

COVID-19 in Pregnancy in Scotland (COPS)

Project protocol

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Version control:

Version number	Date	Change from previous version
0.0	26/05/2020	First version
0.1	01/06/2020	Incorporated comments from SS and DMcA
0.2	08/06/2020	Incorporated comments from CR, Utkarsh Agrawal, and Amaya Azcoaga-Lorenzo Clarifications relating to definition of suspected COVID-19, outcome measures, and inclusion of secondary objectives relating to all confirmed cases of COVID-19 in neonates
0.3	09/06/2020	Incorporated comments from Colin McCowan
1.0	18/06/2020	Incorporated comments on statistical methods from DMcA
1.1	24/06/2020	Comments from SS on terminology, COVID-19 definition
1.2	26/06/2020	Incorporated comments from SS and RW added further comments on case definitions
1.3	23/09/2020	Additional comments from CR to in response to comments on BMJ Open version for publication
1.4	05/03/2021	Updated to reflect additional ICD10 codes for COVID-19 and availability of lateral flow testing for SARS-CoV-2 infection
1.5	05/05/2021	Thromboembolism added as maternal outcome

1. Introduction

The effects of novel coronavirus (SARS-CoV-2) in pregnancy are unknown, but, to inform public health policy, it is crucial to determine both

i) the effects of pregnancy on the susceptibility to, and progression, of COVID-19

and

ii) the effects of COVID-19 on maternal, pregnancy, and neonatal outcomes.

The first of these evidence gaps will be addressed within the related research study, EAVE II (Establishing a real-time national Scottish surveillance platform to identify vulnerable adults and enable contact tracing for COVID-19). EAVE II aims to build a national, real-time, data platform to identify the population groups most at risk from SARS-CoV-2 infection and COVID-19 disease and mortality. Pregnancy will be assessed as one of these at-risk groups. This project protocol clarifies the national datasets that will need to be incorporated within the EAVE II platform to enable pregnant women (and associated pregnancy start and end dates) to be reliably identified as part of this work.

In addition, in this study protocol we outline additional analyses that will be required to address the second uncertainty, i.e. to determine the effects of COVID-19 on pregnancy outcomes, and maternal and newborn health. SARS-CoV-2 transmission from mother to baby (antenatally or intrapartum) appears to be possible¹ but the proportion of pregnancies affected and the clinical significance is uncertain. Potential effects of the virus on miscarriage, congenital anomalies, fetal growth, timing of delivery, and stillbirth are unknown. We know from other viral infections in pregnancy that infections with mild maternal symptomatology can have substantial impacts on the developing fetus (e.g. Cytomegalovirus, Zika virus). There are also plausible links to preterm birth, mediated either through maternal infection itself; or indirectly through increased stress due to the pandemic and containment measures, or through altered physician threshold for iatrogenic preterm delivery in women with infection. Newborns may be affected through true vertical transmission, or, more commonly through exposure to infected family members or nosocomially.

There are a number of surveillance studies gathering data on pregnant women with COVID-19 currently underway in the UK. A [UKOSS](#) study is gathering data on women admitted to hospital in the UK with confirmed COVID-19 at any stage of pregnancy. Reporting is by front line clinicians. Patient consent is not required for data return. Coverage of women admitted to obstetric departments in Scotland is likely to be high. [PAN-COVID](#) is a global study based in the UK gathering data on women admitted to hospital for pregnancy loss or delivery who have had COVID-19 at any stage during pregnancy. Patient consent is required for data return. Coverage of data return in Scotland is not currently known but is likely to be low. The ISARIC Clinical Characterisation Protocol Tier 0 study (also known as [CO-CIN](#)) is gathering patient identifiable data on any patient admitted to hospital in the UK with confirmed COVID-19. Reporting is by research nurses. Patient consent is not required for data return. Data collection from obstetric hospitals/units in Scotland, and hence coverage of pregnant women admitted to hospital, is currently low in Scotland although this may increase.

In addition, a [BPSU](#) study is gathering patient identifiable data on neonates with confirmed SARS-CoV-2 infection, and on all babies born to mothers with COVID-19 who are admitted to neonatal care (whether the baby has SARS-CoV-2 or not). A separate [BPSU](#) study is gathering patient identifiable data on all children (including neonates) with multisystem inflammatory syndrome due to SARS-CoV-2 infection or otherwise unexplained. Reporting for both BPSU studies is by front line

¹ Gajbhiye RK et al. Pregnancy outcomes, newborn complications and maternal-fetal transmission of SARS-CoV-2 in women with COVID-19: A systematic review of 441 cases. MedRxiv preprint doi: <https://doi.org/10.1101/2020.04.11.20062356>

clinicians. Patient consent is not required for data return. Coverage of relevant cases in Scotland is likely to be high.

Collectively these studies can provide detailed characterisation of selected groups of pregnant women (and neonates) affected by SARS-CoV-2 and COVID-19. The study outlined in this protocol will complement these existing studies by providing population-based information (for the whole of Scotland) on the risk of, and outcomes following, confirmed, probable, and possible COVID-19 (+/- serological evidence of SARS-CoV-2 infection) at any stage of pregnancy for women in the community and/or admitted to hospital.

Understanding the effects of SARS-CoV-2 and COVID-19 at different stages in pregnancy and perinatally will help inform policy on shielding strategies, and advice to pregnant women and those considering pregnancy. It is also essential for immunisation strategies when vaccines are available, as different approaches may be preferable. For example, immunisation in early pregnancy may help protect against maternal infection during pregnancy and reduce complications; but immunisation in later pregnancy may be preferential to provide passive immunisation to babies if neonatal infection is the predominant concern.

2. Aims and objectives

2.1 Aims

To extend the EAVE II national, real-time, linked data platform to enable the epidemiology of SARS-CoV-2 infection in pregnancy to be determined, and to examine the effects of COVID-19 on pregnancy and babies.

2.2 Objectives

2.2.1 *Primary objectives*

1. Describe the incidence of COVID-19 in the pregnant population
2. Determine associations between COVID-19 and adverse pregnancy, neonatal and maternal outcomes
3. Determine the proportion of neonates that are positive for SARS-CoV-2 infection associated with COVID-19 in the baby's mother

2.2.2 *Secondary objectives*

4. Assess the proportion of COVID-19 cases in pregnant women and neonates that are included in relevant other enhanced surveillance studies (BPSU, CO-CIN)
5. Assess the safety of any new or existing prophylactic or therapeutic interventions (e.g. new or repurposed therapies, vaccines, antimicrobials) in pregnant women and their babies
6. Set up a platform to enable other and longer-term sequelae of SARS-CoV-2 or therapeutic interventions to mitigate SARS-CoV-2 infections in pregnancy, on childhood outcomes

3. Study Design

3.1 Study design

Prospective cohort study using routinely collected data, in accordance with relevant guidance including RECORD² and STROBE³.

3.2 Setting

Scotland, UK.

3.3 Population

All women in Scotland who were pregnant on, or became pregnant after 1st March 2020 (the date of the first confirmed case of COVID 19 in Scotland). The end date for the study will be determined by the future development – in particular suppression – of the pandemic in Scotland.

(Population for Objective 3 is all live born babies born in Scotland from 1st March 2020 onwards.)

3.4 Data sources

The following national datasets will be linked. Datasets already included in the EAVE II linked data platform are marked in *italics*.

Datasets required to identify pregnant women in the general population and associated pregnancy start and end dates:

- New national data return developed as part of the response to the COVID-19 pandemic providing information on women booking for antenatal care with NHS maternity services: for identification of women with ongoing pregnancies in near real-time (cf all other records that identify end of pregnancy events)
- *GP consultation data: for identification of women with early miscarriage or ectopic pregnancy not managed in hospitals*
- *Scottish Morbidity Record (SMR) 01: for identification of women with early miscarriage or ectopic pregnancy managed in hospitals*
- Termination of pregnancy statutory notifications (AAS records)
- *SMR 02: for identification of later miscarriage, stillbirth, and live births managed in hospital (and some home births)*
- National Records of Scotland (NRS) statutory stillbirth registrations
- National Records of Scotland (NRS) statutory live birth registrations
- New national data return developed as part of the response to the COVID-19 pandemic providing information on live births notified by maternity services to NHS Board child health administrative departments: for near real-time access to data that allows intergenerational linkage of records relating to mothers and their babies whilst statutory live birth registration is suspended

² <http://www.record-statement.org/>

³ <https://www.strobe-statement.org/>

Datasets required to identify women with confirmed or suspected COVID-19:

- *Electronic Communication of Surveillance in Scotland (ECOSS) and other lateral flow, viral PCR and serology results held separately by Public Health Scotland (PHS): for identification of women and neonates with positive lateral flow, viral PCR, and serology tests, and women with negative viral PCR tests*
- *National Records of Scotland (NRS) statutory death registrations: for identification of any women with COVID-19 recorded as cause of death*
- *SMR01, SMR02, and NRS stillbirths will also identify additional women with COVID-19 recorded as cause of admission/stillbirth*
- *GP consultations, GP out of hours attendances, NHS24 calls, COVID-19 phone assessment hub calls, and COVID-19 clinical assessment centre attendances: for identification of women with clinically suspected COVID-19*
- *Scottish Ambulance Service incident and A&E attendance records: for identification of women with clinically suspected COVID-19*

Datasets required to identify relevant outcomes of pregnant women and their neonates:

- Records listed above plus
- *Scottish Intensive Care Society Audit Group (SICSAG) records: to identify women admitted to intensive care*
- *Scottish Birth Record (SBR): to identify neonates admitted to neonatal care*

The following additional datasets will also be linked for the stated purposes:

- *Potential confounders such as comorbidity (GP consultation, SMR01, and community prescribing [PIS] look back records, and the COVID-19 shielded patient list held by PHS)*
- *Inclusion of pregnant women and neonates with COVID-19 in existing enhanced surveillance studies (minimal 'flag' variables from the BPSU neonatal, BPSU MIS (neonates only), and CO-CIN studies*
- *Vaccination provided to prevent COVID-19 (GP consultation and Vaccine Management Tool records)*
- *Healthcare worker records (SWISS+) to identify women eligible for vaccination due to healthcare worker status and infant feeding records (CHSP-PS) to identify women vaccinated during breastfeeding*
- *Treatment provided for COVID-19 (PIS and hospital prescribing [HEPMA])*

An overall schema for the planned linkage is provided in Appendix 1: Overall schema of the COPS data linkage.

3.5 Inclusion/exclusion criteria

All pregnant women identified in one or more of the data sources listed above with estimated date of conception from 20 May 2019 onwards and no end of pregnancy before 1 March 2020 will be included.

Women with date of conception 20 May 2019 would have reached their due date on 10 Feb 2020 and the reasonable upper limit of their pregnancy duration (43⁺⁰ weeks) on 1 March 2020 hence this cohort will capture all women at risk of confirmed or suspected COVID-19 during pregnancy. Whilst

some (unrecognised) imported cases of infection, and low levels of community transmission, may have occurred in Scotland prior to March 2020, the first virologically confirmed case occurred on 1 March 2020.

Women in the cohort with the earliest dates of conception will only have been at risk of COVID-19 at the very end of their pregnancy. Women with more recent dates of conception will have been at risk for longer, up to women with date of conception from 1 March 2020 onwards who will be at risk from conception onwards (until viral transmission is completed suppressed).

We aim to use the entire pregnant population; therefore, selection bias is not anticipated and the dataset will be fully generalisable to Scotland (with extensive generalisability to the other high income nations).

3.6 Sample size calculation

There are approximately 5,000 miscarriages managed in hospital, 13,000 terminations of pregnancy, 200 stillbirths, and 50,000 live births in Scotland per year. The estimated number of women in the population who are pregnant at any one time is around 42,000.

The number of pregnant women with confirmed COVID-19 will be influenced by testing and diagnostic strategies which are evolving over the course of the pandemic. Initially, the threshold for viral PCR testing to detect active infection was high, with testing reserved for patients unwell enough to require hospital admission and for key workers (in particular health and social care staff) to inform decisions about ability to work. Since late May 2020, PCR testing has been more widely available, with all individuals in the general population aged 5 years or older with relevant symptoms also able to access a test. Testing of asymptomatic key workers, and asymptomatic patients receiving care for other conditions, is also increasing as the pandemic progresses. Testing of asymptomatic individuals in the community or educational or work settings using lateral flow, rather than viral PCR, tests is also increasing.

Serological testing to identify antibodies to SARS-CoV-2 and hence prior exposure or infection is also developing over time. A random sample of residual serum samples (from blood tests taken from patients in primary care or in hospital for any indication) processed by the QEUH biochemistry lab in Glasgow have been tested from mid-March 2020 onwards. Further residual serum samples from NHS labs across Scotland, and the national blood transfusion service, have been tested from late April/early May 2020 onwards. From January to August 2020, testing of residual antenatal booking blood samples was undertaken in Boards across Scotland. From September 2020 onwards, testing of residual samples sent from across Scotland to NHS Lothian as part of the first trimester combined ultrasound and biochemical screening for trisomies pathway has been carried out.⁴ In addition, diagnostic serology testing (to inform the care of individual patients with suspected previous COVID-19) was introduced from late May 2020 onwards. The approach to serological testing evolved following introduction of COVID-19 vaccination from Dec 2020 onwards, to ensure that antibodies reflecting previous infection or vaccination could be distinguished.⁵

Reflecting the testing strategies outlined above, the numbers of pregnant women with confirmed COVID-19 is likely to be small in the initial phase of the pandemic, and these women are likely to be the 'tip of the iceberg' with relatively severe disease. As time progresses, numbers of women with confirmed COVID-19 will tend to increase due to increased testing, but this should be offset by decreasing levels of community transmission of infection. Confirmed cases are likely to become more representative of the spectrum of illness caused by SARS-CoV-2 over time.

⁴ [https://www.sehd.scot.nhs.uk/cmo/CMO\(2020\)23.pdf](https://www.sehd.scot.nhs.uk/cmo/CMO(2020)23.pdf)

⁵ [https://www.sehd.scot.nhs.uk/cmo/CMO\(2021\)08.pdf](https://www.sehd.scot.nhs.uk/cmo/CMO(2021)08.pdf)

To account for the variable ascertainment of true incidence over time, as well as examining confirmed cases we will also examine the number of women with possible or probable COVID-19, using information from GP consultations and out of hours attendances, NHS24 community triage and assessment processes, and Scottish Ambulance Service incident and A&E attendance records as noted above, along with diagnostic codes from secondary care records.

We cannot influence the number of women with COVID-19 available for analysis hence sample size calculations will not be performed. We will report the precision with which we are able to estimate any association between COVID-19 and the outcomes of interest using confidence intervals as appropriate.

An approximate estimate of the expected number of confirmed COVID-19 cases in pregnant women is presented below:

	Total number of individuals testing positive (PCR) for SARS-CoV-2 (NHS labs only)	Women aged 15-44 years testing positive (PCR) for SARS-CoV-2 (NHS labs only)	Estimated number of pregnant women testing positive (PCR) for SARS-CoV-2 (NHS labs only)**
March 2020	≈2000	≈333*	≈17
April 2020	≈9000	≈1500*	≈75
May 2020	≈4000	≈667*	≈33
Total	≈15000	≈2500	≈125

* Assuming the distribution over time for this age/sex group is the same as for all tests, as age/sex breakdown only available from published information⁶ for the total

** Assuming that around 5% of the female population aged 15-44 is pregnant at any one time, and that incidence of COVID-19 is the same in pregnant and non-pregnant women

It is likely that there will be further confirmed or probable cases in pregnant women identified through:

- Viral PCR testing processed through UK Government labs
- Clinical diagnoses on discharge (or possibly stillbirth or maternal death) records

In addition, it is likely that there will be considerably more possible cases among pregnant women based on the range of data sources listed above. As serological testing develops we are likely to find further cases of serological evidence of SARS-CoV-2 exposure.

4. Data and data validation

4.1 Data variables available

A full list of variables to be requested from each of the data sources to be linked is provided in a separate file (20200626 COPS data extract request.xlsx).

4.2 Constructed variables

To be confirmed.

4.3 Consistency and error checking

To be confirmed.

⁶ <https://publichealthscotland.scot/our-areas-of-work/sharing-our-data-and-intelligence/coronavirus-covid-19-data/>

5. Statistical analyses

Each research objective is addressed separately.

5.1 Objective 1: Describe the incidence of COVID-19 in the pregnant population

5.1.1 *Population*

All women in Scotland who were pregnant on, or became pregnant after, 1st March 2020.

5.1.2 *Outcomes of interest*

Confirmed COVID-19 defined as:

- Positive lateral flow or viral PCR test for SARS-CoV-2⁷

Probable COVID-19 defined as:

- COVID-19 recorded on a hospital admission, stillbirth, or death record (using ICD10 codes U07.1, U07.2, U07.5)

Possible COVID-19 defined as:

- Coronavirus infection recorded on a hospital admission, stillbirth, or death record (using ICD10 codes B34.2, B97.2 – indicates non SARS-CoV-2 or unspecified type of coronavirus)
- GP consultation or GP out of hours attendance coded as possible COVID-19
- NHS24 call coded as possible COVID-19
- Patient triaged to NHS24 COVID-19 phone assessment hub or clinical assessment centre
- Scottish Ambulance Service call for possible COVID-19
- A&E attendance coded as possible COVID-19
- Negative SARS-CoV-2 viral PCR test (tests taken due to symptoms only, not routine testing of asymptomatic individuals)

The above definitions are hierarchical, e.g. a positive lateral flow or viral PCR test for SARS-CoV-2 assigns a woman to the confirmed COVID-19 group, regardless of the presence of other records.

If possible we will distinguish SARS-CoV-2 viral PCR tests taken for clinical indications from routine testing of asymptomatic individuals. If data quality does not allow us to reliably distinguish between these groups, we will exclude women testing negative from both the 'case' and 'control' groups – and base our possible case definition on presentation to various healthcare settings with relevant symptoms as described above.

In general, cases occurring during pregnancy will be identified if the event of interest (e.g. SARS-CoV-2 viral PCR test taken, admission, A&E attendance, etc) occurs between 14 days prior to the estimated date of conception (gestation 0⁺⁰) and the end of pregnancy.

We will seek to access serological data as it becomes available. We will report the proportion of women with circulating IgG and/or IgM for SARS-CoV-2 and may incorporate serology results in case definitions and/or use in additional analyses as data mature. The timing of exposure to/infection with SARS-CoV-2 is more difficult to ascertain from serology results than from the other indicators of (possible) infection listed above. Seroconversion windows will also be considered for women with sequential serology results.

⁷ Positive lateral flow tests that are followed by a negative viral PCR test within 3 days will be discounted

In addition, we will identify women with a history of (rather than an acute/contemporaneous episode of) COVID-19 recorded on a hospital admission, stillbirth, or death record (using ICD10 codes U07.3, U07.4) and ensure these women are not included as 'controls' in analyses.

Other diagnostic and exposure categories may be added as the pandemic develops and diagnostic criteria change.

The pathway for management of patients in the community with symptoms suggestive of COVID-19 has evolved as the pandemic has progressed. In early March 2020, patients with symptoms were advised to phone their GP in hours or NHS 24 out of hours for advice. Patients requiring face to face assessment were then seen in GP surgeries or GP out of hours centres. On 17 March 2020, the Scottish Government published details of a new national patient pathway, whereby all patients with symptoms (in or out of hours) were encouraged to call NHS 24 as the initial point of contact. Patients thought likely to have COVID-19 were then passed to a new, dedicated NHS24 COVID-19 phone assessment hub. Those requiring face to face assessment in general were then seen in (or visited at home by staff from) an NHS24 COVID-19 clinical assessment centre, although pregnant women could alternatively be directed to their maternity service triage base⁸.

5.1.3 Analytical techniques

We will use summary statistics to describe the cohort by presence and absence of confirmed, probable, or possible COVID-19.

We will perform descriptive analysis of the number of cases over the total number of pregnancies i.e. how many pregnant women have had confirmed, probable or possible COVID-19/ total number of pregnant women. Where timing of infection is known, we will describe incidence of SARS-CoV-2 infection by trimester of exposure - first trimester; second trimester; third trimester (with denominators consisting of ongoing pregnancies in each trimester).

Due to the lag inherent in the various national datasets (see Appendix 2: Additional information on identifying pregnant women, and associated start and end of pregnancy dates, from national data sources), we anticipate being able to identify women who were pregnant in March 2020 (i.e. women becoming pregnant, with a continuing pregnancy, or ending their pregnancy during March), and the subset who had confirmed or possible/probable COVID-19 in March 2020, in July 2020. Our first analyses will therefore provide results for this initial month of interest. Analyses will subsequently be updated monthly, providing results for sequential months, and also information on the cumulative risk of COVID-19 as women progress through their pregnancies.

Simple smoothing techniques such as rolling averages will be used to facilitate presentation and interpretation of findings. We will also present our results as proportions of COVID-19 infection, together with confidence intervals based upon the Wilson method. We will describe the temporal changes in the proportion using cumulative risk models. Covariates such as the trimester of pregnancy, age of the mother and deprivation will also be included with a view to estimating the potential effects of these variables on the risk of COVID-19 infection

5.1.4 Potential confounders and effect modifiers

NA

5.1.5 Sub-group analysis

If/when numbers of cases allow, we will examine incidence of confirmed, probable or possible COVID-19 by:

⁸ <https://www.sehd.scot.nhs.uk/publications/DC20200317Covid-19.pdf>

- Maternal age
- Maternal deprivation level
- Maternal NHS Board area of residence
- Maternal comorbidity status

We will also explore the possibility of examining incidence by maternal ethnicity, although missing data on ethnicity status may preclude this.

5.1.6 *Corrections for multiple testing*

NA – The primary purpose of this analysis is to estimate the effects and we will present effect estimates together with 95% confidence intervals.

5.1.7 *Sensitivity analysis*

We will assess whether findings are robust to more stringent definitions of infection, e.g. by

- Restricting the definition of a possible case to exclude women with just a negative viral PCR result (in particular if the indication for tests [symptoms vs routine/asymptomatic] cannot be distinguished)

5.1.8 *Other analysis*

NA

5.2 Objective 2: Determine associations between COVID-19 and adverse pregnancy, neonatal and maternal outcomes

5.2.1 Population

All women in Scotland who were pregnant on, or became pregnant after, 1st March 2020.

5.2.2 Exposures of interest

Confirmed, probable or possible COVID-19 as defined above.

5.2.3 Outcomes of interest

Maternal outcomes:

- COVID-19 disease requiring any hospital admission
- Severe COVID-19 disease requiring ICU admission or resulting in death
- Thromboembolic events (see below)

Pregnancy outcome:

- Pregnancy outcome categorised as early spontaneous pregnancy loss (any spontaneous loss at <24 weeks, ectopic pregnancy, or molar pregnancy); termination of pregnancy (at any gestation); stillbirth (any spontaneous loss at ≥24 weeks; or live birth (at any gestation)
- (If numbers allow, the early spontaneous pregnancy loss outcome will be split into the more clinically meaningful separate outcome categories of spontaneous loss at <14 weeks; spontaneous loss at 14-23 weeks; ectopic pregnancy, and molar pregnancy)

Fetal and neonatal outcomes:

- Congenital anomaly (major structural anomaly as defined by EUROCAT diagnosed in pregnancy terminated at any gestation due to anomaly; miscarriage or stillbirth at ≥20 weeks; or live born baby diagnosed at <28 days of age)
- Preterm birth (<37 weeks) categorised as spontaneous or medically indicated (i.e. following induction of labour or elective Caesarean section undertaken to mitigate clinical risk)
- Small for gestational age (birthweight <10th centile by WHO-UK90 growth reference)
- Admission to neonatal care
- Neonatal SARS-CoV-2 infection (currently defined as positive viral PCR test on sample taken from baby aged 0-27 days, definition may be expanded to include results of serology tests as evidence and testing options accumulate⁹)
- Neonatal mortality (death of a live born baby at <28 days of age)

The composite outcome of extended perinatal mortality (stillbirth or neonatal mortality) will also be examined.

Thromboembolic events will be examined as a specific maternal outcome due to the increased risks of thromboembolism associated with both pregnancy and COVID-19 disease. In addition, as the COVID-19 vaccination programme has been rolled out, rare but severe immune-mediated, post-vaccination adverse events comprising clotting and thrombocytopenia have been recognised.¹⁰ Examining risk of these outcomes following COVID-19 disease, as well as post vaccination, will provide useful context which will aid interpretation of separate vaccine safety analyses. Initially, the following composite outcomes will be examined:

⁹ <https://www.rcpch.ac.uk/resources/covid-19-guidance-neonatal-settings>

¹⁰ <https://www.gov.uk/government/publications/use-of-the-astrazeneca-covid-19-vaccine-jcvi-statement>

- Intracranial venous thrombosis or haemorrhage (composite of Intracranial venous thrombosis, Intracerebral haemorrhage, and Other non-traumatic intracranial haemorrhage)
- Other deep venous thromboembolism (composite of DVT and PE and Other venous thromboembolism)
- Thrombocytopenia

If required, individual outcomes (i.e. the components of the composite outcomes above) may then be examined separately. The list of ICD10 codes that will be used to identify the outcomes of interest in hospital discharge and death records is provided in Appendix 3. The exact list of thromboembolic events to be examined will be kept under review as understanding of post-vaccination adverse events evolves. For example, it is possible that arterial thromboembolic events will be added.

5.2.4 Analytical techniques

Initially we will focus on describing the above outcomes in women with confirmed, probable or possible COVID-19, and comparing occurrence to that seen in control women at the same stage of pregnancy from the general pregnant population.

So, as above, all women pregnant in March 2020, and the subset with COVID-19 during that month, will be known in July 2020. At that time, we will ascertain the outcomes listed above (occurring at up to end March 2020) for the women with COVID-19. For each woman with COVID-19, we will select at random 10 control women from the general pregnant population, matched on:

- Maternal age (same year of birth)
- Maternal deprivation level (same SIMD quintile based on postcode of residence)
- Gestation at the time of COVID-19 diagnosis (same gestation in completed weeks)

The need to also match on NHS Board area of residence to mitigate differential availability of outcome data by NHS Board (in particular data available from SBR, see Appendix 2: Additional information on identifying pregnant women, and associated start and end of pregnancy dates, from national data sources) and/or pregnancy singleton/multiple status will also be explored.

We will also ascertain the outcomes listed above (occurring at up to end March 2020) for the control women (with separate controls used for confirmed, probable, and possible cases). We will update analyses on a monthly basis, providing results for sequential months, and also additional cumulative information on all outcomes that have accrued to the time of analysis (given that many will be unknown close to the time of the SARS-CoV-2 infection if infection occurs early in a continuing pregnancy).

We will then present summary results for each outcome of interest using a template similar to that shown below. We will take into account that some outcomes are only applicable to women with certain (known) pregnancy outcomes status, for example preterm delivery is only relevant to women who have had a live birth. We will create intuitive visual displays of results that provide information on number and proportion of women in different categories with events of interest.

Number of women with a live birth

Trimester *	March 2020						Repeat for subsequent months	Total since March 2020					
	Confirmed COVID-19	Probable COVID-19	Possible COVID-19	Controls for confirmed cases	Controls for probable cases	Controls for possible cases		Confirmed COVID-19	Probable COVID-19	Possible COVID-19	Controls for confirmed cases	Controls for probable cases	Controls for possible cases
1 st (0-13w)													
2 nd (14-27w)													
3 rd (≥28w)													
Total													

* Trimester at COVID-19 diagnosis or matching

Preterm birth (number of women with a live birth with outcome of interest)

Trimester	March 2020						Repeat for subsequent months	Total since March 2020					
	Confirmed COVID-19	Probable COVID-19	Possible COVID-19	Controls for confirmed cases	Controls for probable cases	Controls for possible cases		Confirmed COVID-19	Probable COVID-19	Possible COVID-19	Controls for confirmed cases	Controls for probable cases	Controls for possible cases
1 st (0-13w)													
2 nd (14-27w)													
3 rd (≥28w)													
Total													

Preterm birth (number of women per 1,000 with a live birth with outcome of interest)

Trimester	March 2020						Repeat for subsequent months	Total since March 2020					
	Confirmed COVID-19	Probable COVID-19	Possible COVID-19	Controls for confirmed cases	Controls for probable cases	Controls for possible cases		Confirmed COVID-19	Probable COVID-19	Possible COVID-19	Controls for confirmed cases	Controls for probable cases	Controls for possible cases
1 st (0-13w)													
2 nd (14-27w)													
3 rd (≥28w)													
Total													

Note that by end March 2020, it is not feasible that any women with COVID-19 in their first trimester during that month will have progressed to a live birth by the end of the month.

In time, however, final pregnancy outcome for all women with COVID-19 in March 2020 will be known.

Occurrence of the outcomes of interest in women with COVID-19 and controls will be compared using simple descriptive statistics (e.g. 95% confidence interval for the difference in proportions, generated using methods which accommodate proportions close to zero¹¹) and visualised appropriately.

¹¹ Brown LD, Cai TT, DasGupta A. Interval estimation for a binomial proportion. *Statistical Science* 2001; 16(2); 101–33.
<https://doi.org/10.1214/ss/1009213286>

If sufficient cases of COVID-19 among pregnant women accrue, and the univariate comparisons described above suggest that outcomes differ between women with and without COVID-19, formal modelling will be undertaken to quantify the impact of COVID-19 on outcomes, taking relevant confounders into account. An appropriate method that can accommodate the competing risk and time to event nature of some of the outcomes (for example time to event analysis and/or multistate modelling) will be used where necessary.

5.2.5 *Potential confounders and effect modifiers*

To be confirmed, but are likely to include clinical co morbidities such as diabetes and BMI.

5.2.6 *Sub-group analysis*

We will consider whether a subgroup analysis restricted to singleton pregnancies only is required.

5.2.7 *Corrections for multiple testing*

We do not propose to make any formal statistical adjustment for the multiple comparisons as the principal aim of the study is to estimate the effect of COVID-19 infection on pregnancy outcomes. The estimated effects and 95% confidence intervals will be reported for the range of outcomes. However, a caveat will be clearly expressed regarding the dangers of over interpreting these data, given the multiple outcomes used, particularly if it transpires that conflicting results are obtained from the differing outcome measures.

5.2.8 *Sensitivity analysis*

As for Objective 1.

5.2.9 *Other analysis*

Other sensitivity and subgroup analyses may be indicated by initial findings. We will clearly state which analyses were pre-specified and which were post-hoc.

5.3 Objective 3: Determine the proportion neonates that are positive for SARS-CoV-2 infection associated with COVID-19 in the baby's mother

5.3.1 *Population*

Live born babies born in Scotland from 1st March 2020 onwards.

5.3.2 *Exposures of interest*

Virologically confirmed COVID-19 in the neonatal period, currently defined as positive viral PCR for SARS-CoV-2 on sample taken from a baby aged 0-27 days.

Note the definition may be expanded to include the results of serology tests as evidence and testing options accumulate.

5.3.3 *Outcomes of interest*

Confirmed, probable or possible COVID-19 in mother, classified as:

- Apparent date of onset of maternal illness >14 days prior to delivery
- Apparent date of onset of maternal illness from 14 days prior to delivery up to date of delivery
- Apparent date of onset of maternal illness from day 1 to day 13 following delivery
- Apparent date of onset of maternal illness from day 14 to day 27 following delivery

5.3.4 *Analytical techniques*

We will use summary statistics to describe the neonatal confirmed COVID-19 cohort by presence of confirmed, probable or possible maternal infection in the different time periods.

5.4 Objective 4: Assess the proportion of COVID-19 cases in pregnant women and neonates that are included in relevant other enhanced surveillance studies (BPSU, CO-CIN)

5.4.1 *Population*

All women in Scotland who were pregnant on, or became pregnant after, 1st March 2020.

Live born babies born in Scotland from 1st March 2020 onwards.

5.4.2 *Exposures of interest*

For women: confirmed, probable or possible COVID-19 during pregnancy.

For babies: confirmed COVID-19 during the neonatal period.

5.4.3 *Outcomes of interest*

Inclusion in relevant existing COVID-19 enhanced surveillance studies, specifically:

- For women and babies: CO-CIN
- For babies only: BPSU enhanced surveillance of neonates with COVID-19
- For babies only: BPSU enhanced surveillance of children with multisystem inflammatory syndrome (neonatal onset only)

Note that as the data collected by UKOSS on pregnant women admitted with COVID-19 is not patient identifiable, this cannot be linked to the study dataset, hence is not included here.

5.4.4 *Analytical techniques*

We will use summary statistics to describe the number and proportion of cases included in the external surveillance studies, and any factors associated with inclusion e.g. hospital admission status and NHS Board area of residence.

5.5 Objective 5: Assess the safety of any new or existing prophylactic or therapeutic interventions (e.g. new or repurposed therapies, vaccines, antimicrobials) in pregnant women and their babies

To be confirmed.

Separate protocols on using the COPS dataset to examine uptake of vaccination in pregnancy and breastfeeding women, and the safety of vaccination during pregnancy, will be prepared.

5.6 Objective 6: Set up a platform to enable other and longer-term sequelae of SARS-CoV-2 or therapeutic interventions to mitigate SARS-CoV-2 infections in pregnancy, on childhood outcomes

To be confirmed.

5.7 Dealing with missing data

The approach to imputing estimated date of conception when gestation is missing on records indicating pregnancy status is detailed in Appendix 2: Additional information on identifying pregnant women, and associated start and end of pregnancy dates, from national data sources.

Missing data is otherwise not anticipated to be a substantial problem (and hence imputation techniques are not anticipated) but this will be confirmed once initial data extracts are available.

5.8 Statistical software

R Version 3.6.1 and RStudio (Version 1.1.456).

6. Reporting results

The results of monthly analyses summarising the incidence of COVID-19 in pregnant women, and outcomes seen in women with COVID-19 and pregnant controls, will be reported through the Public Health Scotland COVID-19 enhanced surveillance cell to the Scottish Government COVID-19 Advisory Group. Any results of formal modelling of outcomes that is undertaken will be reported through the same route. Results reported through this route may be provided as management information (i.e. without application of statistical disclosure control restrictions) as appropriate.

Results will also be submitted for peer reviewed academic publication. All results put into the public domain will be subject to statistical disclosure control according to usual Public Health Scotland processes.

It is currently anticipated that all linkage and analysis will be undertaken within Public Health Scotland. It is possible that the EAVE II linked data platform will be moved to the NHS national safe haven managed by the PHS eDRIS team at some point. If so, it is possible that later analyses may take place within this environment.

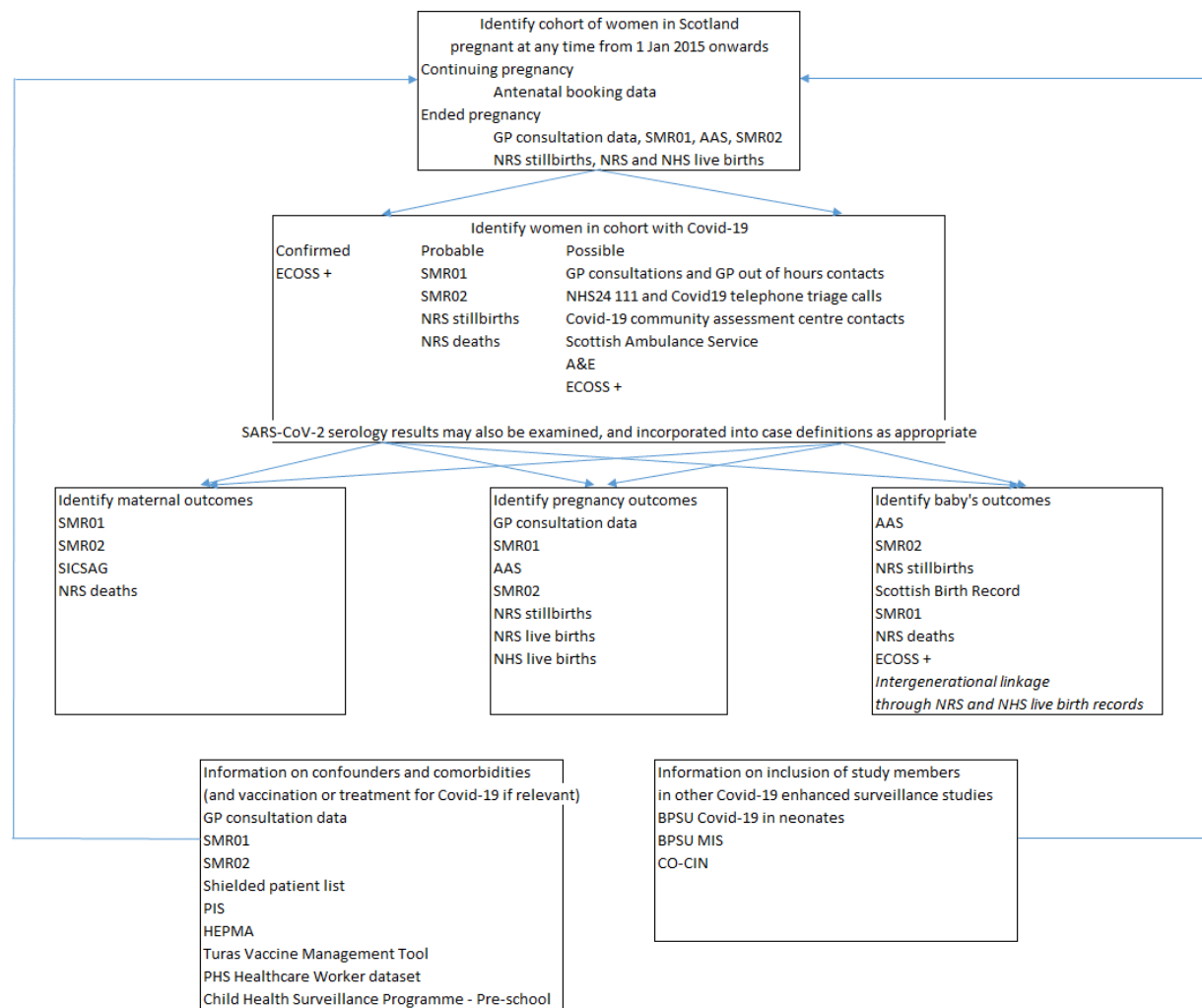
The following governance approvals will be secured prior to any linkage or analysis taking place:

- Ethical approval –through an amendment to the existing NHS research ethics approval in place for the EAVE II study
- Public Benefit and Privacy Panel approval

In addition, as Public Health Scotland and the Chief Medical Officer for Scotland are both (independent) data controllers for the national AAS database of termination of pregnancy notifications, we will write to the Chief Medical Officer to inform him of the intended use of AAS records for this study.

Results submitted for peer reviewed academic publication will be reported according to STROBE and RECORD (via the COVID-19 extension) guidelines. Confidence intervals will be reported where feasible to indicate the level of uncertainty of findings. Where p-values are given, these will be quoted to two decimal places, unless they are less than 0.001 (whereby the p-value will be given as <0.001) or between <0.005 and >0.001, in which case they will be stated to three decimal places.

Appendix 1: Overall schema of the COPS data linkage



Appendix 2: Additional information on identifying pregnant women, and associated start and end of pregnancy dates, from national data sources

National data sources identifying end of pregnancy events

There are three possible outcomes for any pregnancy

Pregnancy outcome	Comments
Spontaneous loss	'Miscarriage' at <24w (here taken to include ectopic pregnancies, although mechanisms underlying spontaneous miscarriage and ectopic pregnancy differ) (Sometime 'late fetal loss' at 20-23w as a subset of miscarriages) 'Stillbirth' at ≥24w
Termination of pregnancy	Legal at <24w under Grounds C and D of the Abortion Act 1967 Legal at any gestation under Grounds A, B, E, F, G
Live birth	No lower gestational limit although in practice around 22w would be considered the lower limit at which live born babies may survive

Various national records may be returned following these end of pregnancy events, as summarised below

National record	Description	Pregnancy outcomes identified	Coding to identify relevant records
Identifying spontaneous pregnancy losses			
SMR01	Record of day case or inpatient admission to any general unit (excluding neonatal, maternity, and mental health care), including admissions under gynaecology specialty	Will identify early (first trimester) spontaneous losses managed in hospital in most Board areas	ICD10: O00 (ectopic pregnancy) O01 (hydatidiform mole) O02 (missed miscarriage) O03, O05, O06 (spontaneous miscarriage), all .5-.9
OR SMR02	Record of day case or inpatient admission to a maternity unit, including admissions under obstetrics or midwifery specialties	Will identify early (first trimester) spontaneous losses managed in hospital in some Board areas Will identify later (second and third trimester) spontaneous losses managed in hospital in all areas	Miscarriages Condition on discharge=2 (aborted) Type of abortion=1, 2, 3, 6, 8, 9 (spontaneous) Stillbirths Condition on discharge=3 (delivered) Outcome of pregnancy=2 (stillbirth)
AND/OR NRS stillbirths	Record of statutory registration of a stillbirth (baby born at ≥ 24 w showing no signs of life)	Will identify spontaneous stillbirths	ICD10: P96.4 not recorded
Identifying terminations of pregnancy			
AAS	Record of statutory notification of a termination of pregnancy	Should identify all terminations of pregnancy but known under-notification of later ToPs done for fetal anomaly from some maternity units	

AND/OR SMR02	As above	Will identify later ToPs done for fetal anomaly in maternity units	Condition on discharge=2 (aborted) Type of abortion=4 (ToP)
AND/OR NRS stillbirths	As above	Will identify the small number of stillbirths following a termination of pregnancy	ICD10: P96.4 recorded in any position
Identifying live births			
SMR02	As above	Will identify live births occurring in hospital SMR02 returns were enabled to cover home (as well as in hospital) births from Apr 2019, and coverage of home births should have been mandatory from Oct 2019, however technical difficulties mean that home births are still not recorded on SMR02 in most Boards	Condition on discharge=3 (delivered) Outcome of pregnancy=1, 3, 4, 5 (live birth)
AND/OR NRS live births	Record of statutory registration of a live birth (live born baby at any gestation)	Usually identifies all live births however statutory registration of live births has been suspended from 23.3.2020 when registrar offices closed The only babies being registered during the lockdown period are those that subsequently die: this is being done remotely along with the death registration to avoid parents having to register the birth in person later	

AND/OR NHS live birth notifications	<p>Notification of live births from NHS Board maternity units to child health administration departments</p> <p>This notification allows a record to be created for the child on the national child health information system: this in turn ensures the child is called for immunisations and child health reviews</p>	<p>As NRS live birth registration was suspended in March 2020 due to COVID-19, PHS has recently developed a new data extraction from the national child health information system of birth notification data</p> <p>This will identify all live births known to NHS maternity services from Aug 2019 onwards</p> <p>A small number of babies who die very soon after birth (before that day's notification data has been sent) will not be included as these babies do not need to be notified for ongoing care, however they will be covered by NRS registration as noted above</p>	
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It is possible that the same woman/pregnancy may have multiple records giving conflicting information on the outcome of the pregnancy.

In general, if any record indicates a termination of pregnancy, this should be taken as the outcome.

If an NRS stillbirth record is available for a baby but the corresponding SMR02 record indicates the baby was live born, this should be taken as a stillbirth.

The relevant gestation and date of event information in the various records, and how to deal with missing gestation information, is summarised below

National record	Gestation information available	Date of event information available	Dealing with missing gestation information (due to not recorded on that record, missing, or recorded but unfeasible)
SMR01	None	Date of admission Date of discharge	Assume 12 weeks gestation at date of admission
SMR02	Gestation in completed weeks at end of pregnancy available on records where Condition on discharge=2 or 3 (aborted or delivered)	Date of admission Date of discharge Date of delivery on records where Condition on discharge=3 (delivered)	Miscarriage records with missing gestation, assume 12 weeks gestation at date of admission ToP records with missing gestation (and not available from AAS), assume 16 weeks gestation at date of admission Stillbirth delivery records with missing gestation (and not available from NRS), assume 32 weeks gestation at date of delivery Live birth delivery records with missing gestation, assume 40 weeks gestation at date of delivery
NRS stillbirths	Gestation in completed weeks at date of stillbirth available	Date of stillbirth	Assume 32 weeks gestation at date of delivery (if not available from SMR02)
AAS	Gestation in completed weeks at date of termination available	Date of termination (date of administration of antiprogesterone for medical ToPs)	Assume 10 weeks gestation at date of termination (if not available from SMR02)
NRS live births	None	Date of birth	Assume 40 weeks gestation at date of birth (if not available from SMR02)

NHS live birth notifications	<p>Gestation in completed weeks at date of birth available</p> <p>(Although note this data has not been used before by PHS so will require checking before use)</p>	Date of birth	Assume 40 weeks gestation at date of birth (if not available from SMR02)
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The time lag inherent in the different data returns is summarised below

National record	Time lag inherent in data source
SMR01	<p>Records should be returned to PHS within 6 weeks of patient's discharge (in practice sometimes longer)</p> <p>Monthly batches (all records received to that point) are then uploaded to the analysis platform (SMRA) around the middle of each month</p> <p>Records are CHI seeded as they are uploaded to the analysis platform (and CHI seeding is refreshed monthly thereafter to pick up any previously unseeded records)</p> <p>CHI seeding usually complete on first attempt</p> <p>So: records relating to discharges in Jan XX should be available for linkage and analysis within PHS in mid Apr XX (2.5 month lag)</p>
SMR02	<p>Records should be returned to PHS within 6 weeks of patient's discharge (in practice sometimes longer)</p> <p>Monthly batches (all records received to that point) are then uploaded to the analysis platform around the middle of each month</p> <p>Records are CHI seeded as they are uploaded to the analysis platform (and CHI seeding is refreshed monthly thereafter to pick up any previously unseeded records)</p> <p>Maternal CHI seeding usually complete on first attempt</p> <p>Baby CHI seeding usually complete on second attempt</p> <p>So: as linkage of SMR02 records is generally through maternal CHI, records relating to discharges in Jan XX should be available for linkage and analysis within PHS in mid Apr XX (2.5 month lag)</p>

NRS stillbirths	<p>Registration required within 21 days of birth</p> <p>Data transferred by NRS to PHS weekly</p> <p>Monthly batches (stillbirths registered up to the end of the previous month) are then uploaded to the analysis platform around the middle of each month</p> <p>In parallel, records are sent to NHSCR monthly for seeding of maternal CHI</p> <p>As seeded records are returned from NHSCR, the CHIs are added to the records on the analysis platform</p> <p>So: records relating to stillbirths occurring in Jan XX should be available for linkage and analysis within PHS in mid May XX (3.5 month lag)</p> <p>(Note: almost all stillbirths will have an SMR02 record so can be identified and linked with 2.5 month lag)</p>
AAS	<p>Notification to CMO required within 7 days of termination</p> <p>Records forwarded to PHS and entered into AAS system (includes automated CHI seeding) within 6 weeks of date of termination</p> <p>So: records relating to terminations occurring in Jan XX should be available for linkage and analysis within PHS in mid Mar XX (1.5 month lag)</p>

NRS live births	<p>Registration required within 21 days of birth</p> <p>Data transferred by NRS to PHS weekly</p> <p>Monthly batches (live births registered up to the end of the previous month) are then uploaded to the analysis platform around the middle of each month</p> <p>Records are seeded with baby CHI as they are uploaded to the analysis platform (and CHI seeding is refreshed monthly thereafter to pick up any previously unseeded records)</p> <p>Baby CHI seeding usually complete on second attempt</p> <p>In parallel, monthly batches are seeded with the mother's CHI by bespoke linkage to SMR02 after a 6 month lag (i.e. records for births in Jan XX and matched against SMR02 in Jul XX)</p> <p>Records with no maternal CHI found are then matched against the full CHI database</p> <p>Residual records with still no maternal CHI are then sent to NHSCR in monthly batches</p> <p>So: as linkage of NRS live birth records generally requires both maternal and baby CHI (to allow intergenerational linkage), records relating to births in Jan XX should be available for linkage and analysis within PHS in mid Oct XX (8.5 month lag)</p> <p>(Note: all live births from Aug 2019 onwards will have a birth notification record available so can be identified and linked with a 1 month lag)</p>
NHS live birth notifications	<p>Live births are notified to the NHS Board child health admin department within 1 working day of date of birth and are keyed into the national child health info system promptly (same or subsequent day)</p> <p>PHS extracts notification data (including baby's CHI) from the national child health info system weekly</p> <p>Maternal CHI is then seeded onto the data extracts weekly</p> <p>So: records relating to births in Jan XX should be available for linkage and analysis within PHS in Feb XX (1 month lag)</p>

National data sources identifying continuing pregnancies as early as possible

As part of the response to COVID-19, PHS has established a new national data return providing information on women booking for antenatal care. This will allow us to identify pregnant women before the end of their pregnancy, and hence monitor SARS-CoV-2 infections occurring in pregnant women in closer to real time. Further information on this data source is provided below.

Data items being requested in the new data feed include

- Maternal CHI
- Mother's Forename, Surname, Date of Birth, and Postcode in case CHI is missing and needs to be appended
- Date of Booking
- Gestation at booking
- Date of Last Menstrual Period (in case gestation is missing)

PHS has asked NHS Boards to provide an initial submission of historic data on all women booking from 1 April 2019, then subsequent weekly updates. The weekly updates will give information on women who have booked in the most recent week, and also update any records relating to the previous 2 weeks if those have changed since the previous submission. The current assumption is that this data will be submitted with maternal CHI complete, hence additional lag for CHI seeding will not be required but this is being kept under review.

This dataset will identify all women booking for NHS antenatal care. The method of providing booking services has changed in many areas due to COVID-19, with many Boards now providing the initial booking appointment remotely, with the woman subsequently attending in person for her initial ultrasound scan and blood tests¹². To ensure that the dataset allows us to identify pregnant women as early as possible in their maternity care journey, the 'booking' event that is captured in the above dataset has therefore been defined as *'the date on which maternity services had the first planned/structured contact with a pregnant woman to assess her history and needs so that local maternity services can provide further care such as an early pregnancy scan and antenatal screening tests'*, i.e. the initial remote contact.

¹² <https://tec.scot/clinical-specialty-guidance/>

Available national data shows that, pre-COVID-19, at least 90% of pregnant woman attended their booking appointment by 12⁺⁶ weeks gestation¹³. There is currently no evidence that gestation at initial booking has increased due to COVID-19. If gestation and LMP are both missing on antenatal booking records, we will therefore assume the woman was at 12 weeks gestation at the date of booking.

¹³ <https://www.isdscotland.org/Health-Topics/Maternity-and-Births/Publications/>

Defining start and end date of pregnancies

For pregnancies that have ended

Pregnancy end dates will be taken from end of pregnancy records as noted above

Pregnancy start date (date of conception) will be imputed from the pregnancy end date and the gestation at pregnancy end – 2 weeks

For continuing pregnancies

Pregnancy start date (date of conception) will be imputed from the date of antenatal booking and the gestation at booking – 2 weeks, or from the date of last menstrual period + 2 weeks if gestation is missing and LMP is provided

Time lags inherent in data sources identifying COVID-19 status and relevant outcomes

In general, the time lags inherent in data sources identifying COVID-19 status and relevant outcomes are less than (or at least no more than) those inherent in the various data sources required to identify pregnancy status.

The only additional lag that needs to be considered is that seen in Scottish Birth Record (SBR) records. SBR records are not returned to PHS as such. Rather, PHS takes a monthly download of data held on the system for analysis purposes. In most NHS Boards, the SBR system is used to generate a CHI number for a baby shortly after birth. Skeleton records with minimal demographic data are therefore available for all babies in a timely manner. For babies admitted to neonatal care, clinical coding staff within NHS Board admin departments are responsible for completing additional variables within a baby's SBR record following their discharge. There is no national standard for when this should be done and in practice the lag between discharge and a completed record being available varies between Boards. Some Boards achieve broadly complete records within 3 months whereas others take considerably longer. Currently (June 2020) NHS Borders and NHS Dumfries & Galloway have not coded any SBR records (or provided comparable data directly to PHS) since June 2017 and April 2018 respectively. SBR data is therefore unlikely to provide a complete picture of neonatal admissions within the timeframes set out for this analysis (i.e. for babies born in March 2020, the data available to PHS on SBR by July 2020 will only provide a partial picture of admissions to neonatal care). PHS may explore getting a new national feed from NHS Boards of more real time data on neonatal admissions to mitigate this problem if feasible.

Appendix 3: ICD10 codes to identify thromboembolic events and thrombocytopenia

Intracranial venous thrombosis

- G08 Intracranial and intraspinal phlebitis and thrombophlebitis
- I63.6 Cerebral infarction due to cerebral venous thrombosis, nonpyogenic
- I67.6 Nonpyogenic thrombosis of intracranial venous system
- O22.5 Cerebral venous thrombosis in pregnancy
- O87.3 Cerebral venous thrombosis in the puerperium

Intracerebral haemorrhage

- I61.0 Intracerebral haemorrhage in hemisphere, subcortical
- I61.1 Intracerebral haemorrhage in hemisphere, cortical
- I61.2 Intracerebral haemorrhage in hemisphere, unspecified
- I61.3 Intracerebral haemorrhage in brain stem
- I61.4 Intracerebral haemorrhage in cerebellum
- I61.5 Intracerebral haemorrhage, intraventricular
- I61.6 Intracerebral haemorrhage, multiple localized
- I61.8 Other intracerebral haemorrhage
- I61.9 Intracerebral haemorrhage, unspecified

Other non-traumatic intracranial haemorrhage

- I60.0 Subarachnoid haemorrhage from carotid siphon and bifurcation
- I60.1 Subarachnoid haemorrhage from middle cerebral artery
- I60.2 Subarachnoid haemorrhage from anterior communicating artery
- I60.3 Subarachnoid haemorrhage from posterior communicating artery
- I60.4 Subarachnoid haemorrhage from basilar artery
- I60.5 Subarachnoid haemorrhage from vertebral artery
- I60.6 Subarachnoid haemorrhage from other intracranial arteries
- I60.7 Subarachnoid haemorrhage from intracranial artery, unspecified
- I60.8 Other subarachnoid haemorrhage
- I60.9 Subarachnoid haemorrhage, unspecified
- I62.0 Subdural haemorrhage (acute) (nontraumatic)
- I62.1 Nontraumatic extradural haemorrhage
- I62.9 Intracranial haemorrhage (nontraumatic), unspecified

Deep venous thrombosis and pulmonary embolism

- I26.0 Pulmonary embolism with mention of acute cor pulmonale
- I26.9 Pulmonary embolism without mention of acute cor pulmonale
- I80.1 Phlebitis and thrombophlebitis of femoral vein
- I80.2 Phlebitis and thrombophlebitis of other deep vessels of lower extremities
- I80.3 Phlebitis and thrombophlebitis of lower extremities, unspecified
- O22.3 Deep thrombophlebitis in pregnancy
- O87.1 Deep phlebothrombosis in the puerperium
- O88.2 Obstetric blood-clot embolism

Other venous thromboembolism

- I80.8 Phlebitis and thrombophlebitis of other sites
- I80.9 Phlebitis and thrombophlebitis of unspecified site
- I81 Portal vein thrombosis
- I82.0 Budd Chiari syndrome
- I82.1 Thrombophlebitis migrans
- I82.2 Embolism and thrombosis of vena cava
- I82.3 Embolism and thrombosis of renal vein
- I82.8 Embolism and thrombosis of other specified veins
- I82.9 Embolism and thrombosis of unspecified vein
- O08.2 Embolism following abortion and ectopic and molar pregnancy
- O22.9 Venous complication in pregnancy, unspecified
- O87.9 Venous complication in the puerperium, unspecified

Thrombocytopenia

- D69.3 Idiopathic thrombocytopenic purpura
- D69.4 Other primary thrombocytopenia
- D69.5 Secondary thrombocytopenia
- D69.6 Thrombocytopenia, unspecified
- M31.1 Thrombotic microangiopathy