VERSION HISTORY

V1	05/12/202	Internal development

PROTOCOL

This document contains the outcome specific elements necessary to implement this protocol: post-covid-events.docx

STUDY POPULATION

No additional criteria.

OUTCOMES

Subcategory	Event	Codelists
Arterial thrombosis events	Acute myocardial infarction	SNOMED ICD-10
Arterial thrombosis events	Ischaemic stroke	SNOMED ICD-10
Venous thromboembolism events	Pulmonary embolism	SNOMED ICD-10
Venous thromboembolism events	Deep vein thrombosis (including during pregnancy)	SNOMED SNOMED ICD-10 ICD-10
Other cardiovascular events	Transient ischaemic attack	SNOMED ICD-10
Other cardiovascular events	Subarachnoid haemorrhage and haemorrhagic stroke	SNOMED ICD-10
Other cardiovascular events	Heart failure	SNOMED ICD-10
Other cardiovascular events	Angina	SNOMED ICD-10
Arterial thrombosis events	Arterial thrombosis events (i.e., any of acute myocardial infarction, ischaemic stroke, and other arterial embolism)	AMI - SNOMED Ischaemic stroke - SNOMED Other arterial embolism – SNOMED AMI - ICD-10 Ischaemic stroke - ICD-10 Other arterial embolism – ICD-10
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	PE - SNOMED DVT - SNOMED DVT pregnancy - SNOMED Other DVT - SNOMED ICVT - SNOMED

	embolism)	Portal vein thrombosis – SNOMED PE - ICD-10 DVT - ICD-10 DVT pregnancy - ICD-10 Other DVT - ICD-10 ICVT - ICD-10 ICVT pregnancy - ICD-10 Portal vein thrombosis - ICD-10

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	Primary care, HES APC

		for obesity; 0 otherwise	
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.