# Version history

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| --- | --- | --- |
| V1 | 05/12/202 | Internal development |

**PROTOCOL**

This document contains the outcome specific elements necessary to implement this protocol: [post-covid-events.docx](https://uob.sharepoint.com/:w:/r/teams/grp-ehr/Shared%20Documents/Protocols/post-covid-events/post-covid-events.docx?d=wf6024a40396c4b02a279e98cffb4ce62&csf=1&web=1&e=bfISrH)

# Study population

No additional criteria.

# Outcomes

|  |  |  |
| --- | --- | --- |
| **Subcategory** | **Event** | **Codelists** |
| Arterial thrombosis events | Acute myocardial infarction | [SNOMED](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-elsie_horne-ami_snomed.csv)  [ICD-10](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-RochelleKnight-ami_icd10.csv) |
| Arterial thrombosis events | Ischaemic stroke | [SNOMED](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-elsie_horne-stroke_isch_snomed.csv)  [ICD-10](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-RochelleKnight-stroke_isch_icd10.csv) |
| Venous thromboembolism events | Pulmonary embolism | [SNOMED](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-elsie_horne-pe_snomed.csv)  [ICD-10](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-RochelleKnight-pe_icd10.csv) |
| Venous thromboembolism events | Deep vein thrombosis (including during pregnancy) | [SNOMED](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-tomsrenin-dvt_main.csv)  [SNOMED](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-tomsrenin-dvt-preg.csv)  [ICD-10](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-RochelleKnight-dvt_dvt_icd10.csv)  [ICD-10](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-elsie_horne-dvt_pregnancy_icd10.csv) |
| Other cardiovascular events | Transient ischaemic attack | [SNOMED](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-hjforbes-tia_snomed.csv)  [ICD-10](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-RochelleKnight-tia_icd10.csv) |
| Other cardiovascular events | Subarachnoid haemorrhage and haemorrhagic stroke | [SNOMED](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-elsie_horne-stroke_sah_hs_snomed.csv)  [ICD-10](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-RochelleKnight-stroke_sah_hs_icd10.csv) |
| Other cardiovascular events | Heart failure | [SNOMED](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-elsie_horne-hf_snomed.csv)  [ICD-10](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-RochelleKnight-hf_icd10.csv) |
| Other cardiovascular events | Angina | [SNOMED](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-hjforbes-angina_snomed.csv)  [ICD-10](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-RochelleKnight-angina_icd10.csv) |
| Arterial thrombosis events | Arterial thrombosis events (i.e., any of acute myocardial infarction, ischaemic stroke, and other arterial embolism) | AMI - [SNOMED](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-elsie_horne-ami_snomed.csv)  Ischaemic stroke - [SNOMED](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-elsie_horne-stroke_isch_snomed.csv)  Other arterial embolism – [SNOMED](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-tomsrenin-other_art_embol.csv)  AMI - [ICD-10](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-RochelleKnight-ami_icd10.csv)  Ischaemic stroke - [ICD-10](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-RochelleKnight-stroke_isch_icd10.csv)  Other arterial embolism – [ICD-10](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-elsie_horne-other_arterial_embolism_icd10.csv) |
| Venous thromboembolism events | Venous thromboembolism events (i.e., any of portal vein thrombosis, deep vein thrombosis (including during pregnancy), intracranial venous thrombosis, other deep vein thrombosis, and pulmonary embolism) | PE - [SNOMED](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-elsie_horne-pe_snomed.csv)  DVT - [SNOMED](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-tomsrenin-dvt_main.csv)  DVT pregnancy - [SNOMED](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-tomsrenin-dvt-preg.csv)  Other DVT - [SNOMED](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-tomsrenin-dvt-other.csv)  ICVT - [SNOMED](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-tomsrenin-dvt_icvt.csv)  Portal vein thrombosis – [SNOMED](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-tomsrenin-pvt.csv)  PE - [ICD-10](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-RochelleKnight-pe_icd10.csv)  DVT - [ICD-10](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-RochelleKnight-dvt_dvt_icd10.csv)  DVT pregnancy - [ICD-10](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-elsie_horne-dvt_pregnancy_icd10.csv)  Other DVT - [ICD-10](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-elsie_horne-other_dvt_icd10.csv)  ICVT - [ICD-10](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-elsie_horne-dvt_icvt_icd10.csv)  ICVT pregnancy - [ICD-10](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-elsie_horne-icvt_pregnancy_icd10.csv)  Portal vein thrombosis - [ICD-10](https://github.com/opensafely/post-covid-vaccinated/blob/main/codelists/user-elsie_horne-portal_vein_thrombosis_icd10.csv) |

# Potential confounders

We will consider the following potential confounders, which will be defined using the most recent data prior to the study start date:

|  |  |  |  |
| --- | --- | --- | --- |
| **Confounder** | **Type** | **Definition** | **Data sources** |
| Sex\* | Categorical | Male, Female | Primary care (see: https://docs.opensafely.org/study-def-variables/#cohortextractor.patients.sex) |
| Age | Continuous | Modelled as age in years using a restricted cubic spline with 3 knots at the 10th, 50th and 90th percentiles | All |
| Ethnicity | Categorical | 1: White  2: Mixed  3: South Asian  4: Black  5: Other  6: Missing | All |
| Deprivation | Categorical | Index of Multiple Deprivation 2019 quintiles | Index of Multiple Deprivation 2019 |
| Region | Categorical | East  East Midlands  London  North East  North West  South East  South West  West Midlands  Yorkshire/Humber | Primary care |
| Patient-GP contact | Continuous | Number of primary care contacts in the year prior to index date | Primary care |
| Smoking status | Categorial | E: Ex smoker  M: Missing  N: Never smoker  S: Current smoker | Primary care |
| Obesity | Binary | 1 if BMI>=30 or coded diagnosis for obesity; 0 otherwise | Primary care, HES APC |
| Acute myocardial infarction | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| All stroke | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| Other arterial embolism | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| Venous thromboembolism events | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| Heart failure | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| Angina | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| Dementia | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| Liver disease | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| Chronic kidney disease | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| Cancer | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| Hypertension | Binary | 1 if diagnosis or prescription present; 0 otherwise | Primary care, HES APC |
| Diabetes | Binary | 1 if diagnosis or prescription present; 0 otherwise | Primary care, HES APC |
| Depression | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| Chronic obstructive pulmonary disease | Binary | 1 if diagnosis present; 0 otherwise | Primary care, HES APC |
| Lipid lowering medications | Binary | 1 if prescription present; 0 otherwise | Primary care |
| Antiplatelet medications | Binary | 1 if prescription present; 0 otherwise | Primary care |
| Anticoagulation medications | Binary | 1 if prescription present; 0 otherwise | Primary care |
| Combined oral contraceptive pill | Binary | 1 if prescription present; 0 otherwise | Primary care |
| Hormone replacement therapy | Binary | 1 if prescription present; 0 otherwise | Primary care |
| Healthcare worker\* | Binary | 1 if healthcare worker; 0 otherwise | NHS England COVID-19 data store (see: https://docs.opensafely.org/study-def-variables/#cohortextractor.patients.with\_healthcare\_worker\_flag\_on\_covid\_vaccine\_record) |
| Care home resident | Binary | 1 if care home resident; 0 otherwise | Address matching CQC database (see: https://docs.opensafely.org/study-def-variables/#cohortextractor.patients.care\_home\_status\_as\_of) |

\* These variables are derived once per patient without a data specification so are an exception to ‘most recent data prior to the study start date’

# proposed outputs

The proposed outputs from this protocol will be like those included in the paper ‘Association of COVID-19 with arterial and venous vascular diseases: a population-wide cohort study of 48 million adults in England and Wales’. Listed here for convenience:

Table 1. Number of patients analysed and, in paratheses, the risk per 100,000 of hospitalized and non-hospitalized SARS-CoV-2 infection

Table 2. Numbers of arterial thrombotic, venous thromboembolic and other vascular events before and after SARS-CoV-2 infection

Figure 1. Hazard ratios (log scale) for different arterial thrombotic, and venous thromboembolic and other vascular events after SARS-CoV-2 infection by time since diagnosis.

Figure 2. Hazard ratios (log scale) for arterial thrombotic events after SARS-CoV-2 infection by time since diagnosis, overall and stratified by whether hospitalised with SARS-CoV-2 infection, prior history of an arterial event, age, sex and ethnicity.

Figure 3. Hazard ratios (log scale) for venous thromboembolic events after SARS-CoV-2 infection by time since diagnosis, overall and stratified by whether hospitalised with SARS-CoV-2 infection, prior history of an arterial event, age, sex and ethnicity.

Figure 4. Absolute increase in risk of arterial thrombotic and venous thromboembolic events over time after SARS-CoV-2 infection, compared with no SARS-CoV-2 infection.

Supplementary Table 1. Derivation of major outcomes in OpenSafely.

Supplementary Table 2. Derivation of covariates.

Supplementary Table 3. Hazard ratios compared with no SARS-CoV-2 infection, according to time since SARS-CoV-2 infection. All results are maximally adjusted unless otherwise stated.

Supplementary Figure 1. Hazard ratios (log scale) for different after SARS-CoV-2 infection by time since diagnosis, stratified by where hospitalised with SARS-CoV-2 infection.

Supplementary Figure 2. Increases in absolute risk of arterial (upper plots) and venous events (lower plots) by time since diagnosis.