Study Protocol P2-C3-002

10/05/2024

Version v2.1

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DOCUMENT HISTORY

Version	Date	Description
V1.0	05/10/2023	**Initial version for EMA review**
V2.0	09/11/2023	**EMA-approved version with implemented comments/feedback**
V2.1	10/05/2024	**Version uploaded in the HMA-EMA Catalogue**

Study Title	DARWIN EU® – Effectiveness of COVID-19 vaccines on severe COVID-19 and post-acute outcomes of SARS-CoV-2 infection
Protocol version identifier	V2.1
Date of last version of protocol	10/05/2024
EU PAS register number	EUPAS107615
Active substance	COVID-19 vaccines BNT162b2 and mRNA-1273
Medicinal products	Comirnaty: Comirnaty original strain (monovalent), Comirnaty original strain + omicron ba1 (adapted, bivalent), Comirnaty original strain + omicron ba4/5 (adapted, bivalent) Spikevax: Spikevax original strain (monovalent), Spikevax original strain + omicron ba1 (adapted, bivalent), Spikevax original strain + omicron ba4/5 (adapted, bivalent)
Research question and objectives	Research question: What is the effectiveness of the EMA-authorized COVID-19 vaccines Comirnaty and Spikevax against severe COVID-19 and post-acute outcomes of SARS-CoV-2 infection? The objectives of the study are: 1. To assess the effectiveness of COVID-19 vaccination for the prevention of severe COVID-19 related outcomes (COVID-19 related hospitalization or COVID-19 related death) 2. To assess waning of the effectiveness of COVID-19 vaccination for the prevention of severe COVID-19 related outcomes (COVID-19 related hospitalization or COVID-19 related death) 3. To assess the effectiveness of COVID-19 vaccination for the prevention of all-cause mortality in the 3- and 6-months following discharge for COVID-19 related hospitalization 4. To assess the effectiveness of COVID-19 vaccination for the prevention of new-onset type 1 Diabetes Mellitus in the 12 months after a SARS-CoV-2 infection 5. To assess the effectiveness of COVID-19 vaccination for the prevention of new-onset type 2 Diabetes Mellitus in the 12 months after a SARS-CoV-2 infection 6. To assess the effectiveness of COVID-19 vaccination for the prevention of cardiovascular events in the 12 months after a SARS-CoV-2 infection
Countries of study	Spain, The UK, The Netherlands
Author	Annika Jödicke, Xintong Li and Martí Català Sabaté

LIST OF ABBREVIATIONS

Abbreviation	Name
CDM	Common Data Model
COVID-19	Coronavirus disease-2019
EHR	Electronic Health Record
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ICU	Intensive care unit
OMOP	Observational Medical Outcomes Partnership
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
RT-PCR	Reverse transcription polymerase chain reaction
IRR	Incidence rate ratio
CPRD	Clinical Practice Research Datalink
IPCI	Integrated Primary Care Information
SIDIAP	The Information System for Research in Primary Care
SNOMED	Systematized Nomenclature of Medicine

1. TITLE

DARWIN EU® – Effectiveness of COVID-19 vaccines on severe COVID-19 and post-acute outcomes of SARS-CoV-2 infection

2. RESPONSIBLE PARTIES – STUDY TEAM

Study team role	Names	Organisation
Principal Investigators	Martí Català Sabaté Annika Jödicke	*University of Oxford* *University of Oxford*
Data Scientist/Statistician	Xintong Li Edward Burn	*University of Oxford* *University of Oxford*
Epidemiologist/Clinical Domain Expert	Albert Prats-Uribe	*University of Oxford*

Data partner	Local Study Coordinator/Data Analyst	Organisation
SIDIAP	Talita Duarte Salles	*IDIAP JGOL*
IPCI	Mees Mosseveld	*Erasmus MC*
CPRD GOLD	Antonella Delmestri	*University of Oxford*

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

Title

DARWIN EU® – Effectiveness of COVID-19 vaccines on severe COVID-19 and post-acute outcomes of SARS-CoV-2 infection

Rationale and Background

The research agenda of the Vaccine Monitoring Platform jointly coordinated by EMA and the European Centre for Disease Prevention and Control (ECDC) includes the continuous assessment of COVID-19 vaccine effectiveness.

COVID-19 vaccines were authorised for use in the European Union. These vaccines, and any (future) adapted vaccines, would therefore benefit from post-authorisation studies to provide real-world evidence to guide regulatory and vaccination policies. A recent post-authorisation study performed in the Nordic countries, where near real-time data is available, showed that receipt of a bivalent BA4/5 mRNA booster as a fourth dose provides 67.8% protection against COVID-19 related hospitalisation. There is also evidence that effectiveness starts to wane after a few months. For regulatory purposes, such data are especially useful for the most recent variants, including XBB and later.

There is mounting evidence on post-acute outcomes of SARS-CoV-2 infection. This can include very specific outcomes such as cardiovascular events or the incidence of new-onset diabetes, or broader definitions such as the WHO clinical case definition for post COVID-19 condition. Data are needed regarding the COVID-19 vaccines effectiveness at preventing these outcomes. This is pertinent for the most recent variants, but equally important for older variants.

Objective(s)

To generate additional evidence on the effectiveness of COVID-19 vaccines at preventing severe COVID-19 and post-acute outcomes of SARS-CoV-2 infection.

Specifically, this study has 6 objectives:

1. To assess the effectiveness of COVID-19 vaccination for the prevention of severe COVID-19 related outcomes (COVID-19 related hospitalisation or COVID-19 related death)
2. To assess waning of the effectiveness of COVID-19 vaccination for the prevention of severe COVID-19 related outcomes (COVID-19 related hospitalisation or COVID-19 related death)
3. To assess the effectiveness of COVID-19 vaccination for the prevention of all-cause mortality in the 3- and 6-months following discharge for COVID-19 related hospitalisation
4. To assess the effectiveness of COVID-19 vaccination for the prevention of new-onset type 1 Diabetes Mellitus in the 12 months after a SARS-CoV-2 infection
5. To assess the effectiveness of COVID-19 vaccination for the prevention of new-onset type 2 Diabetes Mellitus in the 12 months after a SARS-CoV-2 infection
6. To assess the effectiveness of COVID-19 vaccination for the prevention of cardiovascular events in the 12 months after a SARS-CoV-2 infection

Research Methods

Study design: Population-level cohort studies

Data sources:

- Clinical practice Research Datalink (CPRD) GOLD, United Kingdom
- Integrated Primary Care Information Project (IPCI), The Netherlands
- The Information System for Research in Primary Care (SIDIAP), Spain

Additional databases can be added as part of a routine repetition of this study once they are successfully onboarded for DARWIN EU and meet feasibility requirements for this study.

Exposure:
Covid-19 vaccines BNT162b2 (Comirnaty) and mRNA-1273 (Spikevax), particularly the number of received vaccine doses per brand.
For those databases where this information is available, the 4th dose (2nd booster) will be stratified for monovalent (original strain) or adapted, bivalent (original strain + omicron ba1 or original strain + omicron ba4/5).
Analyses will be conducted separately for each vaccine brand.

Primary outcomes of interest:

1) Outcomes assessed from start of rollout of 4th vaccine dose/ 2nd booster dose program onwards:

1. COVID-19 related hospitalisation
2. COVID-19 related death

2) Outcome/s during periods with dominance of any SARS-CoV-2 variants:

3. All-cause mortality in the 3 months after discharge from a COVID-19 hospitalisation
4. All-cause mortality in the 6 months after discharge from a COVID-19 hospitalisation
5. Incidence of new-onset type 1 Diabetes Mellitus beyond the first 30d after SARS-CoV-2 infection
6. Incidence of new-onset type 2 Diabetes Mellitus beyond the first 30d after SARS-CoV-2 infection
7. Incidence of cardiovascular events (cerebrovascular disorders, dysrhythmias, ischemic and non-ischemic heart disease, pericarditis, myocarditis, heart failure and thromboembolic disease) in the 12 months after a SARS-CoV-2 infection

COVID-19 related hospitalisation (outcome 1, part of outcomes 3 and 4) is not available for IPCI and CPRD but will only be assessed in SIDIAP.

Study population:

All subjects aged 12 years and older, with at least 365 days of data availability before index date (ID) [ID defined as the date of the latest vaccine dose administered] AND data availability from 12/2020 onwards (i.e. the time when the roll-out of the vaccination campaign started) in the respective database will be included.

All studies will be carried out comparing the following cohorts, which we defined based on varying degrees of vaccine exposure and period of predominant SARS-CoV-2 variant as shown in Table 1 below.

	Cohort number							
COVID-19 vaccination history	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1 dose only					x			
Complete primary vaccination course (monovalent only)	x	x	x	x		x	x	x
3rd dose, also called 1st booster (monovalent or any of the adapted, bivalent)	x	x	x	x			x	x
4th dose, also called 2nd booster (monovalent or any of the adapted, bivalent)		x						x
4th dose, also called 2nd booster (any of the monovalent)			x					
4th dose, also called 2nd booster (any of the adapted, bivalent boosters)				x				
Study period								
Start of roll-out 4th dose/2nd booster onwards	x	x	x	x				
XBB variant or later dominant	x	x	x	x				
Any variant dominant					x	x	x	x

*Cohorts 3 and 4 will only be created for databases where the vaccine product is reliably recorded in addition to vaccine brand.

Outcomes 1-2 will be assessed in cohorts 1-2 (and 3-4 where available), outcomes 3-7 will be assessed in cohorts 5-8.
Unvaccinated groups will not be used as a comparator in our study for vaccine effectiveness research because they may be very different from vaccinated individuals regarding their risk of infection with SARS-Cov-2. This study therefore focusses on the association of varying degrees of vaccine exposure and COVID-19 related outcomes.

Study period:
Period of "start of roll-out 4th dose/2nd booster dose onwards": from 01/08/2022 - last available data for each database.
Period of "XBB variant or later dominant": 01/03/2023 - last available data for each database. Note: This period is not covered by any of the data cuts onboarded for DARWIN EU at the time of protocol submission.
Period of "any variant dominant": 01/01/2021 (when the wider roll-out of the vaccination campaign started) - last available data for each database.

Statistical analyses:
All analyses will be conducted separately for each database, and will be carried out in a federated manner, allowing analyses to be run locally without sharing patient-level data. For each analysis, we will subsequently pool effect estimates across databases using random effect meta-analyses, I^2 for heterogeneity will be reported.
Cell counts <5 will be suppressed to comply with the database's privacy protection regulations.

Objective 1 and 2: Effectiveness of 2nd COVID-19 vaccine booster dose in people with 1 previous booster dose

Study population

People with a 3rd-vaccine dose (1st booster dose) of Comirnaty or Spikevax will be included from the source population. Cohorts will be generated separately for Comirnaty and Spikevax, respectively.

Study inclusion: Sequential matching

Inclusion will be conducted in a sequential manner as follows.

For each calendar week starting from the day when a 4th vaccine dose (i.e. 2nd booster vaccine) became available/recommended in the respective country, people will be assigned to two cohorts: people who received a 2nd booster dose that week ("boostered") and people who did not receive a 2nd booster ("non-boostered").

Using the first day of the respective week as "preliminary" index date for non-boostered people, and the date of the 4th vaccine dose for boostered people, the following inclusion criteria will be applied:

- At least 365 days of data availability in the respective database
- At least 90days of time elapsed since the last vaccine dose
- At least 90days of time elapsed since the last record of a clinical diagnosis of COVID-19 or positive SARS-COV-2 test.

Among those people in the boostered and non-boostered cohorts who met the inclusion criteria, non-boostered people will be match 1:1 to a boostered person, based on key confounders and large-scale propensity scores using nearest neighbor matching, with caliper width 0.2 standard deviation.
Key confounders will comprise but are not limited to:

- Age (e.g. 5-year age bands)
- Sex (exact)
- Geographic location (exact)
- Previous vaccine brands (e.g. homologous or heterologous vaccination scheme)
- Time from previous vaccination
- History of conditions for prioritization for vaccination
- Immunocompromised status
- Previous COVID-19 diagnoses (>90days before index date)

Large-scale propensity scores (PS) will be computed to estimate the probability of receiving a 4th vaccine dose. Covariates to be included in the large-scale PS will be selected from co-medications and comorbidities recorded prior to cohort-specific index dates. Among those, covariates with a prevalence below 0.5% in the study population will be omitted. Logistic regression with LASSO regularization will then be used for variable selection. The list of selected covariates will be manually screened by 2 epidemiologists/clinical domain experts to exclude potential instrumental variables.

With matching, non-boostered counterparts will be assigned the date of when the boostered counterpart received their 4th vaccine dose as their "final" index date (index date for the matched pair).

In the matched cohorts, people will be followed up from their index date until the earliest of

- End of their observation (i.e. date of data extraction, death)
- next vaccine dose (4th vaccine dose for non-boostered group, 5th vaccine dose for boostered group
- COVID-19 related hospitalization or death

Follow-up will be censored for the matched pair if one counterpart is censored, but not if one counterpart experiences the outcome.

The same procedure will be conducted in the calendar week after, with previously non-boostered people being allowed to be included in the boostered cohort once they change exposure status. Non-boostered people can only be matched once to a boostered counterpart during the whole study.

All boostered and matched non-boostered people from sequential weekly matching will be combined into the exposed and unexposed cohort for subsequent analyses.

Outcomes:

- COVID-19 related hospitalization will be assessed for SIDIAP and ICPI.
- COVID-19 related death will be assessed for CPRD, IPCI and SIDIAP.

Vaccine effectiveness analyses:

Cox proportions hazard models will be used to calculate hazard ratios (HR) for the outcomes of COVID-19 related hospitalisation and COVID-19 related death.
Negative control outcomes and empirical calibration for HR will be used as an additional measure to measure and minimise any potential residual confounding.
Kaplan-Meier plots and/or cumulative incidence plots will be used to illustrate survival analyses.

Vaccine effect waning:

Hazard ratios will be calculated for subsequent time windows after index date, i.e. in bi-weekly intervals. Monthly intervals will be used in case of small event counts to increase sample size and power if needed.
Kaplan-Meier plots and/or cumulative incidence plots will be used to illustrate survival analyses.

Objectives 3-6: Post-acute COVID-19 complications

The following comparisons will be conducted for objectives 3-6:

- First-dose vaccinated vs. second-dose vaccinated [cohort 5 vs. 6]
- Second-dose vaccinated vs. 3rd dose vaccinated (1st booster dose) [cohort 6 vs 7]
- 3rd dose vaccinated vs. 4th dose vaccinated (2nd booster dose) [cohort 7 vs 8]

Objective 3 will be assessed for SIDIAP and IPCI only, whereas objectives 4-6 will be assessed in CPRD, IPCI and SIDIAP.

Study population

The study populations will be derived similar to the inclusion process outlined for objectives 1-2 above, including sequential matching.

For objectives 4 and 5, people with the respective outcome recorded anytime in their history will be excluded for the respective objective. For objective 6, an outcome-free washout window of 365days prior to index date will be implemented.

Outcomes:

- COVID-19 hospitalization + death within 3/6 months from discharge
- SARS-CoV-2 infection + New onset diabetes Type 1 diabetes within 30-365days after COVID-19
- SARS-CoV-2 infection + New onset diabetes Type 2 diabetes within 30-365days after COVID-19
- SARS-CoV-2 infection + cardiovascular events (ccar) in the 12 months after a SARS-CoV-2 infection

For contextualization and interpretation of the study findings, we will also report the number of people with COVID-19 hospitalization and SARS-CoV-2 infections in each group, as these are part of the overall outcomes of "death following discharge from COVID-19 hospitalisation" and post COVID-19 complications.

Vaccine effectiveness analyses for COVID-19 related mortality following hospital discharge:

Incidence rates will be calculated for the matched cohorts and outcome. Cox proportional hazard models will be calculated for each outcome to provide HR. Negative control outcomes will be used as an additional measure to measure residual confounding. In the scenario of potential unmeasured confounding being detected by NCO, empirical calibration[25] for HR might be considered to minimise bias.

Kaplan-Meier plots and/or cumulative incidence plots will be used to illustrate survival analyses.

Vaccine effectiveness analyses for post-acute COVID-19 complications:

We will require at least 12 months of follow-up after SARS-CoV-2 infection to assess post-acute complications for outcomes 5, 6, and 7. If people die within 12months after COVID-19 they will contribute patient-time until death to the analyses. Only infections recorded 12months before the end of data availability will be included.

Incidence rates will be calculated for the matched cohorts and for each outcome. Cox proportional hazard models will be calculated for each outcome to provide HR. As previous research showed, no relevant difference in effect estimates was seen for post-COVID-19 symptoms when used fine-grey models accounting for death as competing risk compared to Cox regression.

Negative control outcomes will be used as an additional measure to measure residual confounding. A list of NCOs used in previous vaccine safety and effectiveness studies will be used. In the scenario of potential unmeasured confounding being detected by NCO, empirical calibration[25] for HR might be considered to minimise bias.

Kaplan-Meier plots and/or cumulative incidence plots will be used to illustrate survival analyses.

4. AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason

5. MILESTONES

STUDY SPECIFIC DELIVERABLE	TIMELINE
Draft Study Protocol	September 2023
Final Study Protocol	End of October 2023
Creation of Analytical code	November 2023
Execution of Analytical Code on the confirmed databases	December 2023
Interim Study Report (if applicable)	NA
Draft Study Report	31st January 2024
Final Study Report	To be confirmed

6. RATIONALE AND BACKGROUND

The research agenda of the Vaccine Monitoring Platform jointly coordinated by EMA and the European Centre for Disease Prevention and Control (ECDC) includes the continuous assessment of COVID-19 vaccine effectiveness.

COVID-19 vaccines were authorised for use in the European Union. These vaccines, and any (future) adapted vaccines, would therefore benefit from post-authorisation studies to provide real world evidence to guide regulatory and vaccination policies. A recent post-authorisation study performed in the Nordic countries, where near real-time data is available, showed that receipt of a bivalent BA4/5 mRNA booster as a fourth dose provides 67.8% protection against COVID-19 related hospitalisation[4]. There is also evidence that effectiveness starts to wane after a few months. For regulatory purposes, such data are especially useful for the most recent variants, including XBB and later.

There is mounting evidence on the occurrence of longer-term outcomes of SARS-CoV-2 infection[5]. This can include very specific outcomes such as cardiovascular events or the incidence of new-onset diabetes, or broader definitions such as the WHO clinical case definition for post COVID-19 condition[6]. Data are needed regarding the COVID-19 vaccines effectiveness at preventing these outcomes. This is pertinent for the most recent COVID-19 variants, but equally important for older variants.
The EMA has therefore requested a study to evaluate the effectiveness of Comirnaty and Spikevax against severe COVID-19 outcomes and post-acute outcomes of SARS-CoV-2 infection.

7. RESEARCH QUESTION AND OBJECTIVES

Research Question

What is the effectiveness of the EMA-authorized COVID-19 vaccines Comirnaty and Spikevax against severe COVID-19 and post-acute outcomes of SARS-CoV-2 infection?

Objective(s)

To generate additional evidence on the effectiveness of COVID-19 vaccines at preventing severe COVID-19 and post-acute outcomes of SARS-CoV-2 infection.

Specifically, this study has 6 objectives:

1. To assess the effectiveness of COVID-19 vaccination for the prevention of severe COVID-19 related outcomes (COVID-19 related hospitalisation or COVID-19 related death)
2. To assess waning of the effectiveness of COVID-19 vaccination for the prevention of severe COVID-19 related outcomes (COVID-19 related hospitalisation or COVID-19 related death)
3. To assess the effectiveness of COVID-19 vaccination for the prevention of all-cause mortality in the 3- and 6-months following discharge for COVID-19 related hospitalisation
4. To assess the effectiveness of COVID-19 vaccination for the prevention of new-onset type 1 Diabetes Mellitus in the 12 months after a SARS-CoV-2 infection
5. To assess the effectiveness of COVID-19 vaccination for the prevention of new-onset type 2 Diabetes Mellitus in the 12 months after a SARS-CoV-2 infection
6. To assess the effectiveness of COVID-19 vaccination for the prevention of cardiovascular events in the 12 months after a SARS-CoV-2 infection

Table 7.1: Primary and secondary research questions and objective

A. Primary research question: Objectives 1-2

Objective:	To assess the effectiveness and waning of effectiveness of COVID-19 vaccination for the prevention of severe COVID-19 related outcomes
Hypothesis:	NA
Population *(mention key inclusion-exclusion criteria):*	All subjects aged 12 years and older, with at least 365 days of data availability in the respective database before index date (ID) with • a 3rd-vaccine dose (1st booster dose) of Comirnaty or Spikevax. • at least 365days of data availability in the respective database • at least 90days of time elapsed since the last vaccine dose (i.e. the 3rd vaccine dose or 1st booster) at the time of study inclusion • at least 90days of time elapsed since the last record of a clinical diagnosis of COVID-19 or positive SARS-COV-2 test at the time of study inclusion.
Exposure:	4th vaccine dose/2nd booster dose of Comirnaty or Spikevax
Comparator:	No 4th vaccine dose/2nd booster dose (only 3rd dose)
Outcome:	COVID-19 related hospitalisation;COVID-19 related death
Time *(when follow up begins and ends):*	Follow-up start: at index date of matched 3-dose vaccinated/4-dose vaccinated people after start of roll-out of vaccination programs for 2nd booster dose End of follow-up: End of their observation (i.e. date of data extraction, database availability or death), next vaccine dose or outcome event, whatever comes first.
Setting:	Primary care electronic health records from SIDIAP [Spain], IPCI [The Netherlands] and CPRD GOLD [UK]
Main measure of effect:	Vaccine effectiveness, calculated as 1 - Hazard ratio (HR)

B. Primary research question: Objectives 3

Outcome:	To assess the effectiveness of COVID-19 vaccination for the prevention of ~~post-acute~~ all-cause mortality in the 3- and 6-months following discharge for COVID-19 related hospitalisation
Hypothesis:	NA
Population *(mention key inclusion-exclusion criteria):*	All subjects aged 12 years and older, with at least 365 days of data availability in the respective database before index date (ID) with • a 1st-vaccine dose [2nd vaccine dose; 3rd vaccine dose] of Comirnaty or Spikevax. • at least 365days of data availability in the respective database. • at least 90days of time elapsed since the last vaccine dose at the time of study inclusion. • at least 90days of time elapsed since the last record of a clinical diagnosis of COVID-19 or positive SARS-COV-2 test at the time of study inclusion.
Exposure:	2nd vaccine dose [3rd vaccine dose; 4th vaccine dose] of Comirnaty or Spikevax
Comparator:	No 2nd vaccine dose [3rd vaccine dose; 4th vaccine dose] of Comirnaty or Spikevax
Outcome:	All-cause mortality within 3/6months following COVID-19 related hospitalisation
Time *(when follow up begins and ends):*	Follow-up start: at index date of matched single-vaccinated/ double-vaccinated people [double-vaccinated vs. triple vaccinated; triple vaccinated vs. 4th dose vaccinated] after start of roll-out of vaccination programs i.e. from 01/01/2021 End of follow-up: End of their observation (i.e. date of data extraction, database availability or death), next vaccine dose or outcome event, whatever comes first.
Setting:	Primary care electronic health records from SIDIAP [Spain], IPCI [The Netherlands] and CPRD GOLD [UK]
Main measure of effect:	• Incidence rate for outcomes-100’000 person-years • Vaccine effectiveness against post COVID-19 mortality, calculated as 1 - HR

C. Primary research question: Objectives 4-6

Outcome:	To assess the effectiveness of COVID-19 vaccination for the prevention of new-onset type 1 Diabetes Mellitus, type 2 Diabetes Mellitus or cardiovascular events in the 12 months after a SARS-CoV-2 infection
Hypothesis:	NA
Population *(mention key inclusion-exclusion criteria):*	All subjects aged 12 years and older, with at least 365 days of data availability in the respective database before index date (ID) with • a 1st-vaccine dose [2nd vaccine dose; 3rd vaccine dose] of Comirnaty or Spikevax. • at least 365days of data availability in the respective database. • at least 90days of time elapsed since the last vaccine dose at the time of study inclusion. • at least 90days of time elapsed since the last record of a clinical diagnosis of COVID-19 or positive SARS-COV-2 test at the time of study inclusion • no diagnosis of the respective outcome in the patients history
Exposure:	2nd vaccine dose [3rd vaccine dose; 4th vaccine dose] of Comirnaty or Spikevax
Comparator:	No 2nd vaccine dose [3rd vaccine dose; 4th vaccine dose] of Comirnaty or Spikevax
Time *(when follow up begins and ends):*	Follow-up start: at index date of matched single-vaccinated/ double-vaccinated people [double-vaccinated vs. triple vaccinated; triple vaccinated vs. 4th dose vaccinated] after start of roll-out of vaccination programs i.e. from 01/01/2021 End of follow-up: End of their observation (i.e. date of data extraction, database availability or death), next vaccine dose or outcome event, whatever comes first.
Setting:	Primary care electronic health records from SIDIAP [Spain], IPCI [The Netherlands] and CPRD GOLD [UK]
Main measure of effect:	• Incidence rate for outcomes-100’000 person-years • Vaccine effectiveness against post- acute COVID-19 complications, calculated as 1 - HR

8. RESEARCH METHODS

8.1 Study type and Study Design

STUDY TYPE	STUDY DESIGN	STUDY CLASSIFICATION
Vaccine Effectiveness Studies	New User Cohorts	Complex Study

8.2 Study Setting and Data Sources

This study will be conducted using routinely collected data from 3 databases in 3 European countries. All databases were previously mapped to the OMOP CDM.

1. Clinical Practice Research Datalink (CPRD GOLD), United Kingdom
2. Integrated Primary Care Information Project (IPCI), The Netherlands
3. Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP), Spain

Detailed information on data sources is described in **Table 8.2.1**.

Database selection

The selection of databases for this study was performed based on data reliability and relevance for the proposed research question among those databases onboarded and available within DARWIN EU. The selected databases fulfil the criteria required for the availability of key information on exposures (i.e. complete recording of vaccines including date and brand), outcomes (except for hospitalization), and covariates, while covering different settings and regions of Europe.

Records on SARS-CoV-2 infection and vaccination will be available in all databases. We have previously published studies showing that these databases can generate reliable evidence on COVID-19 research[1 7-10]. Specifically, the availability of COVID-19 tests results, and linked vaccination records through national/regional immunization program (CPRD, SIDIAP) increased the reliability of the identified study exposures. Information on hospitalization will be available in SIDIAP and IPCI, which provides primary care records with (linked) hospitalization information.

No SARS-CoV-2 variant information from sequencing is available in any of the databases. We will therefore use calendar period with predominance of variants as a proxy for SARS-COV-2 variants in this study.

Information on vaccine products (i.e. monovalent/bivalent booster) are not reliably recorded in the databases, but only the vaccine brand. We will therefore use the number of vaccine doses in combination with vaccine brand for this study.

Potential for future study repetition

This study could be replicated in the future to include additional databases provided those are onboarded for DARWIN EU and fulfill the selection criteria as outlined above.

Table 8.2.1. Description of the selected data sources.

Country	Name of Database	Justification for Inclusion	Health Care setting	Type of Data (EHR, claims, registries)	Number of active subjects	Feasibility count of outcome/exposure (if relevant)	Data lock for the last update	Contributing to objectives
United Kingdom	CPRD GOLD	Complete records on SARS-CoV-2 infection, Covid-19 vaccination, and outcome events of interest (excl. hospitalization for COVID-19)	Primary care	EHR	3M	Covid-19: 360,198 Comirnaty: 2,822,947 Spikevax: 311,069	01/2023	1-2 for outcome "COVID-19 related death" only, 4-6
The Netherlands	IPCI	Complete records on SARS-CoV-2 infection, Covid-19 vaccination, and outcome events of interest	Primary care	EHR	1.39M	Covid-19: 941,329 Comirnaty: 1,173,104 Spikevax: 463,315	12/2022	1-6
Spain	SIDIAP	Complete records on SARS-CoV-2 infection, Covid-19 vaccination, and outcome events of interest; Include inpatient admission information.	Primary care + linkage to hospital data	EHR	5.8M	Covid-19: 3,865,976 Comirnaty: 6,548,545 Spikevax: 3,371,395	06/2022	1-6

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

The Clinical Practice Research Datalink (CPRD) is a governmental, not-for-profit research service, jointly funded by the National Institute for Health and Care Research and the Medicines and Healthcare products Regulatory Agency, a part of the Department of Health, United Kingdom (UK) (https://cprd.com). CPRD GOLD[11] comprises computerized records of all clinical and referral events in primary care in addition to comprehensive demographic information and medication prescription data in a sample of UK patients (predominantly from Scotland (52% of practices) and Wales (28% of practices). The prescription records include information on the type of product, date of prescription, strength, dosage, quantity, and route of administration. Data from contributing practices are collected and processed into research databases. Quality checks on patient and practice level are applied during the initial processing. Data are available for 20 million patients, including 3.2 million currently registered patients. Approval for this study was granted via the Research Data Governance Process.

Integrated Primary Care Information Project (IPCI), The Netherlands (Erasmus)

IPCI is collected from electronic health records (EHR) of patients registered with their general practitioners (GPs) throughout the Netherlands.[12] The selection of 374 GP practices is representative of the entire country. The database contains records from 2.8 million patients out of a Dutch population of 17M starting in 1996[12]. The median follow-up is 4.7 years. The observation period for a patient is determined by the date of registration at the GP and the date of leave/death. The observation period start date is refined by many quality indicators, e.g. exclusion of peaks of conditions when registering at the GP. All data before the observation period is kept as history data. Drugs are captured as prescription records with product, quantity, dosing directions, strength and indication. Drugs not prescribed in the GP setting might be underreported. Indications are available as diagnoses by the GPs and, indirectly, from secondary care providers but the latter might not be complete. Approval for this study was obtained from the Governance Board[12].

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

SIDIAP is collected from EHR records of patients receiving primary care delivered through Primary Care Teams (PCT), consisting of GPs, nurses and non-clinical staff[13]. The Catalan Health Institute manages 286 out of 370 such PCT with a coverage of 5.6M patients, out of 7.8M people in the Catalan population (74%). The database started to collect data in 2006. The mean follow-up is 10 years. The observation period for a patient can be the start of the database (2006), or when a person is assigned to a Catalan Health Institute primary care centre. Date of exit can be when a person is transferred-out to a primary care centre that does not pertain to the Catalan Health Institute, or date of death, or date of end of follow-up in the database. Drug information is available from prescriptions and from dispensing records in pharmacies. Drugs not prescribed in the GP setting might be underreported; and disease diagnoses made at specialist care settings are not included. Approval for this study was granted by both SIDIAP's Scientific and Ethics Committee.

8.3 Study Period

The study period will start on 01/01/2021 for all databases covering the period where "any variant" was dominant. The end of the study period will be the last available date of data collection for each contributing dataset.

For analyses conducted specifically at the time of predominance of "XBB variant or later dominant" variant, the study period would start on the 01/03/2023, when XBB became the dominant variant. However, this

period is not covered by the data cuts currently onboarded for DARWIN EU®. Analyses will therefore start at the time when vaccine booster programs offering the 4th vaccine dose were rolled out in each country.

Table 8.3.1. illustrates the periods of COVID-19 variant dominance across UK, The Netherlands and Spain.

Table 8.3.1. Periods of variant dominance

	UK	The Netherlands	Spain
Any variant	01/2021 - ongoing	01/2021 – ongoing	01/2021 - ongoing
Alpha and earlier variants	01/01/2021 - 01/06/2021	01/01/2021 – 01/07/2021	01/01/2021 – 01/07/2021
Delta	01/06/2021 – 15/12/2021	01/07/2021– 15/12/2021	01/07/2021– 15/12/2021
Omicron	15/12/2021 – 01/03/2023	15/12/2021 – 01/03/2023	15/12/2021 – 01/03/2023
XBB variant or later dominant	01/03/2023 - ongoing	01/03/2023 - ongoing	01/03/2023 - ongoing

[https://ourworldindata.org/grapher/covid-variants-bar?time=latest&facet=none&country=GBR~ESP~FIN~NOR~NLD, accessed 15/08/2023

8.4 Follow-up

For all analyses, follow-up time will start from index date.

End of follow-up for each objective will be the end of a person's observation time (i.e. date of data extraction, database availability or death), the date of their next vaccine dose, fixed duration or the date of the respective outcome event, whatever comes first

Table 8.4.1: Operational Definition of Time 0 (index date) and other primary time anchors

Study population name(s)	Time Anchor Description (e.g. time 0)	Number of entries	Type of entry	Washout window	Care Setting[1]	Code Type	Diagnosis position	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
1 dose only	Vaccination date 1st dose	1	incident	All history	OP	RxNorm	n/a	vaccination	n/a	n/a
Complete primary vaccination course (2 doses)	Vaccination date 2nd dose	1	n/a	21days	OP	RxNorm	n/a	n/a	n/a	n/a
3rd dose (monovalent or adapted/bivalent)	Vaccination date 3rd dose	1	n/a	90days	OP	RxNorm	n/a	n/a	n/a	n/a
4th dose (monovalent or adapted/bivalent)	Vaccination date 4th dose	1	n/a	90days	OP	RxNorm	n/a	n/a	n/a	n/a
4th dose (any monovalent)	Vaccination date 4th dose	1	n/a	90days	OP	RxNorm	n/a	n/a	n/a	n/a
4th dose, (any adapted/bivalent boosters)	Vaccination date 4th dose	1	n/a	90days	OP	RxNorm	n/a	n/a	n/a	n/a

OP = outpatient, n/a = not applicable

8.5 Study Population with inclusion and exclusion criteria

The source population will comprise all subjects aged 12 years and older, with at least 365 days of data availability in the respective database before index date (ID) [ID defined as the date of the "latest" vaccine dose administered] AND data availability from 12/2020 onwards (i.e. the time when the roll-out of the vaccination campaign started) in the respective database will be included.

People will then be matched 1:1 based on the number of vaccines doses they received [exposure], with their matched counterparts having 1 vaccine dose less at the time of matching. Based on the index date of matched counterparts, the following inclusion criteria will be applied:

- At least 365 days of data availability in the respective database
- At least 90days of time elapsed since the last vaccine dosefor >2 doses), at least 21days of time elapsed since the last vaccine dose for 2 doses and no previous vaccine dose recorded for 1st dose).
- At least 90days of time elapsed since the last record of a clinical diagnosis of COVID-19 or positive SARS-COV-2 test.

For analyses where diabetes mellitus or cardiovascular events are assessed as post-acute COVID-19 complications, people must not have had a record of the outcome within 365days before their index date for cardiovascular events, and no record anytime before index date for diabetes.

Operational definitions of Inclusion and Exclusion Criteria are provided in **Tables 8.5.1** and **8.5.2.**

Table 8.5.1. Operational Definitions of Inclusion Criteria

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position [2]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Observation period of 365day prior entry (all cohorts)	Study participants will be required to have 365 days prior history observed before contributing observation time	before	[-365, 0]	n/a	n/a	n/a	All individuals within the selected databases	n/a	n/a
Covid-19 vaccinated: 1 dose only	Exactly 1 Comirnaty/Spikevax vaccination record	after	n/a	OP	RxNorm	n/a			
Covid-19 vaccinated: Completed primary vaccination course	Exactly 2 vaccination records, with the latest being Comirnaty/Spikevax and at least 21days later than the 1st dose.								
Covid-19 vaccinated: 3rd dose	Exactly 3 vaccination records, with the 3rd dose being either monovalent or any of the adapted, bivalent Comirnaty/Spikevax vaccines								
Covid-19 vaccinated: 4th dose, monovalent or adapted/bivalent	Exactly 4 vaccination records, with the latest being Comirnaty/Spikevax								
Covid-19 vaccinated: 4th dose, monovalent	Exactly 4 vaccination records, with the 4rd dose being a monovalent Comirnaty/Spikevax vaccine								
Covid-19 vaccinated: 4th dose, adapted/bivalent	Exactly 4 vaccination records, with the 4rd dose being any of the adapted, bivalent Comirnaty/Spikevax vaccines								

OP = outpatient, n/a = not applicable

Table 8.5.2. Operational Definitions of Exclusion Criteria

Criterion	Details	Order of application	Assessment window	Care Settings[1]	Code Type	Diagnosis position[2]	Applied to study populations:	Measurement characteristics/validation	Source for algorithm
At least 90days of time elapsed since the last vaccine dose at the time of study inclusion [3rd, 4th dose]	Study participants will be required to have at least 90days of time elapsed between their 2nd and 3rd, or 3rd and 4th vaccine dose.	after	[-90, ID]	OP	RxNorm	n/a	People with 3rd and 4th vaccine dose	n/a	n/a
At least 21days of time elapsed since the last vaccine dose at the time of study inclusion. [2nd dose]	Study participants will be required to have at least 21days of time elapsed between their 2nd and 1st, vaccine dose.	after	[-21, ID]	OP	RxNorm	n/a	People with 2nd vaccine dose	n/a	n/a
No record of a previous COVID-19 vaccination [1st dose]	Study participants will be required to have no record of a previous COVID-19 vaccination	after	[-anytime, ID]	OP	RxNorm	n/a	People with 1st vaccine dose	n/a	n/a
At least 90days of time elapsed since the last record of a clinical diagnosis of COVID-19 or positive SARS-COV-2 test at the time of study inclusion	Study participants will be required to have no record of a clinical diagnosis of COVID-19 or positive SARS-COV-2 test within 90days before their index date	after	[-90, ID]	OP	SNOMED	n/a	All study population	n/a	n/a
No diagnosis of the respective outcome in the patient's history [Objectives 4, 5]	Patients included for analyses in objectives 4 and 5 will be excluded if they have the respective outcome of interest (diabetes) recorded in their patient history any time prior to index date	after	[-anytime, ID]	OP	SNOMEDRXNorm	n/a	Patients included for objectives 4 and 5	n/a	n/a
No diagnosis of the respective outcome in the patient's history [Objectives 4, 5]	Patients included for analyses in objective 6 will be excluded if they have the respective outcome of interest (cardiovascular conditions) recorded within the 365days before index date	after	[-365, ID]	OP	SNOMED	n/a	Patients included for objective 6	n/a	n/a

ID = index date, OP = outpatient, n/a = not applicable

8.6 Variables

8.6.1. Exposures

Vaccination against SARS-CoV-2

COVID-19 vaccine exposure status will be defined by number of received doses, i.e. 1 dose only, completed primary vaccination course (2 doses), 3rd dose (1st booster) and 4th dose (2nd booster). For booster doses, we will distinguish between monovalent or adapted/bivalent vaccines where possible. Where such detailed information is not available in the databases, we will use the number of vaccine doses received and the vaccine brand.

Start of the respective studies will depend on when the respective vaccines became available. An overview of dates of marketing approval is provided in **Table 8.6.1.1** below.

Table 8.6.1.1 Marketing approval dates

Country	**UK**	**The Netherlands**	**Spain**
Responsible Agency	**MHRA**	**EMA**	
Comirnaty original strain (monovalent)	08/12/2020	21/12/2020[14]	
Comirnaty original strain + omicron ba1 (adapted, bivalent)	02/09/2022[15]	01/09/2022[16]	
Comirnaty original strain + omicron ba4/5 (adapted, bivalent)	09/11/2022[17]	12/09/2022[18]	
Spikevax original strain (monovalent)	31/03/2021[19]	06/01/2021[20]	
Spikevax original strain + omicron ba1 (adapted, bivalent)	15/08/2022	01/09/2022	
Spikevax original strain + omicron ba4/5 (adapted, bivalent)	21/02/2023[21]	19/10/2022[22]	

Table 8.6.1.1 provides an operational definition of COVID-19 exposure status.

Table 8.6.1.1 Operational definition of exposure status

Exposure group name(s)	Details	Washout window	Assessment Window	Care Setting[1]	Code Type	Applied to study populations:	Incident with respect to…
Covid-19 vaccinated: 1 dose only	Exactly 1 Comirnaty/Spikevax vaccination record	Anytime in a patient's history	[-anytime, ID]	OP	RxNorm	Source population	COVID-19 vaccination
Covid-19 vaccinated: Completed primary vaccination course	Exactly 2 vaccination records, with the latest being Comirnaty/Spikevax	21 days	[-21, ID]				n/a
Covid-19 vaccinated: 3rd dose	Exactly 3 vaccination records, with the 3rd dose being either monovalent or any of the adapted, bivalent Comirnaty/Spikevax vaccines	90 days	[-90, ID]				n/a
Covid-19 vaccinated: 4th dose, monovalent or adapted/bivalent	Exactly 4 vaccination records, with the latest being Comirnaty/Spikevax	90days	[-90, ID]				n/a
Covid-19 vaccinated: 4th dose, monovalent	Exactly 4 vaccination records, with the 4rd dose being a monovalent Comirnaty/Spikevax vaccine	90days	[-90, ID]				n/a
Covid-19 vaccinated: 4th dose, adapted/bivalent	Exactly 4 vaccination records, with the 4rd dose being any of the adapted, bivalent Comirnaty/Spikevax vaccines	90days	[-90, ID]				n/a

8.6.2. Outcomes

Primary outcomes of interest:

1. COVID-19 related hospitalisation
2. COVID-19 related death
3. All-cause mortality in the 3 months after discharge from a COVID-19 hospitalisation
4. All-cause mortality in the 6 months after discharge from a COVID-19 hospitalisation
5. Incidence of new-onset type 1 Diabetes Mellitus beyond the first 30d after SARS-CoV-2 infection
6. Incidence of new-onset type 2 Diabetes Mellitus beyond the first 30d after SARS-CoV-2 infection
7. Incidence of cardiovascular events (cerebrovascular disorders, dysrhythmias, ischemic and non-ischemic heart disease, pericarditis, myocarditis, heart failure and thromboembolic disease) in the 12 months after a SARS-CoV-2 infection.

Preliminary code lists are available in the appendix of this protocol for all outcomes.

SARS-CoV-2 infection and COVID-19

Positive test result for SARS-CoV-2

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

Clinical diagnosis of COVID-19

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

Hospitalization with COVID-19

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

COVID-19 related death

COVID-19 related death will be defined as death within 28days from the date of COVID-19 clinical diagnosis or positive SARS-CoV-2 test.

All-cause mortality

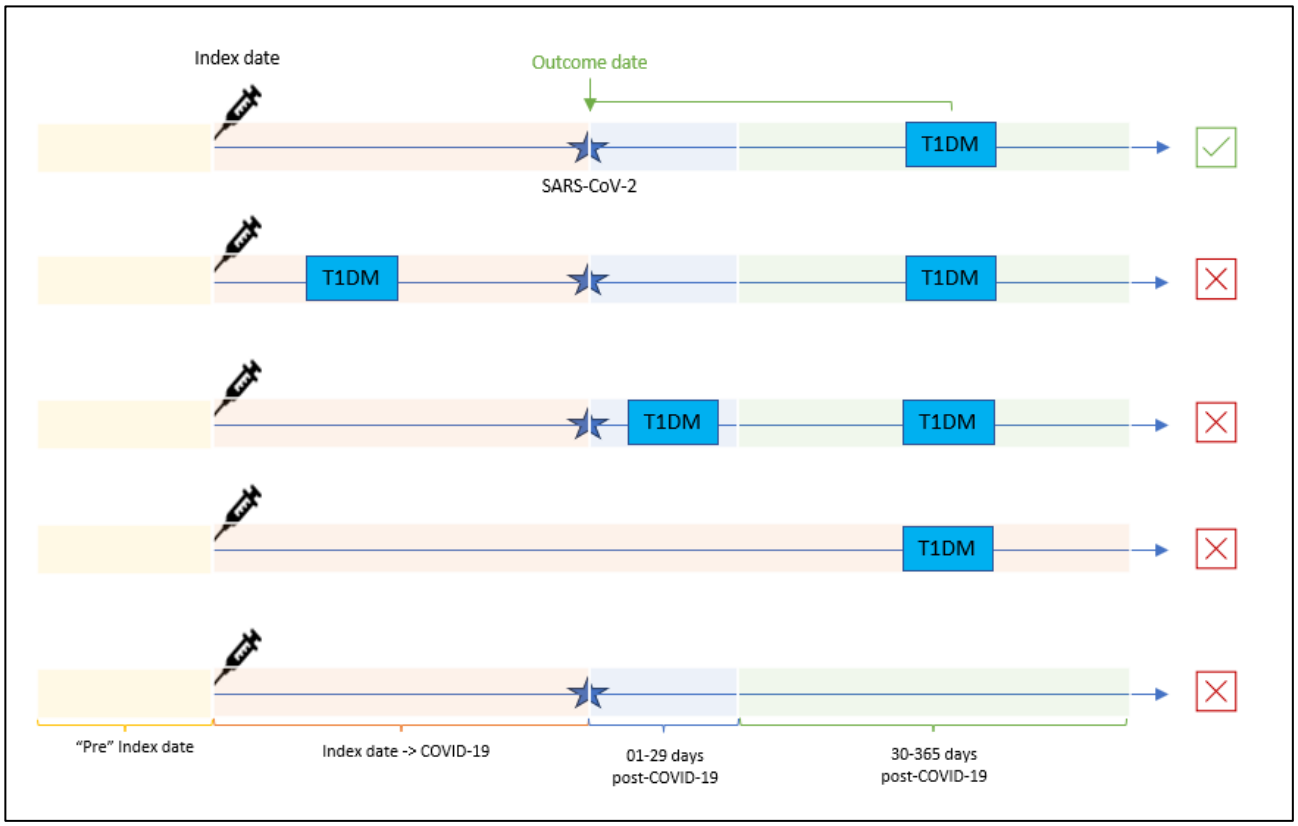
Death from any cause will be assessed from the date of death recorded in primary care records or from linked mortality information.

Post-acute COVID-19 complications

New-onset type 1 Diabetes Mellitus following SARS-COV-2 infection

New onset type 1 diabetes following SARS-COV-2 infection will be defined e.g. as a new diagnosis of Type 1 diabetes or prescription of insulin without concomitant use of other antidiabetic drugs within 30days-365days following SARS-CoV-2 positive test or clinical COVID-19 diagnosis. People with a previous recording of diabetes of any type, including HbA1c >6.5%, will not be included for objectives 4 and 5.

Figure 8.6.2.1 Illustrates the algorithm for the outcome definition of New-onset type 1 Diabetes Mellitus following SARS-COV-2 infection



New-onset type 2 Diabetes Mellitus following SARS-COV-2 infection

New onset type 2 diabetes following SARS-COV-2 infection will be defined as e.g. a new diagnosis of Type 2 diabetes or initiation of an oral antidiabetic medicine (e.g. metformin) within 30days-365days following SARS-CoV-2 positive test or clinical COVID-19 diagnosis. People with a previous recording of diabetes of any type, including HbA1c >6.5%, will not be included for objectives 4 and 5.

Phenotypes for Type 1 and Type 2 Diabetes Mellitus will be developed and tested across all databases before using the definition in this study. Plausibility test will be conducted using CohortDiagnostics, including the review of patient characteristics (e.g. demographics, comorbidities and previous comedication) for people identified with new onset diabetes.

Cardiovascular events

Cardiovascular events will be evaluated as a composite outcome and stratified for relevant subgroups:

Major cardiovascular events (MACE): will be identified by diagnostic codes for heart failure, acute myocardial infarction, stroke, or the occurrence of sudden cardiac death.

Venous thromboembolic events: will be identified by diagnostic codes for pulmonary embolism or deep vein thrombosis.

Arterial thromboembolic events: will be identified by an acute myocardial infarction or acute ischemic stroke.

Cerebrovascular disorders will be identified by acute ischemic stroke, haemorrhagic stroke or transient ischemic attack.

Heart failure, cardiac arrhythmia, angina pectoris, pericarditis and myocarditis will be measured as outcomes.

Phenotypes for these outcomes have been developed and used in previous vaccine safety studies[13].[13]. Code lists are available in the appendix of this protocol.

Table 8.6.2.1 Operational Definitions of Outcome

Outcome name	Details	Primary outcome ?	Type of outcome	Washout window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study:	Measurement characteristics/ validation	Source of algorithm
Hospitalization with COVID-19	COVID-19 clinical diagnosis or SARS-CoV-2 positive test within a time window from 21 days prior to admission to 3 days after hospital admission	Yes	Binary, time-to-event	n/a	IP, OP	SNOMED	any	Cohort 1-4	n/a	n/a
COVID-19 related death	COVID-19 clinical diagnosis or SARS-CoV-2 positive test up to 28days prior to date of death	Yes	Binary, time-to-event	n/a	OP		n/a	Cohort 1-4	n/a	n/a
All-cause mortality	date of death	Yes	Binary, time-to-event	n/a	OP		n/a	Cohort 5-8	n/a	n/a
New-onset type 1 Diabetes Mellitus	New onset Type 1 Diabetes Mellitus within 30-365days following SARS-CoV-2 positive test or COVID-19 diagnosis	Yes	Binary, time-to-event	Anytime prior ID	OP		n/a	Cohort 5-8	n/a	n/a
New-onset type 2 Diabetes Mellitus	New onset Type 2 Diabetes Mellitus within 30-365days following SARS-CoV-2 positive test or COVID-19 diagnosis	Yes	Binary, time-to-event	Anytime prior ID	OP		n/a	Cohort 5-8	n/a	n/a
Cardiovascular events	New Cardiovascular event/complication recorded within 30-365days following SARS-CoV-2 positive test or COVID-19 diagnosis	Yes	Binary, time-to-event	365days prior to index date	OP		n/a	Cohort 5-8	n/a	[1] [3]

OP = outpatient, n/a = not applicable

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

Demographics

Patients´ age at index date and sex will be identified.

Geographic location

We will use geographic location, e.g. GP surgery or healthcare regions to account for local vaccination, infection and testing rates.

Predominant SARS-CoV-2 variant

Calendar time will be used as a proxy to define exposure to the predominant variant, including "Alpha and earlier variants", "Delta", "Omicron" and "XBB variant or later dominant" for databases with sufficient recent data. Time periods are specified in section 8.3 Study Period.

Health conditions pre-index date

Individuals´ history of the comorbidities will be identified over three time periods prior to the index date, and will be used for summary characterisation and calculation of large-scale propensity scores:

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

A range of health conditions will be assessed using the time windows above. Among these, the following conditions will be identified for summary characterisation: anxiety, asthma, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, COVID-19, atrial fibrillation, cancer (excluding non-melanoma skin cancers), dementia, depressive disorder, diabetes, GERD, heart failure, hypertension, hypothyroidism, inflammatory bowel disease (crohn's disease or ulcerative colitis), myocardial infarction, venous thromboembolism, stroke, transient ischaemic attack (TIA), rheumatoid arthritis, osteoporosis, alcohol or drug substance misuse and obesity.

Medications pre-index date

Pre-existing medication use will be identified using 2 time windows, defined as 365 days to one day prior to index date, and 30 days to 1 day prior to index date, and will be used to provide summary characterisation for patients and calculation of large-scale propensity scores.

Immunocompromised status at the index date

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

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

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

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

The same algorithm/phenotype has been used in DARWIN EU Study P2-C3-001.

History of conditions for prioritization for vaccination

Additional conditions used for the identification of priority groups for vaccination not mentioned in any of the lists above (e.g. pregnancy) will be included.

Table 7. Operational Definitions of Covariates

Characteristic	Details	Type of variable	Assessment window	Care Settings[1]	Code Type	Diagnosis Position[2]	Applied to study populations:	Measurement characteristics/ validation	Source for algorithm
Demographics	Age and sex at index date	Numeric, binary	All history	OP		N/A	All cohort	n/a	n/a
Geographic location	Location identifier of GP surgery, healthcare regions	Categorical	All history	OP		N/A	All cohort	n/a	n/a
Predominant SARS-CoV-2 variant	Calendar time as proxy for predominant variant, including “Alpha and earlier variants”, “Delta”, “Omicron” and “XBB variant or later dominant”	Categorical	All history	OP		N/A	All cohort	n/a	n/a
Co-morbidity	Conditions of interest prior to index date	Binary	All history	OP	SNOMED	N/A	All cohort	n/a	n/a
Co-medication	Drug prescriptions prior to index date	Binary	[-183,-1] [-31 –1]	OP	RxNorm	N/A	All cohort	n/a	n/a
Immuno-compromised status	1.) Recording of Conditions: HIV/AIDS, Hematological malignancies, Solid malignancies, Other intrinsic immune conditions 2.) Treatment with antineoplastic and immunomodulating agents 3.) Systemic corticosteroids between 183 days to one day prior to index date + recording of organ transplantations, rheumatologic/inflammatory conditions within 365 days prior to index date	binary	[-365, -1] for condition, [-183,-1] for treatment	OP	SNOMED, RxNorm	N/A	All cohort	n/a	n/a

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

8.7 Study size

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

8.8 Analysis

All analyses will be conducted separately for each database, and will be carried out in a federated manner, allowing analyses to be run locally without sharing patient-level data.

Before sharing the study package, test runs of the analytics will be performed on a subset of the data sources and quality control checks will be performed. After all the tests are passed (see section 11 Quality Control), the final package will be released in a version-controlled study repository for execution against all the participating data sources.

The data partners will locally execute the analytics against the OMOP-CDM in R Studio and review and approve the by default aggregated results. They will then be made available to the Principal Investigators and study team in the Digital Research Environment. All results were locked and timestamped for reproducibility and transparency.

8.8.1 Patient privacy protection

Cell counts <5 will be suppressed to comply with the database's privacy protection regulations.

8.8.2 Descriptive statistics

For each analyses, summary descriptive analyses will be conducted including age, sex, key variables for matching and selected comorbidities where relevant.

8.8.3 Objectives 1-2: Vaccine effectiveness to prevent severe infection

Objectives 1 and 2 will assess the effectiveness of a 4th COVID-19 vaccine dose in people with 3 vaccine doses.

<u>Study population</u>

All people with a 3rd vaccine dose of Comirnaty or Spikevax will be included from the source population. Cohorts will be generated separately for Comirnaty and Spikevax, respectively.

<u>Study inclusion: Sequential matching</u>

Inclusion will be conducted using a sequential matching design, with similar designs being used in previous studies assessing vaccine effectiveness. Previous research showed matching to adequately reduce measured confounding in vaccine effectiveness research when including key variables such as geographic location[24].

Matching process using key confounders and Propensity Scores

For each calendar week starting from the day when a 4th vaccine dose (i.e. 2nd booster vaccine) became available/recommended in the respective country, people will be assigned to two cohorts: people who received a 4th vaccine dose during that week and people who did not receive a 4th dose.

Using the first day of the respective week as "preliminary" index date for non-boostered people, and the date of the 4th dose for booster-vaccinated people, the following inclusion criteria will be applied:

- At least 365 days of data availability in the respective database
- At least 90days of time elapsed since the previous vaccine dose (i.e. the 3rd or 4th vaccine dose)
- At least 90days of time elapsed since the last record of a clinical diagnosis of COVID-19 or positive SARS-COV-2 test.

Among those people in the cohorts who received or not received a 4th dose and met the inclusion criteria, non-boostered people will be matched 1:1 to a person receiving their 4th dose, based on key confounders and large-scale propensity scores using nearest neighbor matching, with caliper width 0.2 standard deviation. Key confounders will comprise but are not limited to:

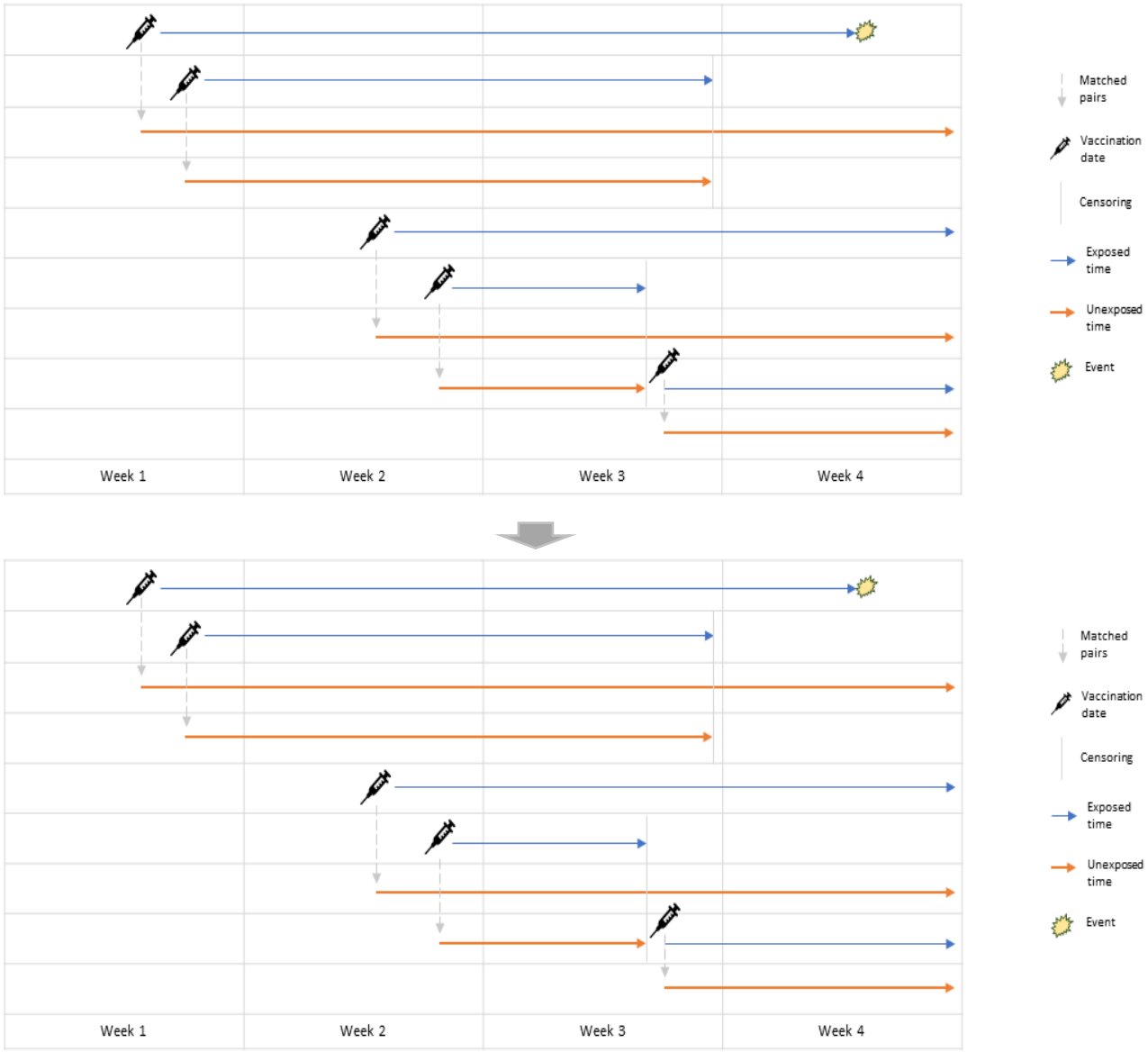
- Age (e.g. 5-year age bands)
- Sex (exact)
- Geographic location (exact)
- Previous vaccine brands (e.g. homologous or heterologous vaccination scheme)
- Time from previous vaccination
- History of conditions for prioritization for vaccination
- immunocompromised status
- previous SARS-CoV-2 diagnosis (>90days before index date)

Large-scale propensity scores (PS) will be computed to estimate the probability of receiving a 4th vaccine dose. Covariates to be included in the large-scale PS will be selected from co-medications and comorbidities recorded prior to cohort-specific index dates. Among those, covariates with a prevalence below 0.5% in the study population will be omitted. Logistic regression with LASSO regularization will then be used for variable selection. The list of selected covariates will be manually screened by 2 epidemiologists/clinical domain experts to exclude potential instrumental variables.

The same procedure will be conducted in the calendar week after, with previously non-boostered people being allowed to be included in the boostered cohort once they change exposure status. Non-boostered people can only be matched once to a boostered counterpart during the whole study.
With matching, non-boostered counterparts will be assigned the date of when the boostered counterpart received their 4th vaccine dose as their “final” index date (index date for the matched pair).

All boostered and matched non-boostered people from sequential weekly matching will be combined into the boostered and non-boostered cohort for subsequent analyses. The study inclusion and sequential matching process is illustrated in **Figure 8.8.3.1** below.

Figure 8.8.3.1 Study inclusion and sequential matching process



Follow-up

In the matched cohorts, people will be followed up from their index date until the earliest of

- End of their observation (i.e. date of data extraction, death)
- 2nd booster vaccination for unvaccinated group, 3rd booster for vaccinated group etc.
- COVID-19 related hospitalization or death, with outcome date being defined as the date of first COVID-19 diagnosis/positive test related to hospitalization or death.

Follow-up will be censored for the matched pair if one counterpart is censored, but not if one counterpart experiences the outcome.

Outcomes

The outcomes are defined in detail in section 8.6.2.
COVID-19 related hospitalization will be assessed for SIDIAP and IPCI. COVID-19 related death will be assessed for CPRD, IPCI and SIDIAP.

Statistical Analyses

Objective 1: Vaccine effectiveness

Cox proportions hazard models will be used to calculate hazard ratios (HR) for the outcomes of COVID-19 related hospitalisation and COVID-19 related death.
Negative control outcomes will be used as an additional measure to measure any potential residual confounding. NCO are outcomes not causally associated with the exposure of interest[26], here COVID-19 vaccination. However, their association with vaccination is ideally impacted by the same type of unmeasured confounding, e.g. healthcare-seeking behavior, as the vaccination-outcome association[27]. In the scenario of potential unmeasured confounding being detected by NCO, empirical calibration[25] for HR might be considered to minimise bias.

Vaccine effectiveness will be calculated as 1 – HR. Kaplan Meier plots and/or cumulative incidence plots will be used to illustrate survival analyses.
The proportional hazard assumption will be tested visual investigation of log(-log) plots. In the scenario of substantial violation of the proportional hazard assumptions, alternative models/model adaptations will be used.

Objective 2: Waning of vaccine effectiveness

Hazard ratios will be calculated for subsequent time windows after index date, i.e. in bi-weekly intervals. Monthly intervals will be used in case of small event counts to increase sample size and power if needed.
Vaccine effectiveness will be calculated as 1 – HR.
Kaplan Meier plots and/or cumulative incidence plots will be used to illustrate survival analyses.

8.8.4 Objective 3: Vaccine effectiveness to prevent COVID-19 related mortality

Objective 3 will assess vaccine effectiveness to prevent all-cause mortality in the 3 months/6 months after discharge from a COVID-19 hospitalisation. This objective will be assessed for SIDIAP and IPCI only, as no information on hospitalisation are available in CPRD.

The following comparisons will be conducted:

- 1st dose vaccinated vs. 2nd dose vaccinated [cohort 5 vs. 6]
- 2nd vaccinated vs. 3rd dose vaccinated [cohort 6 vs. 7]
- 3rd dose vaccinated vs. 4th dose vaccinated [cohort 7 vs. 8]

Study population

The study populations will be derived similar to the inclusion process outlined for objectives 1-2 above, including sequential matching. The following inclusion criteria will be applied:

- At least 365 days of data availability in the respective database
- At least 90days of time elapsed since the previous vaccine dose for the 3rd or 4th vaccine dose
- At least 21days of time elapsed since the previous vaccine dose for the 2nd vaccine dose
- At least 90days of time elapsed since the last record of a clinical diagnosis of COVID-19 or positive SARS-COV-2 test.

Outcomes

For contextualization, we will assess vaccine effectiveness to prevent COVID-19 hospitalization for the mentioned comparisons. The primary study outcome will be COVID-19 hospitalization followed by death within 3 or 6 months from discharge.

Statistical Analyses

Vaccine effectiveness analyses for COVID-19 related mortality following hospital discharge:

Incidence rates will be calculated for the matched cohorts and both outcomes. Cox proportional hazard models will be calculated for each outcome to provide HR. Follow-up will start at index date, i.e. the date of vaccination with respective new dose for matched pairs.
Negative control outcomes will be used as an additional measure to measure potential residual confounding. In the scenario of potential unmeasured confounding being detected by NCO, empirical calibration[25] for HR might be considered to minimise bias.
Kaplan Meier plots and/or cumulative incidence plots will be used to illustrate survival analyses.

8.8.5 Objectives 4-6: Vaccine effectiveness to prevent post-acute COVID-19 complications

Objectives 4-6 evaluate vaccine effectiveness to prevent post-acute COVID-19 complications, namely new onset diabetes and cardiovascular complications, and will be conducted in all 3 databases.

Similar to objective 3, we will compare people with 1st dose vaccination vs. 2nd dose vaccination [cohort 5 vs. 6], 2nd dose vaccination vs. 3rd dose vaccination [cohort 6 vs. 7] and 3rd dose vaccination vs. 4th dose vaccination [cohort 7 vs. 8].

Study population

The study populations will be derived similar to the inclusion process outlined for objectives 1-3 above, including sequential matching. Inclusion criteria will be applied as outline in section 8.8.4 for Objective 3.

For objectives 4 and 5, people with the respective outcomes of interest, i.e. diabetes recorded anytime before their index date will be excluded for the respective objective. For objective 6, an outcome-free washout window of 365days prior to index date will be implemented.

We will require at least 12 months of follow-up after SARS-CoV-2 infection to assess post-acute complications for outcomes 5, 6, and 7. If people die within 12months after COVID-19 they will contribute patient-time until death to the analyses. Only infections recorded 12 months before the end of data availability will be included.

Outcomes

- SARS-CoV-2 infection [for contextualization]
- SARS-CoV-2 infection + New onset diabetes Type 1 diabetes within 30-365days after COVID-19
- SARS-CoV-2 infection + New onset diabetes Type 2 diabetes within 30-365days after COVID-19
- SARS-CoV-2 infection + cardiovascular events (cerebrovascular disorders, dysrhythmias, ischemic and non-ischemic heart disease, pericarditis, myocarditis, heart failure and thromboembolic disease) in the 12 months after a SARS-CoV-2 infection

Vaccine effectiveness analyses for post-acute COVID-19 complications:
Incidence rates will be calculated for the matched cohorts and for each outcome. Cox proportional hazard models will be calculated for each outcome to provide HR. Follow-up will start at index date, i.e. the date of vaccination with respective new dose for matched pairs. As previous research showed, no relevant difference in effect estimates was seen for post-COVID-19 symptoms when used fine-grey models accounting for death as competing risk compared to Cox regression[2]. We therefore will not account for competing risk in this analysis.

Negative control outcomes and will be used as an additional measure to measure any potential residual confounding. A list of NCOs used in previous vaccine safety and effectiveness studies will be used. In the scenario of potential unmeasured confounding being detected by NCO, empirical calibration[25] for HR might be considered to minimise bias.

Kaplan-Meier plots and/or cumulative incidence plots will be used to illustrate survival analyses.

8.8.6 Stratified analyses, subgroup analyses and sensitivity analyses

All analyses will be stratified separately by vaccine brand (Comirnaty and Spikevax), and age at index date (i.e. age <65 years, ≥65years).

Subgroup analyses will be conducted among people with immunocompromised status, recorded within 365days prior to index date.

No sensitivity analyses are planned **(Table 8.8.6.1).**

Table 8.8.6.1 Sensitivity analyses – rationale, strengths and limitations

	What is being varied? How?	Why? (What do you expect to learn?)	Strengths of the sensitivity analysis compared to the primary	Limitations of the sensitivity analysis compared to the primary

8.9 Evidence synthesis

We will report analyses separately for each database and outcome. Additionally, we will pool the effect estimates across databases using random effect meta-analyses, I^2 for heterogeneity will be reported. Forest plots will be used to show results from meta-analyses. DATA MANAGEMENT

9. DATA MANAGEMENT

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

The analytic code for this study will be written in R, and will use standardized analytics wherever possible. Each data partner will execute the study code against their database containing patient-level data, and then return the results (csv files) which will only contain aggregated data. The results from each of the contributing data sites will then be combined in tables and figures for the study report.

9.1 Data storage and protection

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

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

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

10. QUALITY CONTROL

General database quality control

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

evaluated in two contexts: validation and verification. Validation relates to how well data align with external benchmarks with expectations derived from known true standards, while verification relates to how well data conform to local knowledge, metadata descriptions, and system assumptions.

Study specific quality control

Vaccine exposure status, COVID-19 clinical diagnoses, and SARS-CoV-2 tests will be identified from the data using established code-lists used in previous studies. Those lists have been updated for this study to include the latest codes i.e. for new vaccines.
When defining conditions for outcomes of interest, i.e. new onset Type 1 and Type 2 Diabetes Mellitus, a systematic search of possible codes for inclusion will be conducted using CodelistGenerator R package[28]. This software allows the user to define a search strategy and using this will then query the vocabulary tables of the OMOP common data model so as to find potentially relevant codes. Clinicians will review the resulting code lists to exclude irrelevant codes, such as for persisting disease or complications. In addition, the CohortDiagnostics R package (https://github.com/OHDSI/CohortDiagnostics) will be run if needed to assess the use of different codes across the databases contributing to the study and identify any codes potentially omitted in error.
For cardiovascular outcomes, concept sets used in previous vaccine safety studies will be used.

11. LIMITATIONS OF THE RESEARCH METHODS

General limitations:

- The study will be informed by routinely collected health care data and so data quality issues must be considered.
- We will use large-scale propensity scores to minimize measured confounding, and NCOs to assess potential residual confounding. However, given the observational nature of our data, we cannot rule out remaining confounding, which could partially account for findings in this study.

Study-specific limitations:

- Mandatory PCR test for people who tested positive in lateral flow home tests were skipped in early 2022. As not all positive home tests were reported and recorded as clinical diagnoses in primary care databases, it is likely that non-severe SARS-CoV-2 infections are underreported after 02/2022. Moreover, underreporting of COVID-19 for asymptomatic case is to be expected. Underreporting of COVID-19 could lead to misclassification of outcomes for Objectives 4-6, namely post-acute COVID-19 complications (diabetes, cardiac events). For objectives 4-6, we require a minimum follow-up time of 12months after SARS-CoV-2 to identify cases of new-onset diabetes and/or cardiovascular complications. With this, only infections recorded before 02/2022 will be included in the study.
- Routine screening has been impacted by the pandemic, and therefore diagnoses of new conditions, e.g. T2DM might have been delayed depending on testing practices.
- COVID-19 related hospitalization is unlikely to be underreported as people are likely to be asked about previous SARS-CoV-2 infections at hospital admission (Objective 3). However, positive COVID-19 test results that occur around hospitalization do not constitute a hospitalization *due to* COVID-19.

We will use the data cuts currently onboarded for DARWIN EU for CPRD, IPCI and SIDIAP. However, none of those is currently covering the period of XBB variant predominance. We therefore designed the study to assess objectives 1 and 2 to start at the time the 4th vaccine doses were made available for people.

MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse events/adverse reactions were not collected or analyzed as part of this evaluation. The nature of this non-interventional evaluation, through the use of secondary data, does not fulfill the criteria for reporting adverse events, according to module VI, VI.C.1.2.1.2 of the Good Pharmacovigilance Practices (https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf)

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

12. GOVERNANCE BOARD ASPECTS

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

13. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

14. OTHER ASPECTS

N/A

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16. ANNEXES

17. ANNEXES

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

Appendix II: ENCePP checklist for study protocols

APPENDIX I – PRELIMINARY CONCEPTS FOR STUDY VARIABLES

Table 1: Preliminary concepts for COVID-19 Diagnosis and SARS-CoV-2 infection

Concept Id	Concept name	domain
3661405	Acute bronchitis caused by SARS-CoV-2	Condition
3655976	Acute hypoxemic respiratory failure due to disease caused by Severe acute respiratory syndrome coronavirus 2	Condition
3661748	Acute kidney injury due to disease caused by Severe acute respiratory syndrome coronavirus 2	Condition
3661406	Acute respiratory distress syndrome due to disease caused by Severe acute respiratory syndrome coronavirus 2	Condition
3662381	Asymptomatic SARS-CoV-2	Condition
756031	Bronchitis caused by COVID-19	Condition
3656667	Cardiomyopathy due to disease caused by Severe acute respiratory syndrome coronavirus 2	Condition
3656668	Conjunctivitis due to disease caused by Severe acute respiratory syndrome coronavirus 2	Condition
439676	Coronavirus infection	Condition
37311061	COVID-19	Condition
4100065	Disease due to Coronaviridae	Condition
3656669	Dyspnea caused by Severe acute respiratory syndrome coronavirus 2	Condition
37310284	Encephalopathy due to disease caused by Severe acute respiratory syndrome coronavirus 2	Condition
3661885	Fever caused by Severe acute respiratory syndrome coronavirus 2	Condition
37310283	Gastroenteritis caused by SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2)	Condition
37310286	Infection of upper respiratory tract caused by Severe acute respiratory syndrome coronavirus 2	Condition
3663281	Lower respiratory infection caused by SARS-CoV-2	Condition
3661631	Lymphocytopenia due to Severe acute respiratory syndrome coronavirus 2	Condition
37310287	Myocarditis due to disease caused by Severe acute respiratory syndrome coronavirus 2	Condition
37310254	Otitis media due to disease caused by Severe acute respiratory syndrome coronavirus 2	Condition
704995	Patient meets COVID-19 clinical diagnostic criteria	Observation
700297	Patient meets COVID-19 laboratory confirmation criterion (detection of specific RNA in a clinical specimen using a molecular amplification detection test)	Observation
704996	Patient meets COVID-19 laboratory diagnostic criteria	Observation
700296	Patient meets COVID-19 presumptive laboratory evidence criteria (detection of specific antigen in a clinical specimen, OR detection of specific antibody in serum, plasma, or whole blood indicative of a new or recent infection)	Observation
37016927	Pneumonia caused by Human coronavirus	Condition
3661408	Pneumonia caused by SARS-CoV-2	Condition
40479642	Pneumonia due to Severe acute respiratory syndrome coronavirus	Condition
756039	Respiratory infection caused by COVID-19	Condition

3655977	Rhabdomyolysis due to disease caused by Severe acute respiratory syndrome coronavirus 2	Condition
3655975	Sepsis due to disease caused by Severe acute respiratory syndrome coronavirus 2	Condition
320651	Severe acute respiratory syndrome	Condition
37396171	Severe acute respiratory syndrome of upper respiratory tract	Condition
37311060	Suspected COVID-19	Observation
3661632	Thrombocytopenia due to Severe acute respiratory syndrome coronavirus 2	Condition
45763724	Suspected coronavirus infection	Observation
40218804	2019-ncov coronavirus, sars-cov-2/2019-ncov (covid-19), any technique, multiple types or subtypes (includes all targets), non-cdc	Measurement
40218805	Cdc 2019 novel coronavirus (2019-ncov) real-time rt-pcr diagnostic panel	Measurement
44789510	Coronavirus nucleic acid detection	Measurement
44811805	Coronavirus nucleic acid detection assay	Measurement
45770687	Coronavirus RNA (ribonucleic acid) detection assay	Measurement
44807536	Coronavirus RNA (ribonucleic acid) measurement by NAAT (nucleic acid amplification test)	Measurement
3667069	Detection of ribonucleic acid of Severe acute respiratory syndrome coronavirus 2 using polymerase chain reaction	Observation
36660491	Human coronavirus 229E RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection	Measurement
36659667	Human coronavirus HKU1 RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection	Measurement
36660329	Human coronavirus NL63 RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection	Measurement
36660364	Human coronavirus OC43 RNA [Presence] in Lower respiratory specimen by NAA with non-probe detection	Measurement
742224	Infectious agent antigen detection by immunoassay technique, qualitative or semiquantitative, multiple-step method; severe acute respiratory syndrome coronavirus (eg, SARS-CoV, SARS-CoV-2 [COVID-19]) (Coronavirus disease [COVID-19])	Measurement
700360	Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]), amplified probe technique	Measurement
742218	Infectious disease (bacterial or viral respiratory tract infection), pathogen-specific nucleic acid (DNA or RNA), 22 targets including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), qualitative RT-PCR, nasopharyngeal swab	Measurement
742219	Infectious disease (bacterial or viral respiratory tract infection), pathogen-specific nucleic acid (DNA or RNA), 22 targets including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), qualitative RT-PCR, nasopharyngeal swab	Measurement
36661384	Influenza virus A and B and SARS-CoV-2 (COVID-19) and SARS-related CoV RNA panel - Respiratory specimen by NAA with probe detection	Measurement
36661375	Influenza virus A and B and SARS-CoV-2 (COVID-19) identified in Respiratory specimen by NAA with probe detection	Measurement
36661376	Influenza virus A and B RNA and SARS-CoV-2 (COVID-19) N gene panel - Respiratory specimen by NAA with probe detection	Measurement
705104	Measurement of Coronavirus (Coronavirinae subfamily species)	Measurement
705105	Measurement of Coronavirus (Coronavirinae subfamily species) antigen	Measurement
37310257	Measurement of Severe acute respiratory syndrome coronavirus 2 antigen	Measurement

756055	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)	Measurement
586310	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Genetic material using Molecular method	Measurement
704991	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Blood	Measurement
756029	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Respiratory specimen	Measurement
586307	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Saliva	Measurement
705107	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Sample from nose	Measurement
704976	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Sample from oropharynx	Measurement
586309	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Specified specimen	Measurement
756065	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Unspecified specimen	Measurement
702834	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) specific cell-mediated immune response in Blood	Measurement
704992	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Culture method	Measurement
705001	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique	Measurement
705000	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Blood	Measurement
756085	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Respiratory specimen	Measurement
586308	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Saliva	Measurement
705106	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Sample from nose	Measurement
704975	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Sample from oropharynx	Measurement
756084	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Nucleic acid amplification technique in Unspecified specimen	Measurement
704993	Measurement of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) using Sequencing	Measurement
723477	SARS-CoV-2 (COVID-19) Ag [Presence] in Respiratory specimen by Rapid immunoassay	Measurement
706167	SARS-CoV-2 (COVID-19) N gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	Measurement
706157	SARS-CoV-2 (COVID-19) N gene [Cycle Threshold #] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N1	Measurement
706155	SARS-CoV-2 (COVID-19) N gene [Cycle Threshold #] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N2	Measurement
715272	SARS-CoV-2 (COVID-19) N gene [Presence] in Nasopharynx by NAA with probe detection	Measurement
757678	SARS-CoV-2 (COVID-19) N gene [Presence] in Nose by NAA with probe detection	Measurement
706161	SARS-CoV-2 (COVID-19) N gene [Presence] in Respiratory specimen by NAA with probe detection	Measurement

586524	SARS-CoV-2 (COVID-19) N gene [Presence] in Respiratory specimen by Nucleic acid amplification using CDC primer-probe set N1	Measurement
586525	SARS-CoV-2 (COVID-19) N gene [Presence] in Respiratory specimen by Nucleic acid amplification using CDC primer-probe set N2	Measurement
36661378	SARS-CoV-2 (COVID-19) N gene [Presence] in Saliva (oral fluid) by NAA with probe detection	Measurement
586520	SARS-CoV-2 (COVID-19) N gene [Presence] in Serum or Plasma by NAA with probe detection	Measurement
706175	SARS-CoV-2 (COVID-19) N gene [Presence] in Unspecified specimen by NAA with probe detection	Measurement
706156	SARS-CoV-2 (COVID-19) N gene [Presence] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N1	Measurement
706154	SARS-CoV-2 (COVID-19) N gene [Presence] in Unspecified specimen by Nucleic acid amplification using CDC primer-probe set N2	Measurement
723469	SARS-CoV-2 (COVID-19) ORF1ab region [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	Measurement
706168	SARS-CoV-2 (COVID-19) ORF1ab region [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	Measurement
723478	SARS-CoV-2 (COVID-19) ORF1ab region [Presence] in Respiratory specimen by NAA with probe detection	Measurement
723464	SARS-CoV-2 (COVID-19) ORF1ab region [Presence] in Unspecified specimen by NAA with probe detection	Measurement
586516	SARS-CoV-2 (COVID-19) [Presence] in Unspecified specimen by Organism specific culture	Measurement
723471	SARS-CoV-2 (COVID-19) RdRp gene [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	Measurement
723470	SARS-CoV-2 (COVID-19) RdRp gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	Measurement
706160	SARS-CoV-2 (COVID-19) RdRp gene [Presence] in Respiratory specimen by NAA with probe detection	Measurement
706173	SARS-CoV-2 (COVID-19) RdRp gene [Presence] in Unspecified specimen by NAA with probe detection	Measurement
586528	SARS-CoV-2 (COVID-19) RNA [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	Measurement
586529	SARS-CoV-2 (COVID-19) RNA [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	Measurement
715262	SARS-CoV-2 (COVID-19) RNA [Log #/volume] (viral load) in Unspecified specimen by NAA with probe detection	Measurement
706158	SARS-CoV-2 (COVID-19) RNA panel - Respiratory specimen by NAA with probe detection	Measurement
706169	SARS-CoV-2 (COVID-19) RNA panel - Unspecified specimen by NAA with probe detection	Measurement
723476	SARS-CoV-2 (COVID-19) RNA [Presence] in Nasopharynx by NAA with non-probe detection	Measurement
586526	SARS-CoV-2 (COVID-19) RNA [Presence] in Nasopharynx by NAA with probe detection	Measurement
757677	SARS-CoV-2 (COVID-19) RNA [Presence] in Nose by NAA with probe detection	Measurement
706163	SARS-CoV-2 (COVID-19) RNA [Presence] in Respiratory specimen by NAA with probe detection	Measurement
36661377	SARS-CoV-2 (COVID-19) RNA [Presence] in Respiratory specimen by Sequencing	Measurement

715260	SARS-CoV-2 (COVID-19) RNA [Presence] in Saliva (oral fluid) by NAA with probe detection	Measurement
715261	SARS-CoV-2 (COVID-19) RNA [Presence] in Saliva (oral fluid) by Sequencing	Measurement
723463	SARS-CoV-2 (COVID-19) RNA [Presence] in Serum or Plasma by NAA with probe detection	Measurement
706170	SARS-CoV-2 (COVID-19) RNA [Presence] in Unspecified specimen by NAA with probe detection	Measurement
723467	SARS-CoV-2 (COVID-19) S gene [Cycle Threshold #] in Respiratory specimen by NAA with probe detection	Measurement
723468	SARS-CoV-2 (COVID-19) S gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	Measurement
723465	SARS-CoV-2 (COVID-19) S gene [Presence] in Respiratory specimen by NAA with probe detection	Measurement
586519	SARS-CoV-2 (COVID-19) S gene [Presence] in Serum or Plasma by NAA with probe detection	Measurement
723466	SARS-CoV-2 (COVID-19) S gene [Presence] in Unspecified specimen by NAA with probe detection	Measurement
586517	SARS-CoV-2 (COVID-19) whole genome [Nucleotide sequence] in Isolate by Sequencing	Measurement
757685	SARS-CoV+SARS-CoV-2 (COVID-19) Ag [Presence] in Respiratory specimen by Rapid immunoassay	Measurement
706172	SARS-like coronavirus N gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	Measurement
706171	SARS-like coronavirus N gene [Presence] in Unspecified specimen by NAA with probe detection	Measurement
706166	SARS-related coronavirus E gene [Cycle Threshold #] in Unspecified specimen by NAA with probe detection	Measurement
586523	SARS-related coronavirus E gene [Presence] in Respiratory specimen by NAA with probe detection	Measurement
586518	SARS-related coronavirus E gene [Presence] in Serum or Plasma by NAA with probe detection	Measurement
706174	SARS-related coronavirus E gene [Presence] in Unspecified specimen by NAA with probe detection	Measurement
706159	SARS-related coronavirus+MERS coronavirus RNA [Presence] in Respiratory specimen by NAA with probe detection	Measurement
706165	SARS-related coronavirus RNA [Presence] in Respiratory specimen by NAA with probe detection	Measurement
723472	SARS-related coronavirus RNA [Presence] in Unspecified specimen by NAA with probe detection	Measurement

Table 2: Preliminary concepts for cardiovascular events

Concept ID	Concept name
VENOUS THROMBOEMBOLISM	
Outcome	**Deep vein thrombosis**
762047	Acute bilateral thrombosis of subclavian veins
762148	Acute deep vein thrombosis of bilateral iliac veins
761444	Acute deep vein thrombosis of bilateral lower limbs following coronary artery bypass graft

35616028	Acute deep vein thrombosis of left iliac vein
35615035	Acute deep vein thrombosis of left lower limb following procedure
761416	Acute deep vein thrombosis of left upper limb following coronary artery bypass graft
35615031	Acute deep vein thrombosis of left upper limb following procedure
43531681	Acute deep vein thrombosis of lower limb
35616027	Acute deep vein thrombosis of right iliac vein
35615034	Acute deep vein thrombosis of right lower limb following procedure
761415	Acute deep vein thrombosis of right upper limb following coronary artery bypass graft
35615030	Acute deep vein thrombosis of right upper limb following procedure
44782746	Acute deep venous thrombosis
44782751	Acute deep venous thrombosis of axillary vein
762008	Acute deep venous thrombosis of bilateral axillary veins
760875	Acute deep venous thrombosis of bilateral calves
765155	Acute deep venous thrombosis of bilateral ileofemoral veins
762017	Acute deep venous thrombosis of bilateral internal jugular veins
762417	Acute deep venous thrombosis of bilateral legs
762020	Acute deep venous thrombosis of bilateral popliteal veins
765546	Acute deep venous thrombosis of bilateral tibial veins
762004	Acute deep venous thrombosis of both upper extremities
44782742	Acute deep venous thrombosis of calf
44782747	Acute deep venous thrombosis of femoral vein
762015	Acute deep venous thrombosis of ileofemoral vein of left leg
765541	Acute deep venous thrombosis of ileofemoral vein of right lower extremity
44782748	Acute deep venous thrombosis of iliofemoral vein
44782752	Acute deep venous thrombosis of internal jugular vein
762009	Acute deep venous thrombosis of left axillary vein
760876	Acute deep venous thrombosis of left calf
765540	Acute deep venous thrombosis of left femoral vein
765922	Acute deep venous thrombosis of left internal jugular vein
762418	Acute deep venous thrombosis of left lower extremity
765537	Acute deep venous thrombosis of left upper extremity
44782767	Acute deep venous thrombosis of lower extremity as complication of procedure
46270071	Acute deep venous thrombosis of lower limb due to coronary artery bypass grafting
762022	Acute deep venous thrombosis of politeal vein of right leg
44782743	Acute deep venous thrombosis of popliteal vein
762021	Acute deep venous thrombosis of popliteal vein of left leg
762010	Acute deep venous thrombosis of right axillary vein
760877	Acute deep venous thrombosis of right calf
762013	Acute deep venous thrombosis of right femoral vein
762018	Acute deep venous thrombosis of right internal jugular vein
762419	Acute deep venous thrombosis of right lower extremity

762005	Acute deep venous thrombosis of right upper extremity
44782745	Acute deep venous thrombosis of thigh
44782744	Acute deep venous thrombosis of tibial vein
762026	Acute deep venous thrombosis of tibial vein of left leg
765156	Acute deep venous thrombosis of tibial vein of right leg
44782421	Acute deep venous thrombosis of upper extremity
764016	Acute deep venous thrombosis of upper extremity after coronary artery bypass graft
44782766	Acute deep venous thrombosis of upper extremity as complication of procedure
762048	Acute thrombosis of left subclavian vein
45757410	Acute thrombosis of mesenteric vein
762049	Acute thrombosis of right subclavian vein
36712892	Acute thrombosis of splenic vein
44782762	Acute thrombosis of subclavian vein
37109253	Bilateral acute deep vein thrombosis of femoral veins
40478951	Bilateral deep vein thrombosis of lower extremities
4046884	Deep vein thrombosis of leg related to air travel
4133004	Deep venous thrombosis
4181315	Deep venous thrombosis associated with coronary artery bypass graft
45773536	Deep venous thrombosis of femoropopliteal vein
763942	Deep venous thrombosis of left lower extremity
761980	Deep venous thrombosis of left upper extremity
443537	Deep venous thrombosis of lower extremity
4133975	Deep venous thrombosis of pelvic vein
40480555	Deep venous thrombosis of peroneal vein
4322565	Deep venous thrombosis of profunda femoris vein
763941	Deep venous thrombosis of right lower extremity
761928	Deep venous thrombosis of right upper extremity
4207899	Deep venous thrombosis of tibial vein
4028057	Deep venous thrombosis of upper extremity
193512	Embolism and thrombosis of the renal vein
435565	Embolism and thrombosis of the vena cava
4119760	Iliofemoral deep vein thrombosis
4124856	Inferior mesenteric vein thrombosis
4281689	Phlegmasia alba dolens
4284538	Phlegmasia cerulea dolens
4309333	Postoperative deep vein thrombosis
46285905	Provoked deep vein thrombosis
4033521	Splenic vein thrombosis
4055089	Superior mesenteric vein thrombosis
42538533	Thrombosis of iliac vein
44811347	Thrombosis of internal jugular vein

765049	Thrombosis of left peroneal vein
4317289	Thrombosis of mesenteric vein
4203836	Thrombosis of subclavian vein
4175649	Thrombosis of the popliteal vein
4153353	Traumatic thrombosis of axillary vein
46285904	Unprovoked deep vein thrombosis
4221821	Thrombophlebitis of deep veins of lower extremity
46271900	Recurrent deep vein thrombosis
4189004	Deep vein thrombosis of leg related to intravenous drug use
Outcome	**Pulmonary embolism**
4120091	Acute massive pulmonary embolism
45768439	Acute pulmonary embolism
45768888	Acute pulmonary thromboembolism
4309039	Hemorrhagic pulmonary infarction
762808	Infarction of lung due to embolus
40480461	Infarction of lung due to iatrogenic pulmonary embolism
4108681	Postoperative pulmonary embolus
4091708	Pulmonary air embolism
440417	Pulmonary embolism
37109911	Pulmonary embolism due to and following acute myocardial infarction
37016922	Pulmonary embolism on long-term anticoagulation therapy
43530605	Pulmonary embolism with pulmonary infarction
4119608	Pulmonary fat embolism
254662	Pulmonary infarction
4253796	Pulmonary microemboli
45766471	Pulmonary oil microembolism
4121618	Pulmonary thromboembolism
4119610	Pulmonary tumor embolism
4119607	Subacute massive pulmonary embolism
4119609	Subacute pulmonary fat embolism
4236271	Recurrent pulmonary embolism
ATERIAL THROMBOEMBOLISM	
Outcome	**Ischemic stroke**
4045735	Anterior cerebral circulation infarction
4031045	Anterior choroidal artery syndrome
761110	Bilateral cerebral infarction due to precererbral arterial occlusion
4110189	Cerebral infarct due to thrombosis of precerebral arteries
443454	Cerebral infarction
762951	Cerebral infarction due to anterior cerebral artery occlusion
765515	Cerebral infarction due to basilar artery stenosis

43530683	Cerebral infarction due to carotid artery occlusion
762933	Cerebral infarction due to cerebral artery occlusion
762937	Cerebral infarction due to cerebral venous thrombosis
4111714	Cerebral infarction due to cerebral venous thrombosis, non-pyogenic
4108356	Cerebral infarction due to embolism of cerebral arteries
45772786	Cerebral infarction due to embolism of middle cerebral artery
4110190	Cerebral infarction due to embolism of precerebral arteries
762935	Cerebral infarction due to internal carotid artery occlusion
763015	Cerebral infarction due to middle cerebral artery occlusion
46273649	Cerebral infarction due to occlusion of basilar artery
35610084	Cerebral infarction due to occlusion of cerebral artery
46270031	Cerebral infarction due to occlusion of precerebral artery
762934	Cerebral infarction due to posterior cerebral artery occlusion
43531607	Cerebral infarction due to stenosis of carotid artery
35610085	Cerebral infarction due to stenosis of cerebral artery
46270381	Cerebral infarction due to stenosis of precerebral artery
4110192	Cerebral infarction due to thrombosis of cerebral arteries
45767658	Cerebral infarction due to thrombosis of middle cerebral artery
44782773	Cerebral infarction due to vertebral artery occlusion
46270380	Cerebral infarction due to vertebral artery stenosis
37110678	Cerebral ischemic stroke due to occlusion of extracranial large artery
37110679	Cerebral ischemic stroke due to stenosis of extracranial large artery
4043731	Infarction - precerebral
4131383	Infarction of basal ganglia
4046237	Infarction of optic radiation
4119140	Infarction of visual cortex
4141405	Left sided cerebral infarction
37116473	Multifocal cerebral infarction due to and following procedure on cardiovascular system
4077086	Occipital cerebral infarction
4046359	Partial anterior cerebral circulation infarction
4319146	Pituitary infarction
4146185	Right sided cerebral infarction
36717605	Silent cerebral infarct
4142739	Thalamic infarction
4046358	Total anterior cerebral circulation infarction
372924	Cerebral artery occlusion
Outcome	**Myocardial infarction**
4119457	Acute Q wave infarction - anterolateral
4119943	Acute Q wave infarction - anteroseptal
4121464	Acute Q wave infarction - inferior
4121465	Acute Q wave infarction - inferolateral

4124684	Acute Q wave infarction - lateral
4119948	Acute Q wave infarction - widespread
4126801	Acute Q wave myocardial infarction
4296653	Acute ST segment elevation myocardial infarction
46270162	Acute ST segment elevation myocardial infarction due to left coronary artery occlusion
761737	Acute ST segment elevation myocardial infarction due to occlusion of circumflex coronary artery
46270163	Acute ST segment elevation myocardial infarction due to right coronary artery occlusion
43020460	Acute ST segment elevation myocardial infarction involving left anterior descending coronary artery
45766076	Acute ST segment elevation myocardial infarction of anterior wall involving right ventricle
761736	Acute ST segment elevation myocardial infarction of anteroapical wall
46270159	Acute ST segment elevation myocardial infarction of anterolateral wall
46270160	Acute ST segment elevation myocardial infarction of anteroseptal wall
45766116	Acute ST segment elevation myocardial infarction of inferior wall
45766151	Acute ST segment elevation myocardial infarction of inferior wall involving right ventricle
35611570	Acute ST segment elevation myocardial infarction of inferolateral wall
35611571	Acute ST segment elevation myocardial infarction of inferoposterior wall
46274044	Acute ST segment elevation myocardial infarction of lateral wall
46270161	Acute ST segment elevation myocardial infarction of posterior wall
46273495	Acute ST segment elevation myocardial infarction of posterobasal wall
46270158	Acute ST segment elevation myocardial infarction of posterolateral wall
46270164	Acute ST segment elevation myocardial infarction of septum
45766075	Acute anterior ST segment elevation myocardial infarction
4178129	Acute anteroapical myocardial infarction
4267568	Acute anteroseptal myocardial infarction
312327	Acute myocardial infarction
44782769	Acute myocardial infarction due to left coronary artery occlusion
44782712	Acute myocardial infarction due to right coronary artery occlusion
45766115	Acute myocardial infarction during procedure
434376	Acute myocardial infarction of anterior wall
45766150	Acute myocardial infarction of anterior wall involving right ventricle
438438	Acute myocardial infarction of anterolateral wall
4243372	Acute myocardial infarction of apical-lateral wall
4108669	Acute myocardial infarction of atrium
4151046	Acute myocardial infarction of basal-lateral wall
4275436	Acute myocardial infarction of high lateral wall
438170	Acute myocardial infarction of inferior wall
45771322	Acute myocardial infarction of inferior wall involving right ventricle
438447	Acute myocardial infarction of inferolateral wall
441579	Acute myocardial infarction of inferoposterior wall
436706	Acute myocardial infarction of lateral wall
4324413	Acute myocardial infarction of posterobasal wall

4051874	Acute myocardial infarction of posterolateral wall
4303359	Acute myocardial infarction of septum
4147223	Acute myocardial infarction with rupture of ventricle
4145721	Acute non-Q wave infarction
4119944	Acute non-Q wave infarction - anterolateral
4119456	Acute non-Q wave infarction - anteroseptal
4119945	Acute non-Q wave infarction - inferior
4119946	Acute non-Q wave infarction - inferolateral
4121466	Acute non-Q wave infarction - lateral
4124685	Acute non-Q wave infarction - widespread
4270024	Acute non-ST segment elevation myocardial infarction
35610091	Acute nontransmural myocardial infarction
319039	Acute posterior myocardial infarction
444406	Acute subendocardial infarction
35610093	Acute transmural myocardial infarction
4119947	Acute widespread myocardial infarction
37109912	Arrhythmia due to and following acute myocardial infarction
438172	Atrial septal defect due to and following acute myocardial infarction
4124687	Cardiac rupture due to and following acute myocardial infarction
4215259	First myocardial infarction
4108678	Hemopericardium due to and following acute myocardial infarction
4173632	Microinfarct of heart
45771327	Mitral valve regurgitation due to acute myocardial infarction with papillary muscle and chordal rupture
45766214	Mitral valve regurgitation due to acute myocardial infarction without papillary muscle and chordal rupture
45766212	Mitral valve regurgitation due to and following acute myocardial infarction
4323202	Mixed myocardial ischemia and infarction
4329847	Myocardial infarction
37309626	Myocardial infarction due to demand ischemia
4170094	Myocardial infarction in recovery phase
4200113	Non-Q wave myocardial infarction
TRANSIENT ISCHEMIC ATTACK	
373503	Transient cerebral ischemia
VENTRICULAR ARRYTHMIA, CARDIAC ARREST	
4247537	Accelerated idioventricular rhythm
4216773	Asystole
45766074	Bradycardic cardiac arrest
321042	Cardiac arrest
4309332	Cardiac arrest as a complication of care
4172822	Cardiac arrest due to cardiac disorder

4301015	Cardiac arrest due to pacemaker failure
4173446	Cardiac arrest due to respiratory disorder
4306984	Cardiac arrest due to trauma
4311273	Cardiac arrest during AND/OR resulting from a procedure
37398951	Cardiac arrest during surgery
761738	Cardiac arrest following cardiac surgery
317669	Cardiac arrest in fetus OR newborn
4120088	Cardiac arrest with successful resuscitation
4256374	Cardiorespiratory arrest
44783658	Cardiorespiratory arrest with successful resuscitation
4303238	Catecholaminergic polymorphic ventricular tachycardia
4128968	Circulatory arrest
4122762	Electromechanical dissociation
4148028	Electromechanical dissociation with successful resuscitation
36675005	Extrasystoles, short stature, hyperpigmentation, microcephaly syndrome
4124703	Familial ventricular tachycardia
4305862	Fascicular ventricular tachycardia
4029303	Fusion beats
4120086	His bundle tachycardia
764719	Idiopathic cardiac arrest
37109917	Idiopathic ventricular fibrillation not Brugada type
4171193	Idioventricular rhythm
4119600	Incessant infant ventricular tachycardia
4121482	Induced ventricular tachycardia
37017187	Intraoperative cardiorespiratory arrest
4091899	Junctional ectopic tachycardia
46272503	Mahaim fiber tachycardia
4088985	Multiple premature ventricular complexes
4089463	Multiple ventricular interpolated complexes
4088982	Narrow QRS ventricular tachycardia
44782707	Nonsustained paroxysmal ventricular tachycardia
40480274	Nonsustained ventricular tachycardia
4037682	O/E - collapse -cardiac arrest
4089464	Paired ventricular premature complexes
4119604	Paroxysmal familial ventricular fibrillation
437579	Paroxysmal ventricular tachycardia
4124701	Postoperative His bundle tachycardia
4233619	Pulseless ventricular tachycardia
45771051	Recurrent ventricular tachycardia
4121483	Right ventricular outflow tract ventricular tachycardia
4091904	Run of ventricular premature complexes

4088350	Slow ventricular response
4325850	Sustained ventricular fibrillation
4139206	Sustained ventricular tachycardia
37397458	Torsade de pointes with short coupling interval syndrome
37110729	Torsades de pointe caused by drug
4135823	Torsades de pointes
4185572	Ventricular arrhythmia
4008580	Ventricular bigeminy
4327066	Ventricular escape beat
4218242	Ventricular escape rhythm
36714539	Ventricular extrasystoles with syncope, perodactyly and Robin sequence syndrome
437894	Ventricular fibrillation
4111700	Ventricular fibrillation and flutter
433225	Ventricular flutter
4092010	Ventricular interpolated complexes
4244893	Ventricular parasystole
4066289	Ventricular premature beats
4088506	Ventricular quadrigeminy
40622721	Ventricular tachyarrhythmia
4103295	Ventricular tachycardia
4119599	Ventricular tachycardia with normal heart
4091900	Ventricular tachycardia, monomorphic
4088349	Ventricular tachycardia, polymorphic
4088501	Ventricular tachycardia, polymorphic without Q-T prolongation
4088505	Ventricular trigeminy
4088348	Wide QRS ventricular tachycardia
4064453	EKG: ventricular arrhythmia
4064455	EKG: ventricular fibrillation
4064871	EKG: ventricular tachycardia
4111552	Re-entry ventricular arrhythmia
Myocarditis and Pericarditis	
4289908	Viral pericarditis
4138837	Pericarditis
314383	Myocarditis
4149913	Systemic lupus erythematosus with pericarditis
318072	Histoplasmosis with pericarditis
44782774	Chest pain due to pericarditis
HEART FAILURE	
44782718	Acute combined systolic and diastolic heart failure
4023479	Acute congestive heart failure

312927	Acute cor pulmonale
40481042	Acute diastolic heart failure
44782655	Acute exacerbation of chronic congestive heart failure
442310	Acute heart failure
764877	Acute heart failure co-occurrent with normal ejection fraction
4108245	Acute left ventricular failure
4327205	Acute left-sided congestive heart failure
4267800	Acute left-sided heart failure
44782733	Acute on chronic combined systolic and diastolic heart failure
40481043	Acute on chronic diastolic heart failure
764874	Acute on chronic heart failure co-occurrent with normal ejection fraction
37309625	Acute on chronic right-sided congestive heart failure
40480602	Acute on chronic systolic heart failure
4215446	Acute right-sided congestive heart failure
4233424	Acute right-sided heart failure
40480603	Acute systolic heart failure
4193236	Ayerza's syndrome
439698	Benign hypertensive heart disease with congestive cardiac failure
4030258	Bernheim's syndrome
4242669	Biventricular congestive heart failure
4215802	Cardiac asthma
4177493	Cardiac insufficiency due to prosthesis
4233224	Cardiac insufficiency during AND/OR resulting from a procedure
4264636	Cardiac insufficiency following cardiac surgery
4259490	Cardiorespiratory failure
44782719	Chronic combined systolic and diastolic heart failure
4229440	Chronic congestive heart failure
4195892	Chronic cor pulmonale
40479576	Chronic diastolic heart failure
444031	Chronic heart failure
764876	Chronic heart failure co-occurrent with normal ejection fraction
4206009	Chronic left-sided congestive heart failure
4009047	Chronic left-sided heart failure
4284562	Chronic right-sided congestive heart failure
4014159	Chronic right-sided heart failure
40479192	Chronic systolic heart failure
4108244	Compensated cardiac failure
319835	Congestive heart failure
44784345	Congestive heart failure as early postoperative complication
762002	Congestive heart failure as post-operative complication of cardiac surgery
762003	Congestive heart failure as post-operative complication of non-cardiac surgery

44782428	Congestive heart failure due to cardiomyopathy
4139864	Congestive heart failure due to left ventricular systolic dysfunction
4142561	Congestive heart failure due to valvular disease
36713488	Congestive heart failure stage B
36712928	Congestive heart failure stage B due to ischemic cardiomyopathy
43021826	Congestive heart failure stage C
36712927	Congestive heart failure stage C due to ischemic cardiomyopathy
43021825	Congestive heart failure stage D
44782713	Congestive heart failure with right heart failure
4307356	Cor pulmonale
4111554	Decompensated cardiac failure
4311437	Decompensated chronic heart failure
443587	Diastolic heart failure
43530643	Diastolic heart failure stage B
43021842	Diastolic heart failure stage C
43021841	Diastolic heart failure stage D
43022068	Exacerbation of congestive heart failure
316139	Heart failure
4124705	Heart failure as a complication of care
37311948	Heart failure with mid range ejection fraction
40486933	Heart failure with normal ejection fraction
45766164	Heart failure with reduced ejection fraction
45766167	Heart failure with reduced ejection fraction due to cardiomyopathy
45766165	Heart failure with reduced ejection fraction due to coronary artery disease
45773075	Heart failure with reduced ejection fraction due to heart valve disease
45766166	Heart failure with reduced ejection fraction due to myocarditis
4004279	High output heart failure
44782728	Hypertensive heart AND chronic kidney disease with congestive heart failure
439696	Hypertensive heart and renal disease with (congestive) heart failure
439694	Hypertensive heart and renal disease with both (congestive) heart failure and renal failure
314378	Hypertensive heart disease with congestive heart failure
444101	Hypertensive heart failure
439846	Left heart failure
4185565	Low cardiac output syndrome
4103448	Low output heart failure
316994	Malignant hypertensive heart disease with congestive heart failure
4141124	Postvalvulotomy syndrome
764873	Reduced ejection fraction co-occurrent and due to acute heart failure
764871	Reduced ejection fraction co-occurrent and due to acute on chronic heart failure
764872	Reduced ejection fraction co-occurrent and due to chronic heart failure
4199500	Refractory heart failure

4138307	Right heart failure due to pulmonary hypertension
4195785	Right heart failure secondary to left heart failure
4273632	Right ventricular failure
35615055	Saddle embolus of pulmonary artery with acute cor pulmonale
4079695	Sepsis-associated left ventricular failure
4079296	Sepsis-associated right ventricular failure
44784442	Symptomatic congestive heart failure
443580	Systolic heart failure
43530642	Systolic heart failure stage B
36717359	Systolic heart failure stage B due to ischemic cardiomyopathy
43020421	Systolic heart failure stage C
36712929	Systolic heart failure stage C due to ischemic cardiomyopathy
43021840	Systolic heart failure stage D
40482857	Cardiorenal syndrome
4153875	Cardiac insufficiency as a complication of care
4215511	Emergency hospital admission for heart failure
4215689	Heart failure confirmed
4173819	Impaired left ventricular function
CARDIAC ARRYTHMIA	
4088502	AV junctional (nodal) arrest
4088503	AV junctional (nodal) tachycardia
4038688	AV junctional rhythm
4089459	AV nodal re-entry tachycardia
4228836	AV node arrhythmia
4088983	AV-junctional (nodal) bradycardia
4091901	Aberrant premature complexes
4092011	Aberrantly conducted complex
4057008	Accelerated atrioventricular conduction
4247537	Accelerated idioventricular rhythm
37312140	Acquired Brugada syndrome
37116420	Acquired complete atrioventricular block
40479264	Acquired long QT syndrome
4224848	Andersen Tawil syndrome
35608001	Ankyrin-B syndrome
313224	Anomalous atrioventricular excitation
4296729	Anterior fascicular block, posterior fascicular block AND incomplete right bundle branch block
4121481	Antidromic atrioventricular re-entrant tachycardia
37109912	Arrhythmia due to and following acute myocardial infarction
43020930	Arrhythmia due to vegetation of infective endocarditis
37108582	Arrhythmia during surgery
4101624	Arrhythmogenic right ventricular dysplasia

4102252	Asymptomatic sinoatrial node dysfunction
4068155	Atrial arrhythmia
4088504	Atrial bigeminy
4088986	Atrial escape complex
313217	Atrial fibrillation
4108832	Atrial fibrillation and flutter
44782442	Atrial fibrillation with rapid ventricular response
314665	Atrial flutter
4088987	Atrial parasystole
4108830	Atrial paroxysmal tachycardia
4115173	Atrial premature complex
37110775	Atrial septal defect, atrioventricular conduction defect syndrome
42872924	Atrial standstill
4171269	Atrial tachycardia
4091903	Atrial trigeminy
316135	Atrioventricular block
43020929	Atrioventricular block due to endocarditis
4305210	Atrioventricular conduction disorder
4175473	Atrioventricular dissociation
42536726	Atrioventricular reciprocating tachycardia
4081675	Atrioventricular tachycardia
36712986	Atypical atrial flutter
4250169	Bifascicular block
321587	Bilateral bundle branch block
4088984	Blocked premature atrial contraction
4228448	Bradyarrhythmia
4169095	Bradycardia
45766074	Bradycardic cardiac arrest
4303408	Brugada syndrome
313791	Bundle branch block
40484036	Bundle branch reentrant ventricular tachycardia
44784217	Cardiac arrhythmia
38001137	Cardiac arrhythmia & conduction disorders w CC
38001138	Cardiac arrhythmia & conduction disorders w/o CC/MCC
44784234	Cardiac arrhythmia associated with genetic disorder
45757098	Cardiac arrhythmia in mother complicating childbirth
44784235	Cardiac channelopathy
4303238	Catecholaminergic polymorphic ventricular tachycardia
42536725	Cavotricuspid isthmus dependent macroreentry tachycardia
36715042	Chronic atrial and intestinal dysrhythmia
4141360	Chronic atrial fibrillation
4137382	Chronic atrial flutter
4098133	Chronic ectopic atrial tachycardia

320744	Complete atrioventricular block
46269694	Complete atrioventricular block as complication of atrioventricular nodal ablation
4267892	Complete left bundle branch block
4088337	Complete right bundle branch block
4121615	Concealed accessory pathway
316999	Conduction disorder of the heart
4117112	Controlled atrial fibrillation
4304839	Diffuse intraventricular block
4236004	Ectopic atrial beats
4121479	Ectopic atrial tachycardia
4121480	Ectopic atrioventricular node tachycardia
4143042	Ectopic beats
4164083	Ectopic rhythm
4122762	Electromechanical dissociation
4148028	Electromechanical dissociation with successful resuscitation
36675005	Extrasystoles, short stature, hyperpigmentation, microcephaly syndrome
37395821	Familial atrial fibrillation
35624231	Familial dilated cardiomyopathy with conduction defect due to LMNA mutation
37399476	Familial isolated arrhythmogenic right ventricular dysplasia
4121613	Familial isolated complete right bundle branch block
4119603	Familial sick sinus syndrome
4124703	Familial ventricular tachycardia
4305862	Fascicular ventricular tachycardia
4226399	Fibrillation
314379	First degree atrioventricular block
4029303	Fusion beats
46284985	HHS - holiday heart syndrome
320425	Heart block
40481891	Heart block due to drug
36715370	Heart-hand syndrome type 2
36717434	Heart-hand syndrome type 3
43020494	High degree second degree atrioventricular block
4120086	His bundle tachycardia
4078058	Holt-Oram syndrome
4320474	Idiojunctional tachycardia
37109917	Idiopathic ventricular fibrillation not Brugada type
4171193	Idioventricular rhythm
4137871	Inappropriate sinus tachycardia
4124697	Incessant atrial tachycardia
4119600	Incessant infant ventricular tachycardia
4304095	Incisional tachycardia
4298806	Incomplete atrioventricular block with atrioventricular response
4088336	Incomplete left bundle branch block

4088338	Incomplete right bundle branch block
4121482	Induced ventricular tachycardia
4088332	Intermittent second degree atrioventricular block
4243143	Interpolated PVCs
4166844	Intraventricular conduction defect
4221549	Irregular tachycardia
4161597	Jervell and Lange-Nielsen syndrome
4091899	Junctional ectopic tachycardia
4166380	Junctional escape beats
4218739	Junctional premature beats
4088351	Junctional premature complex
4295336	Left anterior fascicular block
4171887	Left atrial incisional tachycardia
316998	Left bundle branch block
313209	Left bundle branch hemiblock
4111543	Left main stem bundle branch block
4268046	Left posterior fascicular block
4153404	Lev's syndrome
4119601	Lone atrial fibrillation
314664	Long QT syndrome
37396235	Long QT syndrome caused by drug
37117768	Long thumb brachydactyly syndrome
45768480	Longstanding persistent atrial fibrillation
437892	Lown-Ganong-Levine syndrome
42536724	Macro re-entrant atrial tachycardia
46272503	Mahaim fiber tachycardia
4088347	Marked sinus arrhythmia
35608087	Microcephalus, cerebellar hypoplasia, cardiac conduction defect syndrome
4088496	Minor intraventricular conduction defect
4205137	Mobitz type I incomplete atrioventricular block
313780	Mobitz type II atrioventricular block
4034164	Monofascicular block
4023336	Multifocal PVCs
4176112	Multifocal atrial tachycardia
4271464	Multifocal premature beats
4089460	Multiple atrial premature complexes
4088985	Multiple premature ventricular complexes
4089463	Multiple ventricular interpolated complexes
4088982	Narrow QRS ventricular tachycardia
37398927	Naxos disease
4217221	Nodal rhythm disorder
42539038	Non-cavotricuspid isthmus dependent atrial tachycardia
4119602	Non-rheumatic atrial fibrillation

44784220	Non-specific intraventricular conduction delay
4191222	Nonparoxysmal AV nodal tachycardia
44782789	Nonsustained paroxysmal supraventricular tachycardia
44782707	Nonsustained paroxysmal ventricular tachycardia
40480274	Nonsustained ventricular tachycardia
4124700	Orthodromic atrioventricular re-entrant tachycardia
4030583	Pacemaker twiddler's syndrome
4089464	Paired ventricular premature complexes
4006208	Parasystole
4154290	Paroxysmal atrial fibrillation
4146580	Paroxysmal atrial flutter
4190306	Paroxysmal atrial tachycardia with block
4108241	Paroxysmal atrioventricular tachycardia
4119604	Paroxysmal familial ventricular fibrillation
4111546	Paroxysmal junctional tachycardia
4111698	Paroxysmal nodal tachycardia
317893	Paroxysmal supraventricular tachycardia
313792	Paroxysmal tachycardia
437579	Paroxysmal ventricular tachycardia
4111570	Partial atrioventricular block
4232691	Permanent atrial fibrillation
4124702	Permanent junctional reciprocating tachycardia
4232697	Persistent atrial fibrillation
4258998	Persistent sinus bradycardia
4124701	Postoperative His bundle tachycardia
43020495	Postoperative atrioventricular block
4119605	Postoperative complete heart block
4124704	Postoperative sinus node dysfunction
42539346	Preexcited atrial fibrillation
4109365	Premature atrial contraction
316429	Premature beats
44784218	Progressive familial heart block
44784219	Progressive familial heart block, type IB
44782643	Progressive familial heart block, type II
4233619	Pulseless ventricular tachycardia
4199501	Rapid atrial fibrillation
4124696	Re-entrant atrial tachycardia
4124698	Re-entrant atrioventricular node tachycardia
4124699	Re-entrant atrioventricular tachycardia
4111552	Re-entry ventricular arrhythmia
45771051	Recurrent ventricular tachycardia
4302802	Right atrial incisional tachycardia
4249027	Right branch block, incomplete anterior fascicular block AND incomplete posterior fascicular block

314059	Right bundle branch block
4184950	Right bundle branch block AND incomplete left bundle branch block
316432	Right bundle branch block AND left anterior fascicular block
321590	Right bundle branch block AND left posterior fascicular block
4138973	Right bundle branch block with left bundle branch block
4244693	Right bundle branch block, anterior fascicular block AND incomplete left bundle branch block
4217860	Right bundle branch block, anterior fascicular block AND incomplete posterior fascicular block
4138545	Right bundle branch block, anterior fascicular block AND posterior fascicular block
4280348	Right bundle branch block, posterior fascicular block AND incomplete anterior fascicular block
4032785	Right bundle branch block, posterior fascicular block AND incomplete left bundle branch block
4121483	Right ventricular outflow tract ventricular tachycardia
4049219	Romano-Ward syndrome
4089461	Run of atrial premature complexes
4091904	Run of ventricular premature complexes
37312595	Scar mediated macro re-entrant atrial tachycardia
318448	Second degree atrioventricular block
4169261	Severe sinus bradycardia
44784236	Short QT syndrome
4261842	Sick sinus syndrome
4028322	Sinoatrial arrest with nodal/ventricular escape
4277903	Sinoatrial block
4303256	Sinoatrial nodal reentrant tachycardia
36674897	Sinoatrial node dysfunction and deafness
4120084	Sinoatrial node tachycardia
4210313	Sinus arrest
4088352	Sinus arrest with atrial escape
4088210	Sinus arrest with junctional escape
4091446	Sinus arrest with ventricular escape
4171683	Sinus bradycardia
317302	Sinus node dysfunction
4088350	Slow ventricular response
4188347	Stokes-Adams syndrome
4248028	Supraventricular arrhythmia
4091902	Supraventricular bigeminy
42538755	Supraventricular bradyarrhythmia
441872	Supraventricular premature beats
4275423	Supraventricular tachycardia
4120085	Supraventricular tachycardia with functional bundle branch block
4325850	Sustained ventricular fibrillation
4139206	Sustained ventricular tachycardia
40480216	Symptomatic sinus bradycardia
315643	Tachyarrhythmia
4254116	Tachycardia-bradycardia

4262389	Tic-tac rhythm
44783199	Timothy syndrome type 1
36714606	Timothy syndrome type 2
37397458	Torsade de pointes with short coupling interval syndrome
37110729	Torsades de pointe caused by drug
4135823	Torsades de pointes
321315	Trifascicular block
36714994	Typical atrial flutter
4120087	Unidirectional retrograde accessory pathway
4099778	Unifocal PVCs
4106715	Vagal autonomic bradycardia
43021222	Vagal autonomic bradycardia of prematurity
4185572	Ventricular arrhythmia
4008580	Ventricular bigeminy
4327066	Ventricular escape beat
4088507	Ventricular escape complex
4218242	Ventricular escape rhythm
36714539	Ventricular extrasystoles with syncope, perodactyly and Robin sequence syndrome
437894	Ventricular fibrillation
4111700	Ventricular fibrillation and flutter
433225	Ventricular flutter
4092010	Ventricular interpolated complexes
4244893	Ventricular parasystole
4108828	Ventricular pre-excitation
4066289	Ventricular premature beats
4089462	Ventricular premature complex
4088506	Ventricular quadrigeminy
40622721	Ventricular tachyarrhythmia
4103295	Ventricular tachycardia
4119599	Ventricular tachycardia with normal heart
4091900	Ventricular tachycardia, monomorphic
4088349	Ventricular tachycardia, polymorphic
4088501	Ventricular tachycardia, polymorphic without Q-T prolongation
4088505	Ventricular trigeminy
4088348	Wide QRS ventricular tachycardia
4086313	Withdrawal arrhythmia
40483798	Bifascicular block on electrocardiogram
4064452	ECG: atrial fibrillation
4065290	ECG: partial atrioventricular block - 2:1
4064458	ECG: partial atrioventricular block - 3:1
4064873	ECG: partial atrioventricular block - long PR
4065289	ECG: partial sinoatrial block
4138456	ECG: sinus bradycardia

4138921	EKG: Mobitz type II atrioventricular block
4065285	EKG: atrial ectopics
4065288	EKG: atrial flutter
4064874	EKG: complete atrioventricular block
4064872	EKG: complete sinoatrial block
4064457	EKG: heart block
4064453	EKG: ventricular arrhythmia
4064455	EKG: ventricular fibrillation
4064869	Electrocardiogram: paroxysmal atrial tachycardia
40482086	Left anterior fascicular block on electrocardiogram
40482505	Left posterior fascicular block on electrocardiogram
4064459	Mobitz type I second degree atrioventricular block on electrocardiogram
4061093	O/E - pulse rate - bradycardia
40482887	Right bundle branch block and left anterior fascicular block on electrocardiogram
40483359	Right bundle branch block and left posterior fascicular block on electrocardiogram
40482938	Trifascicular block on electrocardiogram

APPENDIX II: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 4)

Study title:
DARWIN EU® – Effectiveness of COVID-19 vaccines on severe COVID-19 and post-acute outcomes of SARS-CoV-2 infection

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

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	5. Milestones, 8.2 Data Sources
1.1.2 End of data collection[2]	☒	☐	☐	
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☐	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

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

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1 Study type and Study Design
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.2 Study Setting and Data Sources

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

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	8.8 Analysis
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	8.8 Analysis
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☐	☐	☒	

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	8.5 Study Population
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	8.3 Study Period
4.2.2 Age and sex	☒	☐	☐	8.6.3. Other covariates
4.2.3 Country of origin	☒	☐	☐	8.2 Study Setting and Data Sources
4.2.4 Disease/indication	☒	☐	☐	8.6.1. Exposures
4.2.5 Duration of follow-up	☒	☐	☐	8.4 Follow-up
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	8.5 Study Population with inclusion and exclusion criteria

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.6.1. Exposures
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☒	☐	☐	8.6.1. Exposures
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	8.6.1. Exposures
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	8.8 Analysis

Comments:

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.6.2. Outcomes
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.6.2. Appendix I
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	8.8 Analysis
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☒	8.8 Analysis

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	8.8 Analysis

Comments:

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.6.1. Exposures
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.6.2. Outcomes
9.1.3 Covariates and other characteristics?	☒	☐	☐	8.6.3. Other covariates
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.2 Study Setting and Data Sources
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.2 Study Setting and Data Sources

Section 9: Data sources	Yes	No	N/A	Section Number
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.2 Study Setting and Data Sources
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.6.1. Exposures
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	8.6.2. Outcomes, Appendix I
9.3.3 Covariates and other characteristics?	☒	☐	☐	8.6.3. Other covariates
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.8 Analysis
10.2 Is study size and/or statistical precision estimated?	☐	☐	☒	
10.3 Are descriptive analyses included?	☒	☐	☐	8.8.2 Descriptive statistics
10.4 Are stratified analyses included?	☒	☐	☐	8.8 Analysis
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	8.8 Analysis
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9. Data management
11.2 Are methods of quality assurance described?	☒	☐	☐	10. Quality Control
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of: 12.1.1 Selection bias? 12.1.2 Information bias?	☒ ☒	☐ ☐	☐ ☐	11. Limitations of the

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

Comments:

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

Comments:

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

Comments:

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

Comments:

Name of the main author of the protocol: Annika Jödicke

Date: 05/10/2023

Signature: A Jödicke