VERSION HISTORY

V1	24-05-21	Internal development by VW and RD
V2	23-01-23	Updated following comments from JQ
V3	27-01-23	Update following initial results and discussion with JQ, RD, JS, VW, AW restructuring to account for different outcomes across populations with and without pre-existing conditions and repeat events.

PROTOCOL

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

STUDY POPULATION

The study population will be split into those that have a symptomatic pre-existing chronic obstructive airway condition (as defined below) on the index date, and those that do not.

Condition	Definition	Codelist
Asthma	Asthma diagnosis code recorded in the last two years	OpenCodelists: Asthma Diagnosis (SNOMED)
Chronic obstructive pulmonary disease	Ever diagnosed	OpenCodelists: Current COPD

OUTCOMES

Outcomes will be split into analyses considering only the first event recorded in primary care during the study period and analyses considering repeat events.

For the population with no pre-existing condition, outcomes are defined as follows:

Event	**Analysis type**	**Codelist**
Symptom: Breathlessness	Repeat events	OpenCodelists: Breathlessness
Symptom: Cough	Repeat events	OpenCodelists: Cough
Upper respiratory infection (including sinusitis, pharyngitis, tonsillitis, and laryngitis)	Repeat events	OpenCodelists: URTI (SNOMED) [updated]
Pneumonia	First event	OpenCodelists: Pneumonia (SNOMED) [updated] OpenCodelists: Pneumonia (ICD-10)
Asthma	First event	OpenCodelists: Asthma Diagnosis (SNOMED) OpenCodelists:

		Asthma exacerbation (ICD-10) Asthma (ICD-10)
COPD, including bronchitis	First event	OpenCodelists: Current COPD [updated] OpenCodelists: COPD-secondary care COPD_icd10
Pulmonary fibrosis (interstitial lung disease)	First event	OpenCodelists: ILD (SNOMED) ICD-10

For analysis of repeat events, an event occurring within seven days (inclusive) of the previous event will be considered part of the same event.

For the population with a pre-existing condition, outcomes are defined as follows:

Event	**Analysis type**	**Codelist**
Symptom: Breathlessness	Repeat events	OpenCodelists: Breathlessness
Symptom: Cough	Repeat events	OpenCodelists: Cough
Upper respiratory infection (including sinusitis, pharyngitis, tonsillitis, and laryngitis)	Repeat events	OpenCodelists: URTI (SNOMED)
Pneumonia	First event	OpenCodelists: Pneumonia (SNOMED)
Acute exacerbation of asthma: diagnosis code and medication code within 1 day of diagnosis code	Repeat events	OpenCodelists: Asthma exacerbations (SNOMED) [updated] OpenCodelists: Asthma medications (BNF)
Acute exacerbations of COPD, including bronchitis: diagnosis code and medication code within 1 day of diagnosis code	Repeat events	OpenCodelists: COPD exacerbations (SNOMED) [updated] OpenCodelists: COPD medications (BNF) OpenCodelists: COPD exacerbation medications (BNF)
Pulmonary fibrosis (interstitial lung disease)	First event	OpenCodelists: ILD (SNOMED)

For analysis of repeat events, an event occurring within 14 days (inclusive) of the previous event will be considered part of the same event.

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
Age	Continuous	Modelled as age in years using a restricted cubic spline with 3 knots at the 10th, 50th and 90th percentiles	Primary care
Ethnicity	Categorical	1: White 2: Mixed 3: South Asian 4: Black 5: Other	Opensafely-ethnicity
Deprivation	Categorical	10 categories from Index of Multiple Deprivation 2019	Index of Multiple Deprivation
Region	Categorical	East of England London Midlands North East and Yorkshire North West South East South West Scotland Wales	Primary care
Consultation rate	Continuous	Number of primary care contacts in the year prior to index date	Primary care
Smoking status	Categorial	E: Ever smoker M: Missing N: Never smoker S: Current smoker	Opensafely - smoking
Obesity	Binary	1 if BMI>=30 or coded diagnosis for obesity; 0 otherwise	SNOMED CT ICD10
Healthcare worker	Binary	1 if healthcare worker; 0 otherwise	NHS England COVID-19 data store
Care home resident	Binary	1 if care home resident; 0 otherwise	Address matching CQC database
Acute myocardial infarction	Binary	1 if diagnosis present; 0 otherwise	AMI SNOMED CT AMI ICD10 AMI Prior ICD10
Ischaemic stroke	Binary	1 if diagnosis present; 0 otherwise	Ischaemic Stroke SNOMED Ischaemic Stroke ICD10

Dementia	Binary	1 if diagnosis present; 0 otherwise	Dementia SNOMED Dementia ICD10 Dementia Vascular SNOMED Dementia Vascular ICD10
Liver disease	Binary	1 if diagnosis present; 0 otherwise	Liver Disease ICD10 Liver Disease SNOMED
Chronic kidney disease	Binary	1 if diagnosis present; 0 otherwise	CKD SNOMED CKD ICD10
Cancer	Categorical	1 if diagnosis present; 0 otherwise	Cancer SNOMED Cancer ICD10
Hypertension	Binary	1 if diagnosis present; 0 otherwise	Hypertension Drugs DMD Hypertension ICD10 Hypertension SNOMED
Diabetes	Binary	1 if diagnosis present; 0 otherwise	
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
History of pneumonia	Binary	1 if diagnosis present; 0 otherwise	
History of asthma	Binary	1 if diagnosis present; 0 otherwise	
History of pulmonary fibrosis	Binary	1 if diagnosis present; 0 otherwise	

SUBGROUP ANALYSES

In addition to the subgroup analyses listed in the main protocol, we will repeat the main analysis to estimate subgroup post-exposure hazard ratios as detailed below:

- Subgroups according to smoking status (ever / never / current)

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 events before and after SARS-CoV-2 infection

Figure 1. Hazard ratios (log scale) for different events after SARS-CoV-2 infection by time since diagnosis.

Figure 2. Hazard ratios (log scale) for events after SARS-CoV-2 infection by time since diagnosis, overall and by subgroups.

Figure 4. Absolute increase in risk of 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.