Protocol for Vaccine safety analyses wrt cerebral venous thrombosis and related potential acute haematological events

Epidemiology Research Cell , Intelligence and Research Directorate, and Clinical & Protecting Health Directorate Public Health Scotland

V6.0 22/04/21

V1 drafted 21/03/21

Contact : Professor Helen Colhoun, PHS 07791652665 helen.colhoun@igmm.ed.ac.uk

Aims:

Primary Objectives

- To estimate the background rate of certain acute "haematological" events including acute venous thromboses / disseminated intravascular coagulation /thrombocytopenia / haemolytic anaemia, combined and by event type.
- To estimate the rate ratio associated with vaccination for certain acute haematological events combined and by type of event.

Secondary objectives

- To understand risk factors associated with acute haematological events overall and by type of event among the vaccinated and in background population.
- To specifically test for interaction between OCP/ HRT and vaccination in increasing risk of acute haematological events overall and by type of event post vaccination

Methods

Designs used

i) Cohort study

ii) Case crossover study

These are detailed later in this document.

Case ascertainment:

Approach aims to have a very inclusive (sensitive) definition of acute haematological events overall but then to have a highly specific definition for specific event types such as CVST and for the combination of DVT or PE. We describe here definitions for incident events.

Acute haematological events:

These comprise

- acute venous thromboses
- disseminated intravascular coagulation
- thrombocytopenia
- haemolytic anaemia

Acute venous thrombotic/embolic events

These comprise Cerebral Venous Thrombosis (CVT), Deep venous thrombosis (DVT),Pulmonary embolism (PE) and Other thrombotic embolic event

CVT:

SMR01 discharge diagnosis anywhere on discharge or NRS death cert anywhere on death cert with the following ICD-10 codes

I67.6 Nonpyogenic thrombosis of intracranial venous system : Nonpyogenic thrombosis of: cerebral vein or intracranial venous sinus, *Excl.:* when causing infarction (I63.6)

OR

I63.6 Cerebral infarction due to cerebral venous thrombosis, nonpyogenic

OR

G08 Septic: embolism phlebitis/ thrombosis of intracranial or intraspinal venous sinuses and veins

OR

Cerebral venous thrombosis identified on any radiology image across NHS Boards in Scotland

See appendix for details of ascertainment of these events

DVT/ PE

SMR01 or A&E database or SMR00 with the following ICD-10 codes anywhere on the discharge , or NRS death with these ICD-10 codes anywhere on death cert

I80.2Phlebitis and thrombophlebitis of other deep vessels of lower extremities

Deep vein thrombosis NOS

I80.3Phlebitis and thrombophlebitis of lower extremities, unspecified

Embolism or thrombosis of lower extremity NOS

I26 Pulmonary embolism

OR

a new onset anticoagulant prescription AND a recent acute hospital attendance visit (A&E or an outpatient clinic or a hospital stay)in the absence of a recent AFIB (I48) diagnosis AND in the absence of co administration of anti-arrhythmic (BNF code 2.3), Beta-adrenoceptor blocking (BNF code 2.4), the rate-limiting calcium channel blocking drugs Diltiazem Hydrochloride (BNF code 0206020C0) and Verapamil Hydrochloride (BNF code 0206020T0) (NB ATC code C08D) – or Digoxin (BNF code 0201010F0)) AND in the absence of any concurrent admission for another cause for anticoagulant prescription.

Source databases are SMR01, RAPID, SMR00 A&E database and PIS – we will differentiate into DVT PE where possible but these may not always be distinguishable.

Note LMWH use cannot be captured from prescriptions this approach (intravenous drug use, alcohol problems, falls risk, and very elevated BMI).

Other acute venous thrombosis events

These comprise

I82.2Embolism and thrombosis of vena cava

I82.3Embolism and thrombosis of renal vein

I82.8Embolism and thrombosis of other specified veins

I82.9Embolism and thrombosis of unspecified vein

Anywhere on SMR01 discharge, on A&E data, on OPD SMR00, or on death cert

Disseminated Intravascular Coagulation (DIC)

D65X code onSMR01 or death cert

Thrombocytopenia

D69.3 Idiopathic thrombocytopenic purpura

D69.4 Other primary thrombocytopenia

D69.5 Secondary thrombocytopenia

D69.6 Thrombocytopenia unspecified

M31.1 Thrombotic microangiopathy/ Thrombotic thrombocytopenic purpura

Anywhere on SMR01 discharge, on A&E data, on OPD SMR00, or on death cert

Acquired haemolytic anaemia

D59.0Drug-induced autoimmune haemolytic anaemia

D59.1Other autoimmune haemolytic anaemias

D59.3Haemolytic-uraemic syndrome

D59.4 Other nonautoimmune haemolytic anaemias (Haemolytic anaemia: mechanical, microangiopathic or toxic)

D59.8Other acquired haemolytic anaemias

D59.9Acquired haemolytic anaemia, unspecified

Anywhere on SMR01 discharge, on A&E data, on OPD SMR00, or on death cert

Exposure status

Vaccination by type of vaccine and date of first and second exposure sourced from the vaccination database of Scotland

Potential Covariates:

Age

Sex,

prescribing history including concurrent OCP HRT, recent anticoagulant use, CVD drugs,

history of events under study,

prior COVID status,

baseline and incident cancers

Data sources : CHI, PIS, SMR01, ECOSSE, SICSAG, RAPID, NRS Deaths, SMR06 (Ca registry)

Specific considerations for each objective

Cohort study:

Period of study:

From 1 Jan 2015 – to latest available outcomes data

Population under study: Anyone alive and resident in Scotland and aged 16 years and upward during the study period as identified using the CHI database

Baseline exclusion criteria: none other than age <16 years Time in – alive and resident in Scotland at the start of the period in question

Time out- the first of : event of interest, de-registered/exit from Scotland using CHI, death from other cause, end of study period in question and for DVT/PE analyses prescription of anticoagulant not meeting the event of interest.

- To estimate the background rate of events

Incidence rate per 100,000 person years at risk will be reported overall and by age sex band for the total period in question and then for

the period pre COVID-19 ie 1/1/2015-1/3/2020

then COVID-19 period prior to vaccination ie, 1/3/2020- 8/12/2020

then vaccination period 8/12/20-end of follow up

Data will be arrayed in survival format and simple events/ pyar reported

The ratio of the event rate in the Vaccination period to the rate in the i) COVID-19 period ii) pre-COVID period will be computed overall and by age sex band

These analyses will be done at the level of i) all events combined ii) acute venous thromboses/ DIC/thrombocytopenia /haemolytic anaemia separately iii) CVST/DVT or PE/ Other acute thrombotic event

- To estimate the rate ratio for events associated with vaccination

Here the rate ratio a Cox regression model using calendar time as timescale will be constructed

Covariates will be time updated across the cohort on every day of an incident event in the cohort

Covariates included: age, sex, OCP in last 90 days, HRT in last 90 days, prior COVID-19, vaccinated in the last 14 days (encoded as 0,1 for any)

Repeat model with vaccination encoded as vaccination in the last 14 days (0=none, 1=AZ, 2=Pfizer)

Repeat model with vaccination encoded as vaccination in the last 14 days (0,-none, 1= first vacc,2= 2nd vacc)

Repeat model with vaccination encoded as vaccination in the last 28 days (0= none ,1= any)

Repeat model including a test for interaction of OCP and vaccination

Repeat model including a test for interaction of HRT and vaccination

Repeat model including a test for interaction of prior COVID-19 and vaccination

Repeat model excluding those on prior anticoagulants and right censoring at first use

Repeat model right censoring for cancer at baseline or new cancer diagnosis during follow up

These analyses will be done at the level of i) all events combined Ii) acute venous thromboses/ DIC/thrombocytopenia /haemolytic anaemia separately iii) CVST/DVTor PE/ Other acute thrombotic event

Case-crossover

To obtain estimates of the association between vaccination and outcomes unconfounded by between-individual factors.

Use the same survival format dataset as for cohort study above

From this all first events since the start of vaccination in Scotland (8 Dec 2020) will be ascertained

Exposure will be defined in relation to the preceding 2 consecutive intervals of 14 days

The conditional odds ratio of the odds of exposure in the 14 days prior to an including the case date versus the preceding 14 days will be estimated the ratio of the number of cases exposed in the recent versus less recent rime window, a significance test and p value will be obtained from the binomial likelihood.

Since a fundamental assumption of no variation in exposure by time overall is violated then this analysis needs to be stratified by calendar week.

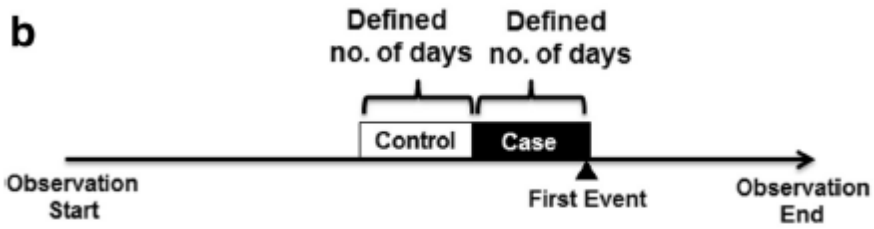
Sensitivity analyses:

the above will be repeated using 28 day time window

Subgroup analysis

the above will be conducted within age sex strata and within females below age 50 stratified by OCP use and within females over age 50 stratified by HRT use.

These analyses will be done at the level of i) all events combined Ii) acute venous thromboses/ DIC/thrombocytopenia /haemolytic anaemia separately iii) CVST/DVTor PE/ Other acute thrombotic event



Secondary objectives

- To understand risk factors associated with events overall and by type of event among the vaccinated and in background population
    - see covariate effect in cohort study above
- To specifically test for interaction between OCP/ HRT and vaccination in increasing risk of acute events overall and by type of event post vaccination
    - See interaction tests in cohort study and stratum effects in case crossover above for acute events

Analysis priority set 1: Focus on cerebral venous thromboses

The priority is complete ascertainment of all relevant CVT events since the start of the vaccination programme and evaluation of evidence for causal association with vaccination

The reporting of relative risks of CVT associated with vaccination using background rates is of interest but is of secondary importance

Ascertainment of the other events described above, conduct of case cross over and the reporting of relative risks of associated with vaccination using background rates is of interest but is of secondary importance

Therefore priority steps are:

- Identify all possible cases of CVT using SMR01 , NRS deaths and imported Radiology reports from 1/1/2015 to today: Prioritise From 8 Dec 2020 in the first instance.

- Using the combined data tabulate the agreement between SMR01 and radiology ascertainment for the weeks where there is coverage from both sources

- Merge with vaccination database and tabulate the vaccination status of cases by age and sex band since 8 Dec 2020: repeat this by vaccine type and by number of vaccine doses

- Describe these cases wrt age and sex, prior cancer and prior anticoagulants, hormone use (all in the six month time window prior to event) and batch number

- Conduct case cross over analysis of vaccine exposure in all cases as described above using vaccine exposure status in 0-14 days, 14-28, > 28 days prior to caseness, repeat by vaccine type, repeat stratified by sex and broad age band (</>50 years) and batch number

- Do a sensitivity check of what happens in this when we drop any cases where there is associated ca treatment or hormone use

- Do a sensitivity check wrt ascertainment bias date (set 23 March as date before which bias unlikely)

- Ascertain directly via clinicians the blood profile on cases wrt any evidence of thrombocytopenia or D –Dimer levels etc

- Do a sensitivity check of possible misclassification of arachnoid/ Pacchionian granulation

- Using the data back to 2015 express the frequency of events by mid year population age and sex strata

- Do a simple tabulation of pre covid covid-era and vaccination era counts of average monthly cases by age and sex

- For cases arising since March 1 2020 cross tabulate caseness by prior covid-19

- Proceed to formal relative risk estimation as described above using CHI derived at risk populaton

Dataset needed	What for
Radiology reports	Past and incident events
CHI database	Population under study observability age and sex
Vaccination database	exposure
SMR00	DVT/PE events
SMR01	Past and incident events
SMR02	Past spontaneous abortion
SMR06	Cancers baseline and incident
A&E	DVT/PE events
DCVP DISPENSED	Covariates and sensitivity analyses
SICSAG episodes	COVID

ECOSSE	COVID
RAPID stay	COVID and DVT/PE presentation
NRS Deaths	Whether events are fatal

Concepts	Database needed for derivation
Covariates	
Age	CHI
Sex	CHI
prescribing history including concurrent OCP HRT, recent anticoagulant use, CVD drugs,	DCVP DISPENSED
history of events under study,	SMR01, A&E SMR00, DCVP dispensed, Radiology
prior COVID status	ECOSSE SICSAG RAPID 24 SMR01
Events	
CVST	Radiology, SMR01, NRS deaths
DVT/PE	SMR01/ NRS deaths PIS/ A&E/ SMR00
Other venous embolic thrombotic events	SMR01/ NRS deaths
DIC	SMR01 /NRS deaths
Thrombocytopenia	SMR01 / NRS deaths
Acquired Haemolytic Anaemia	SMR01 / NRS deaths
Exposure	
Vaccination	Vaccination database
At risk population	
CHI longitudinal view	CHI database
Censoring –	
events of interest as above	As above
Death	Nrs deaths
Sensitivity analyses	
Anticoagulants	PIS
Cancers	SMR06

Appendix Ascertainment of CVT events via Radiology systems

Acronyms

PACS: Picture Archiving and Communications Systems

SRTP: Scottish Radiology Transformation Project

SCIN: Scottish Clinical Imaging Network

RIS: Radiology Information Systems

NSS: National Services Scotland

PHS: Public Health Scotland

Summary

In brief this involves running an SQL query on the National Services Scotland PACS national archive, secondary data centre (SDC) and securely transferring the outputted radiology reports to PHS (technical details below).

Clinical Oversight and Input

Prof Helen Colhoun, Co-Chair COVID-19 Epidemiology Research PHS

Dr Raj Burgul Consultant Radiologist SRTP/SCIN & National PACS Clinical advisor

Dr David McAllister, Consultant in Public Health, Public Health Scotland

Methodology

- XX (already authorised to have national PACS access in his role) will write and run an SQL Query on the national PACS SDC that identifies all instances of key radiology procedures from all Scottish health boards PACS.
- For each of these instances the following fields will be outputted
    - Date range 1/1/2015 onwards
    - Approx size of dataset – 6000 studies
    - Fields required :
        - Study date, study description, RIS code, Report text
        - Accession number, CHI number, Age, sex.
    - Note no images are to be extracted only image report text

- The data file will be uploaded to the xxx server from within the SDC environment. The extract will be compressed and encrypted and password protected. Named recipient (xxx) will be provided with a link to the xxx Share site and an account will be created for them. The account password and the file password will be shared with the named recipients in separate emails.
- A Regular Expression (ReGeX) query will be run on these PACS reports by Dr D McAllister to pull out all possible CVST- we expect this to return ~600 files
- Dr xxx and other governance trained PHS medical staff will then parse each record returned by the ReGeX query redacting any identifying text and marking up the file as showing

    - primary acute CVT
    - follow up of prior CVT noting date of primary,
    - secondary CVT (to trauma brain neoplasm or head and neck infection) , possible CVT, missing ie failed scan,
    - chronic thrombosis.
- In addition, for ALL reports since 1/12/20 Dr xx and Dr xxx will manually parse every record and classify as above- all classification will be done independently and then adjudicated if there are any differences
- If there are reports where interpretation is equivocal the de-identified report text will be discussed with radiologist Dr xxx to clarify interpretation
- Some of the recent PACS reporting systems instituted in some Boards store their report as a DICOM image file that can only be viewed within a PACS workstation. For these instances the relevant Board Radiologist/ designated radiology systems manager wll use the local use the RIS system to extract these files and transmit securely to PHS by approved secure transfer protocol as per the original plan.
- Agreement between SMR01 and the above process in classifying events will be examined for the period Dec8 2020 onwards. This may indicate a need to review the initial search strategy within PACS.
- key stakeholders representing the radiology community have approved this plan as have clinical directors of radiology, the PBPP, as well as internal NSS and PHS governance (DPIAS completed)

Overview of linkage and analysis for examining risk of CVST