE
45767658	Cerebral infarction due to thrombosis of middle cerebral artery	SNOMED	FALSE	FALSE
44782773	Cerebral infarction due to vertebral artery occlusion	SNOMED	FALSE	FALSE
46270380	Cerebral infarction due to vertebral artery stenosis	SNOMED	FALSE	FALSE
37110678	Cerebral ischemic stroke due to occlusion of extracranial large artery	SNOMED	FALSE	FALSE
37110679	Cerebral ischemic stroke due to stenosis of extracranial large artery	SNOMED	FALSE	FALSE
4043731	Infarction - precerebral	SNOMED	FALSE	FALSE

4131383	Infarction of basal ganglia	SNOMED	FALSE	FALSE
4046237	Infarction of optic radiation	SNOMED	FALSE	FALSE
4119140	Infarction of visual cortex	SNOMED	FALSE	FALSE
4141405	Left sided cerebral infarction	SNOMED	FALSE	FALSE
37116473	Multifocal cerebral infarction due to and following procedure on cardiovascular system	SNOMED	FALSE	FALSE
4077086	Occipital cerebral infarction	SNOMED	FALSE	FALSE
4046359	Partial anterior cerebral circulation infarction	SNOMED	FALSE	FALSE
4319146	Pituitary infarction	SNOMED	FALSE	FALSE
4146185	Right sided cerebral infarction	SNOMED	FALSE	FALSE
36717605	Silent cerebral infarct	SNOMED	FALSE	FALSE
4142739	Thalamic infarction	SNOMED	FALSE	FALSE
4046358	Total anterior cerebral circulation infarction	SNOMED	FALSE	FALSE
372924	Cerebral artery occlusion	SNOMED	FALSE	FALSE

A4.7. Myocardial infarction

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4119457	Acute Q wave infarction - anterolateral	SNOMED	FALSE	FALSE
4119943	Acute Q wave infarction - anteroseptal	SNOMED	FALSE	FALSE
4121464	Acute Q wave infarction - inferior	SNOMED	FALSE	FALSE
4121465	Acute Q wave infarction - inferolateral	SNOMED	FALSE	FALSE
4124684	Acute Q wave infarction - lateral	SNOMED	FALSE	FALSE
4119948	Acute Q wave infarction - widespread	SNOMED	FALSE	FALSE
4126801	Acute Q wave myocardial infarction	SNOMED	FALSE	FALSE
4296653	Acute ST segment elevation myocardial infarction	SNOMED	FALSE	FALSE
46270162	Acute ST segment elevation myocardial infarction due to left coronary artery occlusion	SNOMED	FALSE	FALSE
761737	Acute ST segment elevation myocardial infarction due to occlusion of circumflex coronary artery	SNOMED	FALSE	FALSE
46270163	Acute ST segment elevation myocardial infarction due to right coronary artery occlusion	SNOMED	FALSE	FALSE
43020460	Acute ST segment elevation myocardial infarction involving left anterior descending coronary artery	SNOMED	FALSE	FALSE
45766076	Acute ST segment elevation myocardial infarction of anterior wall involving right ventricle	SNOMED	FALSE	FALSE
761736	Acute ST segment elevation myocardial infarction of anteroapical wall	SNOMED	FALSE	FALSE
46270159	Acute ST segment elevation myocardial infarction of anterolateral wall	SNOMED	FALSE	FALSE
46270160	Acute ST segment elevation myocardial infarction of anteroseptal wall	SNOMED	FALSE	FALSE

45766116	Acute ST segment elevation myocardial infarction of inferior wall	SNOMED	FALSE	FALSE
45766151	Acute ST segment elevation myocardial infarction of inferior wall involving right ventricle	SNOMED	FALSE	FALSE
35611570	Acute ST segment elevation myocardial infarction of inferolateral wall	SNOMED	FALSE	FALSE
35611571	Acute ST segment elevation myocardial infarction of inferoposterior wall	SNOMED	FALSE	FALSE
46274044	Acute ST segment elevation myocardial infarction of lateral wall	SNOMED	FALSE	FALSE
46270161	Acute ST segment elevation myocardial infarction of posterior wall	SNOMED	FALSE	FALSE
46273495	Acute ST segment elevation myocardial infarction of posterobasal wall	SNOMED	FALSE	FALSE
46270158	Acute ST segment elevation myocardial infarction of posterolateral wall	SNOMED	FALSE	FALSE
46270164	Acute ST segment elevation myocardial infarction of septum	SNOMED	FALSE	FALSE
45766075	Acute anterior ST segment elevation myocardial infarction	SNOMED	FALSE	FALSE
4178129	Acute anteroapical myocardial infarction	SNOMED	FALSE	FALSE
4267568	Acute anteroseptal myocardial infarction	SNOMED	FALSE	FALSE
312327	Acute myocardial infarction	SNOMED	FALSE	FALSE
44782769	Acute myocardial infarction due to left coronary artery occlusion	SNOMED	FALSE	FALSE
44782712	Acute myocardial infarction due to right coronary artery occlusion	SNOMED	FALSE	FALSE
45766115	Acute myocardial infarction during procedure	SNOMED	FALSE	FALSE
434376	Acute myocardial infarction of anterior wall	SNOMED	FALSE	FALSE
45766150	Acute myocardial infarction of anterior wall involving right ventricle	SNOMED	FALSE	FALSE
438438	Acute myocardial infarction of anterolateral wall	SNOMED	FALSE	FALSE
4243372	Acute myocardial infarction of apical-lateral wall	SNOMED	FALSE	FALSE
4108669	Acute myocardial infarction of atrium	SNOMED	FALSE	FALSE
4151046	Acute myocardial infarction of basal-lateral wall	SNOMED	FALSE	FALSE
4275436	Acute myocardial infarction of high lateral wall	SNOMED	FALSE	FALSE
438170	Acute myocardial infarction of inferior wall	SNOMED	FALSE	FALSE
45771322	Acute myocardial infarction of inferior wall involving right ventricle	SNOMED	FALSE	FALSE
438447	Acute myocardial infarction of inferolateral wall	SNOMED	FALSE	FALSE
441579	Acute myocardial infarction of inferoposterior wall	SNOMED	FALSE	FALSE
436706	Acute myocardial infarction of lateral wall	SNOMED	FALSE	FALSE

4324413	Acute myocardial infarction of posterobasal wall	SNOMED	FALSE	FALSE
4051874	Acute myocardial infarction of posterolateral wall	SNOMED	FALSE	FALSE
4303359	Acute myocardial infarction of septum	SNOMED	FALSE	FALSE
4147223	Acute myocardial infarction with rupture of ventricle	SNOMED	FALSE	FALSE
4145721	Acute non-Q wave infarction	SNOMED	FALSE	FALSE
4119944	Acute non-Q wave infarction - anterolateral	SNOMED	FALSE	FALSE
4119456	Acute non-Q wave infarction - anteroseptal	SNOMED	FALSE	FALSE
4119945	Acute non-Q wave infarction - inferior	SNOMED	FALSE	FALSE
4119946	Acute non-Q wave infarction - inferolateral	SNOMED	FALSE	FALSE
4121466	Acute non-Q wave infarction - lateral	SNOMED	FALSE	FALSE
4124685	Acute non-Q wave infarction - widespread	SNOMED	FALSE	FALSE
4270024	Acute non-ST segment elevation myocardial infarction	SNOMED	FALSE	FALSE
35610091	Acute nontransmural myocardial infarction	SNOMED	FALSE	FALSE
319039	Acute posterior myocardial infarction	SNOMED	FALSE	FALSE
444406	Acute subendocardial infarction	SNOMED	FALSE	FALSE
35610093	Acute transmural myocardial infarction	SNOMED	FALSE	FALSE
4119947	Acute widespread myocardial infarction	SNOMED	FALSE	FALSE
37109912	Arrhythmia due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
438172	Atrial septal defect due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
4124687	Cardiac rupture due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
4215259	First myocardial infarction	SNOMED	FALSE	FALSE
4108678	Hemopericardium due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
4173632	Microinfarct of heart	SNOMED	FALSE	FALSE
45771327	Mitral valve regurgitation due to acute myocardial infarction with papillary muscle and chordal rupture	SNOMED	FALSE	FALSE
45766214	Mitral valve regurgitation due to acute myocardial infarction without papillary muscle and chordal rupture	SNOMED	FALSE	FALSE

45766212	Mitral valve regurgitation due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
4323202	Mixed myocardial ischemia and infarction	SNOMED	FALSE	FALSE
4329847	Myocardial infarction	SNOMED	FALSE	FALSE
37309626	Myocardial infarction due to demand ischemia	SNOMED	FALSE	FALSE
4170094	Myocardial infarction in recovery phase	SNOMED	FALSE	FALSE
4200113	Non-Q wave myocardial infarction	SNOMED	FALSE	FALSE
4030582	Postoperative myocardial infarction	SNOMED	FALSE	FALSE
35610087	Postoperative nontransmural myocardial infarction	SNOMED	FALSE	FALSE
4206867	Postoperative subendocardial myocardial infarction	SNOMED	FALSE	FALSE
35610089	Postoperative transmural myocardial infarction	SNOMED	FALSE	FALSE
4207921	Postoperative transmural myocardial infarction of anterior wall	SNOMED	FALSE	FALSE
4209541	Postoperative transmural myocardial infarction of inferior wall	SNOMED	FALSE	FALSE
37109911	Pulmonary embolism due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
4108679	Rupture of cardiac wall without hemopericardium as current complication following acute myocardial infarction	SNOMED	FALSE	FALSE
4108219	Rupture of chordae tendinae due to and following acute myocardial infarction	SNOMED	FALSE	FALSE
4124686	Silent myocardial infarction	SNOMED	FALSE	FALSE
765132	Subendocardial myocardial infarction	SNOMED	FALSE	FALSE
45766114	Subsequent ST segment elevation myocardial infarction	SNOMED	FALSE	FALSE
45766113	Subsequent ST segment elevation myocardial infarction of anterior wall	SNOMED	FALSE	FALSE
45773170	Subsequent ST segment elevation myocardial infarction of inferior wall	SNOMED	FALSE	FALSE
4108217	Subsequent myocardial infarction	SNOMED	FALSE	FALSE
4108677	Subsequent myocardial infarction of anterior wall	SNOMED	FALSE	FALSE
4108218	Subsequent myocardial infarction of inferior wall	SNOMED	FALSE	FALSE
45766241	Subsequent non-ST segment elevation myocardial infarction	SNOMED	FALSE	FALSE
4108680	Thrombosis of atrium, auricular appendage, and ventricle due to and following acute myocardial infarction	SNOMED	FALSE	FALSE

439693	True posterior myocardial infarction	SNOMED	FALSE	FALSE
37109910	Ventricular aneurysm due to and following acute myocardial infarction	SNOMED	FALSE	FALSE

A4.8. Other arterial thromboembolism

- Intestinal infarction

Concept ID	Concept name	Vocabulary	Is excluded?	Include descendants?
4195665	Gastrointestinal tract vascular insufficiency	SNOMED	FALSE	FALSE
4148299	Ischemic colitis	SNOMED	FALSE	FALSE
4173167	Mesenteric embolus	SNOMED	FALSE	FALSE
4317289	Thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
4319280	Acute bowel infarction	SNOMED	FALSE	FALSE
4144032	Mesenteric thrombus and/or embolus	SNOMED	FALSE	FALSE
45757410	Acute thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
45757409	Chronic thrombosis of mesenteric vein	SNOMED	FALSE	FALSE
44811741	Acute ischaemia of large intestine	SNOMED	FALSE	FALSE
44811740	Acute ischaemia of small intestine	SNOMED	FALSE	FALSE
37117790	Insufficiency of mesenteric artery	SNOMED	FALSE	FALSE
37016198	Epiploic appendagitis	SNOMED	FALSE	FALSE
35622081	Nongangrenous ischemic colitis	SNOMED	FALSE	FALSE
35622080	Gangrenous ischemic colitis	SNOMED	FALSE	FALSE
4345926	Abdominal angina	SNOMED	FALSE	FALSE
4342767	Transient ischemic colitis	SNOMED	FALSE	FALSE
4341648	Hemorrhagic infarction of intestine	SNOMED	FALSE	FALSE
4341646	Occlusive mesenteric ischemia	SNOMED	FALSE	FALSE
4340939	Non-occlusive mesenteric ischemia	SNOMED	FALSE	FALSE
4340378	Transmural infarction of intestine	SNOMED	FALSE	FALSE
4340375	Focal segmental ischemia of small intestine	SNOMED	FALSE	FALSE
4318537	Large bowel gangrene	SNOMED	FALSE	FALSE
4318407	Thrombophlebitis of mesenteric vein	SNOMED	FALSE	FALSE

4240850	Acute ischemic enterocolitis	SNOMED	FALSE	FALSE
4239942	Embolic mesenteric infarction	SNOMED	FALSE	FALSE
4237654	Ischemic enterocolitis	SNOMED	FALSE	FALSE
4215949	Nonocclusive intestinal infarction	SNOMED	FALSE	FALSE
4214720	Thrombotic mesenteric infarction	SNOMED	FALSE	FALSE
4192856	Acute ischemic colitis	SNOMED	FALSE	FALSE
4188336	Chronic ischemic enterocolitis	SNOMED	FALSE	FALSE
4174014	Inferior mesenteric artery embolus	SNOMED	FALSE	FALSE
4149013	Mesenteric infarction	SNOMED	FALSE	FALSE
4148257	Chronic gastrointestinal tract vascular insufficiency	SNOMED	FALSE	FALSE
4148256	Acute GIT vascular insufficiency	SNOMED	FALSE	FALSE
4124856	Inferior mesenteric vein thrombosis	SNOMED	FALSE	FALSE
4055089	Superior mesenteric vein thrombosis	SNOMED	FALSE	FALSE
4055025	Superior mesenteric artery embolus	SNOMED	FALSE	FALSE
4045408	Ischemic stricture of intestine	SNOMED	FALSE	FALSE
201894	Acute vascular insufficiency of intestine	SNOMED	FALSE	FALSE
192673	Vascular insufficiency of intestine	SNOMED	FALSE	FALSE

A4.9. Medications of interest

Concept ID	Code	Concept Name	Domain	Vocabulary
21603933	M01A	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS	Drug	ATC
21601386	L	ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	Drug	ATC
21600961	B01A	ANTITHROMBOTIC AGENTS	Drug	ATC
21602722	H02	CORTICOSTEROIDS FOR SYSTEMIC USE	Drug	ATC
21603991	M01AH	Coxibs	Drug	ATC
21602472	G03A	HORMONAL CONTRACEPTIVES FOR SYSTEMIC USE	Drug	ATC
21601853	C10	LIPID MODIFYING AGENTS	Drug	ATC
21602471	G03	SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM	Drug	ATC
21603831	L02BA01	tamoxifen; oral	Drug	ATC

Annex 5. Preliminary list of negative control outcomes

- *Negative outcome Concept ID*

Concept Id	Outcome Name
438945	Accidental poisoning by benzodiazepine-based tranquilizer
434455	Acquired claw toes
316211	Acquired spondylolisthesis
201612	Alcoholic liver damage
438730	Alkalosis
441258	Anemia in neoplastic disease
432513	Animal bite wound
4171556	Ankle ulcer
4098292	Antiphospholipid syndrome
77650	Aseptic necrosis of bone
4239873	Benign neoplasm of ciliary body
23731	Benign neoplasm of larynx
199764	Benign neoplasm of ovary
195500	Benign neoplasm of uterus
4145627	Biliary calculus
4108471	Burn of digit of hand
75121	Burn of lower leg
4284982	Calculus of bile duct without obstruction
434327	Cannabis abuse
78497	Cellulitis and abscess of toe
4001454	Cervical spine ankylosis
4068241	Chronic instability of knee
195596	Chronic pancreatitis
4206338	Chronic salpingitis
4058397	Claustrophobia
74816	Contusion of toe
73302	Curvature of spine
4151134	Cyst of pancreas
77638	Displacement of intervertebral disc without myelopathy
195864	Diverticulum of bladder
201346	Edema of penis
200461	Endometriosis of uterus
377877	Esotropia
193530	Follicular cyst of ovary

Concept Id	Outcome Name
4094822	Foreign body in respiratory tract
443421	Gallbladder and bile duct calculi
135215	Hashimoto thyroiditis
442190	Hemorrhage of colon
43020475	High risk heterosexual behavior
194149	Hirschsprung's disease
443204	Human ehrlichiosis
4226238	Hyperosmolar coma due to diabetes mellitus
4032787	Hyperosmolarity
197032	Hyperplasia of prostate
140362	Hypoparathyroidism
435371	Hypothermia
138690	Infestation by Pediculus
4152376	Intentional self poisoning
192953	Intestinal adhesions with obstruction
196347	Intestinal parasitism
137977	Jaundice
317510	Leukemia
765053	Lump in right breast
378165	Nystagmus
434085	Obstruction of duodenum
4147016	Open wound of buttock
4129404	Open wound of upper arm
438120	Opioid dependence
75924	Osteodystrophy
432594	Osteomalacia
30365	Panhypopituitarism
4108371	Peripheral gangrene
440367	Plasmacytosis
439233	Poisoning by antidiabetic agent
442149	Poisoning by bee sting
4314086	Poisoning due to sting of ant
4147660	Postural kyphosis
434319	Premature ejaculation
199754	Primary malignant neoplasm of pancreas
4311499	Primary malignant neoplasm of respiratory tract
436635	Primary malignant neoplasm of sigmoid colon

Concept Id	Outcome Name
196044	Primary malignant neoplasm of stomach
433716	Primary malignant neoplasm of testis
133424	Primary malignant neoplasm of thyroid gland
194997	Prostatitis
80286	Prosthetic joint loosening
443274	Psychostimulant dependence
314962	Raynaud’s disease
37018294	Residual osteitis
4288241	Salmonella enterica subspecies arizonae infection
45757269	Sclerosing mesenteritis
74722	Secondary localized osteoarthrosis of pelvic region
200348	Secondary malignant neoplasm of large intestine
43020446	Sedative withdrawal
74194	Sprain of spinal ligament
4194207	Tailor’s bunion
193521	Tropical sprue
40482801	Type II diabetes mellitus uncontrolled
74719	Ulcer of foot
196625	Viral hepatitis A without hepatic coma
197494	Viral hepatitis C
4284533	Vitamin D-dependent rickets