| | |
|---|---|
| **FULL/LONG TITLE OF THE STUDY** | **Understanding COVID-19 infection in pregnant women and their babies** |
| **SHORT STUDY TITLE / ACRONYM** | **periCOVID** |
| **PROTOCOL VERSION NUMBER AND DATE** | **V1.1 dated 21Jan2021** |
| **IRAS Number:** | **287478** |
| **JRES Reference Number** | **2020.0276** |
| **This protocol has regard for the HRA guidance and order of content** | |

**SIGNATURE PAGE**

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

**For and on behalf of the Study Sponsor:**

Date:
17/11/2020

Signature: J. Montebello

Name (please print): Joe Montebello

Position: Senior Clinical Research Facilitator

**Chief Investigator:**

Date: 17/11/20.

Signature: kirsty mehring le doare

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Name: (please print): Professor Kirsty Le Doare

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| KEY STUDY CONTACTS | |
|---|---|
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| Study Co-ordinator | Dr Sarah Sturrock<br>Institute of Infection of Immunity<br>St Georges University of London<br>Crammer Terrace<br>Tooting<br>London<br>SW17 0RE |
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| Funder(s) | Action Medical Research for Children |
| Key Protocol Contributors | Dr Melanie Etti (metti@sgul.ac.uk) |

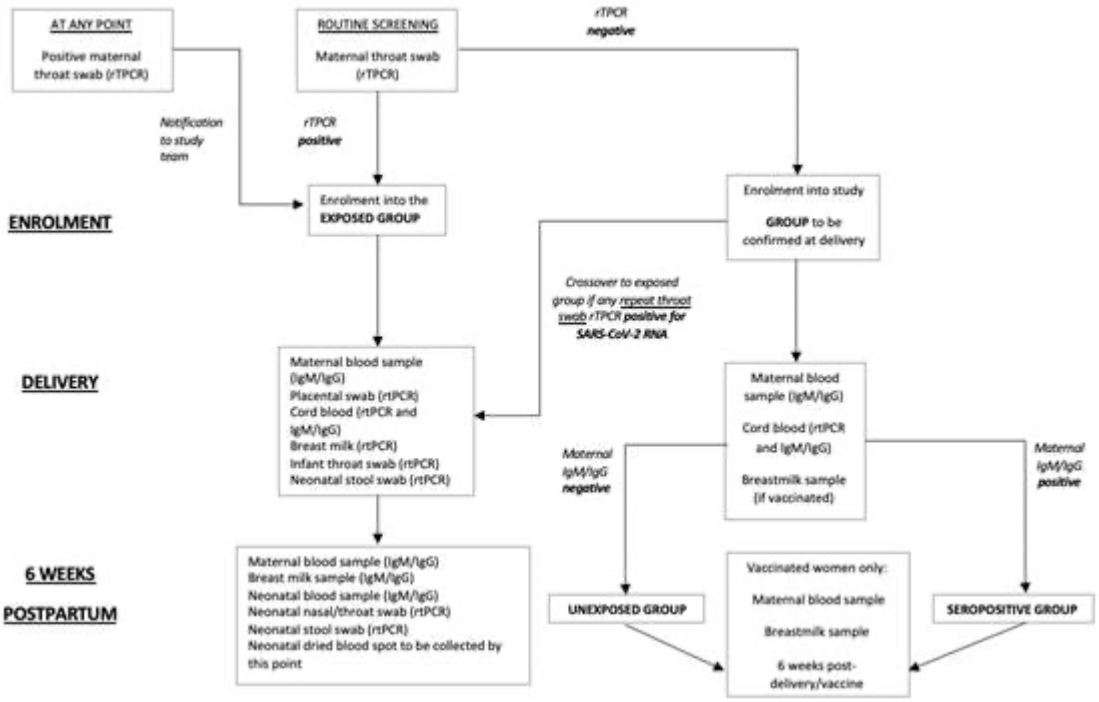
| STUDY SUMMARY | |
|---|---|
| Study Title | Understanding COVID-19 infection in pregnant women and their babies |
| Internal ref. no. (or short title) | periCOVID |
| Study Design | Observational cohort |
| Study Participants | Pregnant women in England, any gestation ≥24 weeks |
| Planned Size of Sample (if applicable) | 1200 |
| Follow up duration (if applicable) | 1 month |
| Planned Study Period | 12 months |
| Research Question/Aim(s) | To determine the seroepidemiology of SARS-CoV-2 in pregnant women in England |

| FUNDING AND SUPPORT | |
|---|---|
| **FUNDER(S)** | **FINANCIAL AND NON FINANCIALSUPPORT GIVEN** |
| **Action Medical Research** | **£199,995** |

## PROTOCOL CONTRIBUTORS

Dr Kirsty Le Doare, Dr Paul Heath, Dr Melanie Etti, and Dr Sarah Sturrock all contributed to the design of this protocol.

## STUDY Schematic



| ABBREVIATIONS | |
|---|---|
| AE | Adverse Event |
| AR | Adverse Reaction |
| CI | Chief Investigator |
| CRF | Case Report Form |
| GCP | Good Clinical Practice |
| GP | General Practitioner |
| HRA | Health Research Authority |
| ICF | Informed Consent Form |
| ISF | Investigator Site File |
| NHS | National Health Service |
| NIHR | National Institute for Health Research |
| PI | Principal Investigator |
| REC | Research Ethics Committee |
| SAE | Serious Adverse Event |
| SGUL | St Georges, University of London |
| SGHFT | St Georges, University Hospitals NHS Foundation Trust |
| JRES | (St Georges) Joint Research and Enterprise Services |

**STUDY PROTOCOL**

Understanding COVID-19 infection in pregnant women and their babies (periCOVID)

## 1 BACKGROUND

This protocol is intended to follow on from the existing PHE periCOVID national surveillance programme, to provide further clarity on the seroepidemiology of the disease in pregnant women, and the risk of vertical transmission between mothers and their infants.

Since the first report (December 2019) of the novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the number of cases, mortality and morbidity have increased rapidly[1]. Pregnant women are a high risk group because of the possible effect of COVID-19 during and after pregnancy, and on their infants[2]. Early reviews of COVID-19 in pregnancy mostly included case reports and series that were often inappropriately meta-analysed. Subsequent reviews differed little from each other, many with duplicate data[3]. Moreover, sampling frames in primary studies have varied from universal SARS-CoV-2 testing for all hospitalised pregnant women to symptom-based testing. Testing strategies have differed widely, with diagnosis in many studies based on epidemiological risk assessment and clinical features without confirmed infection[4]. Limitations in the external and internal validity of studies make it challenging to provide recommendations regarding SARS-COV-2 in pregnancy and for infants of women who may be affected[4].

Coronaviruses have caused two previous significant outbreaks: MERS and SARS. In both, pregnancy complications were more common in infected women[5][6]. In 2009, pregnant women accounted for 1% of patients infected with influenza A subtype H1N1 virus but 5% of all H1N1-related deaths[7][8]. A systematic review of published reports on Coronaviruses (COVID-19, SARS and MERS) found preterm birth <37 weeks to be the most common adverse pregnancy outcome (14/32 pregnancies; 41%)[6]. A retrospective multicentre cohort study of 388 pregnant women testing positive for SARS-COV-2 supported this finding, with preterm birth implicated in 23% with a 4.1% rate of perinatal death[9]. Our systematic review and meta-analysis, including 2567 pregnant women who tested positive for SARS-COV-2 by rT-PCR, has also indicated that preterm birth is common (21.8%) [10]. Another review found an increased risk of admission to the neonatal unit (odds ratio 3.13, 95% confidence interval 2.05 to 4.78; 1 study, 1121 neonates) in infants born to mothers testing positive for SARS-COV-2[2]. In a living systematic review that includes 2557 neonates born to women testing positive for SARS-COV-2, 25% were admitted to the neonatal intensive care unit (including because of COVID-19 policy), fetal distress was observed in 8% and 4% of neonates were diagnosed with neonatal sepsis[11].

Vertical transmission has been documented in several small case studies, but without standardised definitions and sampling methods. In an unreviewed systematic review of case reports / series, the vertical transmission rate was estimated to be 11% [12]. However, other studies do not substantiate this finding and it remains unclear whether this transmission occurred at or soon after birth. A case series tested amniotic fluid, cord blood, neonatal throat swabs and breastmilk samples from SARS-CoV-2 infected mothers and all samples tested negative[13]. In other studies, by the same group, three placentas of infected mothers tested negative for the virus, and none of three infants born to symptomatic mothers had positive tests for COVID-19. The most comprehensive review to date of 31 pregnancies complicated by SARS-COV-2 did not find evidence of vertical transmission. However, whilst these data are reassuring, other studies have found SARS-CoV-2 in the placentas of mothers with COVID-19[14][15].

## 2 RATIONALE

We at SGUL propose a rapid national study which aligns closely with the WHO MNCAH generic protocol, to inform public health policy within a 12 month timeframe by collecting samples from pregnant women during pregnancy and at delivery and from their infants to assess exposure and immunity to SARS-CoV-2. We are already linked with existing UK surveillance studies (UKOSS, PAN COVID, BPSU) to ensure a joined up approach to data collection. Our study also leverages an existing framework, iGBS3, set up to understand the seroepidemiology of Group B Streptococcal disease in 320,000 pregnant women in the UK. Knowledge of protective immunity will also be of critical value in considering the role for COVID-19 vaccines in pregnant women.

## 3 THEORETICAL FRAMEWORK

Approximately 650,000 women deliver annually in the UK[16], and approximately 7% of pregnant women have been exposed to SARS-COV-2[17]. These data represent women with severe disease requiring hospitalisation, so may not represent the full impact of SARS-CoV-2 on pregnancy and infant outcomes, as many may be asymptomatic(16,17,18). Studying women for SARS-CoV-2 antibodies and viral DNA regardless of symptomatology is required to estimate the true burden among mothers and babies and to determine the extent of mother-to-child transmission.

Placental transfer of IgG during pregnancy provides passive immunity that is critical in protecting newborns against infections[20]. Maternal immunization can boost protective IgG, reducing neonatal morbidity, as seen with tetanus [21] and influenza [22,23]. A number of COVID-19 vaccines are now in clinical development[24], which may be suitable for pregnant women. We must now gather data on natural immunity to SARS-CoV-2 in pregnant women, including seroprevalence, placental transfer and the duration of antibody persistence in infants to understand the role for maternal vaccination, ensure equitable inclusion of pregnant women into trials of candidate vaccines and, ultimately, to provide effective and safe COVID-19 vaccines [25].

Many maternity units are now routinely swabbing pregnant women, presenting a unique opportunity to understand the seroepidemiology of SARS-CoV-2 in pregnancy and the peripartum and to prospectively monitor vertical transmission. By collecting samples from a large cohort of pregnant women, and from the newborns of women who had COVID-19 infection during pregnancy (irrespective of symptoms), we hope to understand the seroepidemiology of SARS-COV-2 and the risk and mode of perinatal transmission of the novel coronavirus. This study will provide a robust evidence base to inform guidance and policy decisions for the clinical and public health management of pregnant women, their infants and the staff that care for them.

## 4 RESEARCH QUESTION/AIM(S)

### 4.1 Objectives

Primary objectives

- Determine the seroepidemiology of SARS-CoV-2 in pregnant women and infants in England

Secondary objectives

- Determine the placental transfer ratio of antibodies specific to SARS-CoV-2

- Determine the concentration of SARS-CoV-2 antibodies in breastmilk of mothers who have tested rtPCR positive at any point during pregnancy
- Determine the rate of mother to child transmission of SARS-CoV-2 in women who have tested rtPCR positive at any point during pregnancy
- Determine the quantity (of both DNA and live virus) of SARS-COV-2 in maternal bodily fluids, including breastmilk, and in the placenta, in women who have tested positive for SARS-COV-2 by rtPCR at any point during pregnancy

### 4.2 Outcomes

1. Antibody concentrations in maternal and cord blood in pregnant women in England and in infant blood if mothers are rtPCR positive for SARS-COV-2
2. Number (%) of mother who have antibodies specific to SARS-CoV-2 in breastmilk
3. Number (%) of mother-infant pairs who are both rtPCR positive in blood or secretions at birth and at six weeks and number (%) in whom the virus can be grown in vitro
4. Number (%) of breastmilk samples that are rtPCR positive and number (%) in whom the virus can be grown in vitro.
5. Number (%) of placental samples that are rtPCR positive and number (%) in whom the virus can be grown in vitro.

## 5 STUDY DESIGN and METHODS of DATA COLLECTION AND DATA ANALYIS

An online CRF will be designed to capture the following information from all enrolled women:

- Maternal characteristics (age, ethnicity, significant past medical history)
- Pregnancy information (gestational age at diagnosis, number of foetuses, pregnancy related complications, radiology findings, laboratory findings, ventilation support, ICU admission, estimated foetal weight, foetal abnormalities). Delivery information (Gestational age at delivery, delivery method, intrapartum complications, postpartum complications, placental pathology)
- Maternal SARS-CoV-2 vaccination status, dates and manufacturers of any vaccinations given against SARS-CoV-2
- Neonatal outcomes (evidence of COVID-19, NICU admission, respiratory morbidity, duration and type of ventilation support, infectious morbidity, neurological morbidity, weight at day 5 postpartum check)
- Onset and duration of symptoms of COVID-19 (if present)
- Breastfeeding outcomes

All women will enter the study either having had a positive throat or nasopharyngeal aspirate (NPA) swab for SARS-CoV-2 RNA (as part of routine screening or due to symptom development), or having been recruited at one of our partner sites. Therefore, women will effectively be screened for COVID-19 by throat or nasopharyngeal aspirate (NPA) swab for SARS-CoV-2 RNA prior to enrolment into the study.

If the rTPCR result for the throat/NPA swab is **positive** for SARS-CoV-2 RNA, the woman will be invited to enrol into the **exposed** group within the study.

If the rTPCR result for the throat/NPA swab is negative for SARS-CoV-2 RNA, the woman will have a blood sample taken for SARS-CoV-2 IgM/IgG at the time of delivery.

If the SARS-CoV-2 IgM/IgG result is **positive**, the woman should be placed into the **seropositive** group within the study.

If the SARS-CoV-2 IgM/IgG result is **negative**, the woman should be placed into the **unexposed** group within the study.

Participants in the **exposed** group will have the following samples taken at delivery:

- Maternal blood sample (5ml) – serology (SARS-CoV-2 IgM/IgG)
- Placental tissue (swabs of both sides) – for rtPCR for SARS-CoV-2
- Cord blood (5mls) or neonatal blood sample (2mls)–serology (SARS-CoV-2 IgM/IgG)
- Breast milk sample – for rtPCR for SARS-CoV-2, viral culture and SARS-COV-2 IgA/G/M
- Neonatal nasal/throat swab – for rtPCR for SARS-CoV-2 and viral culture
- Neonatal stool swab – for rtPCR for SARS-CoV-2 and viral culture

Participants in the **exposed** group will have the following samples taken at 6 weeks postpartum:

- Maternal blood sample (5ml) – serology (SARS-CoV-2 IgM/IgG)
- Breast milk sample – SARS-CoV-2 IgM/IgG
- Neonatal blood sample (2ml)– serology (SARS-CoV-2 IgM/IgG)
- Neonatal nasal/throat swab – for rtPCR for SARS-CoV-2 and viral culture
- Neonatal stool sample – for rtPCR for SARS-CoV-2 and viral culture
- Neonatal dried blood spot – serology (SARS-CoV-2 IgM/IgG), to be taken by 6 weeks postpartum

Participants in the **seropositive** group will have the following samples taken at delivery:

- Maternal blood sample (SARS-CoV-2 IgM/IgG)
- Cord blood (SARS-CoV-2 IgM/IgG)

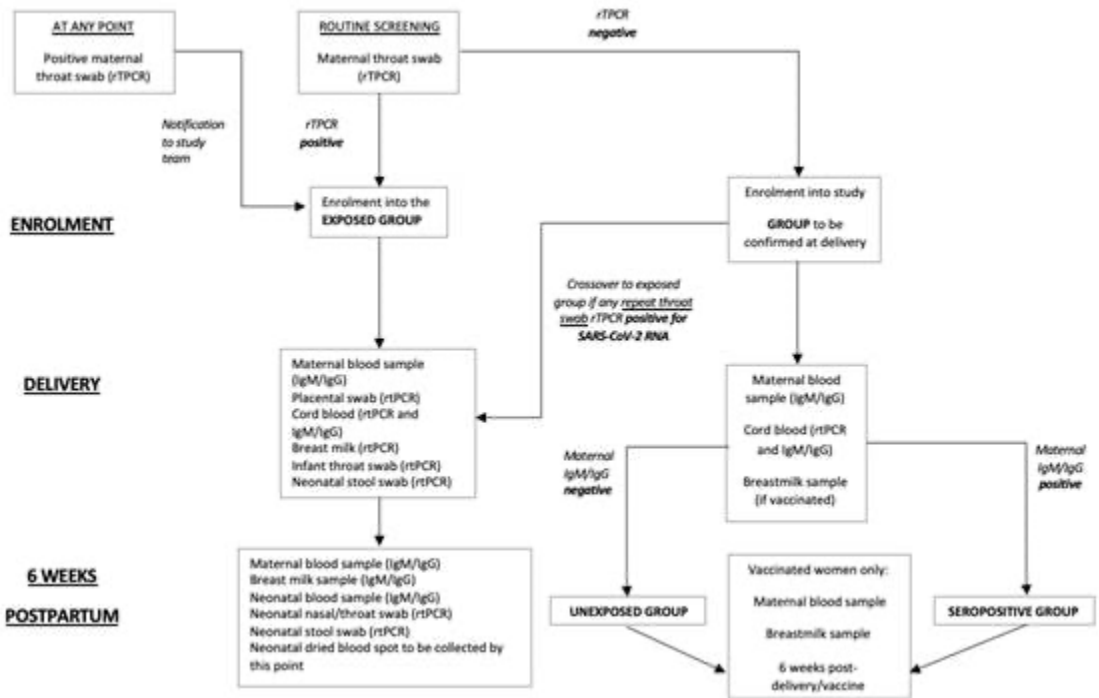
Participants in the **unexposed** group will have the following samples taken at delivery:

- Maternal blood sample (SARS-CoV-2 IgM/IgG)
- Cord blood (SARS-CoV-2 IgM/IgG)

Crossover between the study groups will be permitted; women may move from the unexposed group to the exposed group if a repeat throat/NPA swab performed after enrolment is positive for SARS-CoV-2 RNA.

Women who have received a SARS-CoV-2 vaccine will be included in the unexposed or seropositive groups depending on their antibody test results, but will have an additional blood sample taken at 6 weeks postpartum, or 6 weeks following their vaccination if the vaccine is given postpartum. Women who have received a vaccine will also be asked for a breastmilk sample at birth and at 6 weeks postpartum, or at 6 weeks following their vaccination if the vaccine is given postpartum.

The flow chart below describes the sequence of events for all women who are screened and enrolled into the study:




**Laboratory tests**

All samples will be sent to St. George's, University of London using appropriate pre-addressed packaging supplied on sites joining the study. Samples will be processed at the PHE laboratory at St George's. Secretions, placental tissue and breastmilk samples will be analysed by rT-PCR and if positive for viral culture using standard NHS methods[26]. Serum and dried blood spots will be frozen at -70C and will be analysed by validated assays at National Institute for Health Protection laboratories using previously published methods[17,27]:

Swab, breastmilk, urine faeces testing

Briefly, RNA will be extracted using commercial kits and run in the rTPCR published in February 2020 by the CDC *"CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time RT-PCR Diagnostic Panel".*

Serum testing

Serum samples will be tested in a commercial ELISA (EDI$^{TM}$) that uses an immunocomplex of the novel CoVID19 recombinant antigen-human anti-CoVID19 IgG/IgM HRP-labelled anti-human IgG/IgM tracer antibody, already in use at PHE Porton.

Sequencing

Extracted viral genomic material will be sent to the COVID-19 genetics consortium UK based at the Sanger Centre for sequencing.

**Data Analysis**
We will perform descriptive analyses of the characteristics of our cohort of mother and infant pairs. This will take place at St George's University, London. Pseudonymised test results will be transferred from the PHE laboratory and inputted to REDCap to facilitate this. Maternal factors will include age, maternal comorbidities, parity, and antenatal history and COVID-19 symptoms. Infant factors will include gestational age, birth weight, condition at birth, breastfeeding status, weight at 6 weeks, symptoms and admission to the special care baby unit.
We will estimate seroprevalence of COVID-19 in women/infants as the proportion with a positive antibody test. The proportion of women PCR positive during pregnancy will be estimated with 95% CI. The proportion of infants PCR positive at day 0 based on the various tissue samples tested will be calculated with 95% CI overall and within the subset of infected or PCR positive. Antibody transfer ratios (with 95% CI) for mother-baby pairs where the mother or baby is antibody positive at birth will be calculated with analysis of logged antibody concentrations. Antibody kinetics will be assessed in mothers who are antibody positive prior to birth and their infants by assessing geometric mean fold changes between diagnosis, birth and six weeks post-delivery and by fitting decline curves with a mixed model. Multivariable logistic regression will assess risk factors associated with the outcomes.

## 6 STUDY SETTING

This is a multisite study which will be open to and recruiting participants from all maternity units (obstetric unit or alongside maternity unit) in England.

## 7 SAMPLE AND RECRUITMENT

### 7.1 Eligibility Criteria

All pregnant women ≥ 24 weeks gestation in England.

OR

All women in England who are breastfeeding and have been vaccinated for SARS-CoV-02

#### 7.1.1 Inclusion criteria

- Signed informed consent form
- Any woman pregnant in selected hospitals in England who has no signs or symptoms of COVID-19 disease during pregnancy and is rtPCR negative at delivery
- Any woman pregnant in any hospital in England who tests positive by rtPCR at any point during pregnancy, regardless of signs and symptoms

- Any woman in any hospital in England who is breastfeeding and has been vaccinated for SARS-CoV-02

### 7.1.2 Exclusion criteria

- If the woman is under 18 years in prison or unable to make an informed consent for other reasons (e.g. learning difficulties, language barriers)

## 7.2 Sampling

### 7.2.1 Size of sample

We aim to recruit 1200 women over a period of 12 months.

Seroepidemiology: around 1000 women will allow good precision for estimation of an overall seroprevalence in the woman population.

The precision (95% CI width)

| Observed % with antibodies | 95% CI (N=1000) | 95%CI (N=2000) |
|---|---|---|
| 5% | 3.7%-6.5% | 4.1%-6.0% |
| 10% | 8.2%12.0% | 8.7%11.3% |
| 15% | 12.8%-17.4% | 13.5%16.6% |

Vertical transmission: around 200 rT-PCR positive women will allow good precision for estimation of the infant also being rT-PCR positive:

| Observed % with PCR detected in baby | 95% CI (N=100) | 95% CI (N=200) |
|---|---|---|
| 5% | 1.6%-11.2% | 2.4%-9.0% |
| 10% | 4.9%-17.6% | 6.2%-15.0% |
| 15% | 8.6%-23.5% | 10.4%-20.7% |

### 7.2.2 Sampling technique

All eligible women should be sensitised to the study by staff at the maternity units. Allocation to each of the study groups will be dependent on the outcome of their screening samples.

## 7.3 Recruitment

We anticipate that many (or all) hospitals in England will begin to screen all pregnant women for SARS-CoV-2. There will be two possible entry points to the study. Women will either enter the study after testing positive for SARS-CoV-2 (by rtPCR) during their antenatal care at any hospital in England

and will then be referred to the study team at St George's University of London or will be recruited from one of the participating NHS sites.

### 7.3.1 Participant identification

Participants who fulfil the eligibility criteria will be identified by the direct care team who are involved in their care. The responsibility of sensitisation and recruitment of participants will be delegated to research staff based at the NHS maternity units where these women are receiving their care.

Eligible participants should be sensitised to the study by their direct care team. Women should be sensitised and recruited during their routine appointments where possible to minimise the number of additional visits required for the study. Participants will also be able to self-refer to the study via the study website.

### 7.3.2 Consent

Eligible women should be sensitised to the study through the provision of a participant information leaflet and informed consent form (ICF) which will be made available to hospital-based recruiting clinicians and will also be available to download from the periCOVID website (http://www.pericovid.com).

The woman should be given sufficient time by the clinician to consider the information provided and ask any questions. If she agrees to take part, then she will be asked to complete and sign the ICF. The woman should then be provided with a copy of the ICF for her records and the original document stored locally.

Women who cannot provide informed consent (e.g. due to learning difficulties) are not eligible for the study. Women will be asked to give consent for collection of samples from their infant.

#### 7.3.2.1 Process for obtaining consent by post/telephone

1. If interested, the patient information sheet and consent form will be sent by post to the patient's home address or sent electronically (via email) or by the Investigators. In the case of seeking electronic consent, the documents will be sent to a private email address of the patient which only they can access (or a shared email address, having been made aware by the investigators of the data confidentiality implications).
2. Approached patients will be given at least 24 hours to consider the implications of their participation in the research and to think about any questions they have. However, if the patient may be consented prior to this 24 hour period, providing it is their decision and they have had the opportunity to fully consider the implications of their participation. The investigators will agree a date and time to contact the patients again to seek informed consent, if they are willing to participate.
3. Following initial contact, the Investigators will contact the patients again by telephone and if the patient is agreeable, informed consent will be taken over the phone with the patient able to complete a paper (postal) or electronic version of the informed consent form. The procedure of

obtaining informed consent will be undertaken in exactly the same way as would usually occur with a face-to-face visit. The signed informed consent form will be returned to the Investigators by email or by post and will be counter-signed and saved in a secure file location on Trust IT infrastructure by the Investigators, with one fully-signed copy returned to the patient and another saved in the medical notes.

#### 7.3.2.2 Consent provisions for collection and use of participant data and biological specimens

Data and biological specimens will be acquired locally, and transferred and stored as detailed above. Data collection will be coordinated between the PHE laboratory at St George's and SGUL, where all the data will be held and all data analysis performed. A secure electronic database using REDCap will be developed for this purpose and sites will be asked to complete questionnaires directly online.

Pseudonymised demographic and clinical data may also be obtained from our collaborative partners working within the UKOSS and PANCOVID studies via REDCap, a secure web-browser based application designed to capture data for clinical research. Each participant will be allocated a study number, and demographic and clinical data relating to each participant will be recorded into REDCap under their study number. This relates only to participants who are co-enrolled in these studies and who provide consent to their data being shared.

Anonymised data collected during this study will be reported monthly to the WHO so that important results can be widely disseminated in real time. Anonymised data and/or samples may also be transferred to our other collaborators for use in research that is being conducted at their site(s). Participants will also be asked to provide consent for this in the informed consent form.

If a participant loses the capacity to consent during the study, they will be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant. Participants will also be able to withdraw their consent at any time, and hence withdraw from the study. If participants withdraw consent, we will retain samples and data already collected, with their consent.

### 7.3.3 **Data collection tool**

Case Report Forms will be designed by the CI and uploaded to REDCap to facilitate data collection.

The CI or delegated individual on behalf of the Sponsor will provide logins to relevant and trained site level members of the research team.

It is the Investigator's responsibility to ensure the accuracy of all data entered and recorded in the CRFs. The Staff Delegation of Responsibilities Log should identify all trial personnel responsible for data collection, entry, handling and managing the database.

### 7.3.4 **Biological Sample Handling**

All samples will be stored at -70C until analysis. Samples will be sent to St George's, and then analysed in the PHE laboratory at St George's. Pending ethical approval, samples will be held in long-term storage in the Institute of Infection and Immunity Research Tissue Bank for as yet unidentified, future research projects.

5.4.3.1. Throat/NPA swab, breastmilk, cord blood, amniotic fluid, placental and stool swab testing
Briefly, RNA will be extracted using commercial kits and run in the rTPCR published in February 2020 by the CDC *"CDC 2019-Novel Coronavirus (2019-nCoV) Real-Time RT-PCR Diagnostic Panel".*

5.4.3.2. Serum and cord blood testing
Serum and cord blood samples will be tested in a commercial ELISA (EDI$^{TM}$) that uses an immunocomplex of the novel CoVID19 recombinant antigen-human anti-CoVID19 IgG/IgM HRP-labelled anti-human IgG/IgM tracer antibody, already in use at PHE Porton.

## 8 ETHICAL AND REGULATORY CONSIDERATIONS

### 8.1 Assessment and management of risk

Where possible, we will ask site level study staff to collect samples at the same time that routine samples are being collected and will work with the obstetric and neonatal teams to ensure that samples are collected by experienced members of staff to minimise the risk of harm and discomfort to participants. Participants may have the burden of extra visits for sample collection and follow-up if self-isolating. There is the risk of causing worry to participants who are asymptomatic but are antibody positive on testing. There is the risk of exposing study staff to SARS-CoV-2, but standard infection control practices from participating trusts will be followed to minimise this risk.

### 8.2 Research Ethics Committee (REC) and other Regulatory review & reports

Before the start of the study, a favourable opinion will be sought from an appropriate REC for the study protocol, informed consent forms and other relevant documents e.g. advertisements.

**For HRA- NHS REC reviewed research**

- Substantial amendments that require review by NHS REC will not be implemented until that review is in place and other mechanisms are in place to implement at site.
- It is the Chief Investigator's responsibility to produce the annual reports and submit the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.
- The Chief Investigator will notify the REC of the end of the study within one year after the end of the study.

- If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

**Regulatory Review & Compliance**

Before any site can enrol patients into the study, the Chief Investigator/Principal Investigator or designee will ensure that appropriate approvals from participating organisations are in place. Specific arrangements on how to gain approval from participating organisations are in place and comply with the relevant guidance.

**Amendments**

For any amendment to the study, the Chief Investigator or designee, in agreement with the sponsor will submit information to the appropriate body in order for them to issue approval for the amendment. The Chief Investigator or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

### 8.3 Peer review

The protocol has been reviewed and amended in collaboration with members of the Infection and Immunity Research Institute at St George's University. The statistics have been reviewed by Public Health England and the London School of Hygiene and Tropical Medicine.

### 8.4 Patient & Public Involvement

As part of our study, periCOVID is committed to ensuring that our research into SARS-CoV-2 in pregnant women and their babies is participant friendly and ethically sound by fostering patient and public involvement in order to help us;

- Define the most relevant research question to ask within the study;
- Identify the outcomes of importance to be measured within;
- Develop the study protocol appropriate to the needs and lifestyles of the patient community it serves;
- Identify appropriate and ethically acceptable research tools and methods;
- Develop study participant materials, including but not limited to the patient information sheet and consent form, patient diaries and questionnaires;
- Conduct the study in a participant friendly and ethically acceptable way;
- Provide a public perspective on the interpretation of trial findings;

We have set up an online periCOVID patient and public group using social media that members of the public can access to learn about the most recent research into SARS-CoV-2 in pregnancy. We have used this platform to generate and disseminate online surveys and questionnaires in order to ascertain

what research questions the public would like answered, the results of which have been instrumental to the design of our study.

### 8.5 Protocol compliance

All protocol deviations will be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

### 8.6 Data protection and patient confidentiality

All data should be handled in accordance with the Data Protection Act 2018 (UK implementation of the EU General Data Protection Regulation (GDPR)).

Any Case Report Forms (CRFs), including the electronic study database, will not bear the participant's name or other directly identifiable data. The participant's trial Identification Number (ID) only, will be used for identification. The Subject ID log can be used to cross reference participant's identifiable information.

Once written informed consent has been obtained for study participation, the patient will be allocated a unique study identifier (consisting of a site number and sequential participant number), which will be utilised to code all depersonalised data. The patient's unique study number (ID) only, will be used for identification.

The Subject ID log can be used to cross reference participant's identifiable information, which will be a minimum of 2 patient identifiers (such as name and date of birth) in order to avoid errors in the allocation of a unique subject ID. The subject ID log will be stored on Trust computers at each participating site and will only be accessible to the researchers via unique username and password.

Only delegated members of the research team, who form part of the direct clinical care team will have access to patient identifiable data.

The informed consent forms will contain patient identifiable data (name), but these will be stored in a locked filing cabinet, in an office at each participating site which will only be accessible to the researchers.

As no personal identifiable data is being collected, there will be no personal identifiable data included in the results.

Data collected will comprise the de-identified clinical information from the clinical care team, and the results of analyses conducted on the study samples. They will be stored on a secure local computer (with appropriate back-up) that can only be accessed by the CI/PI and delegated members of the research team for patients recruited at their sites.

Data collection will be co-ordinated between the PHE laboratory and SGUL. Samples will be received at St George's and processed in the PHE laboratory at St George's. Results will be communicated via secure channels to St George's, where all the data will be held and all data analysis performed. A secure electronic database will be developed for this purpose and sites will be asked to complete questionnaires directly online. Anonymised demographic and clinical data may also be obtained from our collaborative partners working within the UKOSS and PANCOVID studies via our secure REDCap

database. This relates only to participants who are co-enrolled in these studies and who provide consent to their data being shared.

All data collected during this study will be anonymised and reported monthly to the WHO so that important results can be widely disseminated in real time. Anonymised data and/or samples may also be transferred to our other collaborators for use in research that is being conducted at their site(s) (see Appendix 4 for details of collaborating study sites). Participants will also be asked to provide consent for this in the informed consent form.

We will perform interim analysis weekly. We will produce an interim report for the PHE COVID response team. The final results will be reported to relevant authorities. A paper containing the overall results may be submitted for publication in a peer-reviewed journal.

### 8.7 Indemnity

**St George's University of London sponsored research:**
St George's University of London holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that St George's has been negligent. This includes negligence in the writing of the protocol, or selection of trial resources.

Where the Trial is conducted in a hospital, the hospital has a duty of care to participants. St George's University of London will not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. .

If a participant indicates that they wish to make a claim for compensation, this needs to be brought to the attention of St George's University of London immediately.

Failure to alert St George's University of London without delay and to comply with requests for information by the sponsor or any designated Agents may lead to a lack of insurance cover for the incident.

### 8.8 Access to the final study dataset

The final study dataset will contain only de-identified patient data, and should be accessible only to the Chief Investigator and delegated members of the research team.

## 9 DISSEMINIATION POLICY

### 9.1 Dissemination policy

Publication: "Any activity that discloses, outside of the circle of trial investigators, any final or interim data or results of the Trial, or any details of the Trial methodology that have not been made public by the Sponsor including, for example, presentations at symposia, national or regional professional meetings, publications in journals, theses or dissertations."

All scientific contributors to the Trial have a responsibility to ensure that results of scientific interest arising from Trial are appropriately published and disseminated. The Sponsor has a firm commitment to publish

the results of the Trial in a transparent and unbiased manner without consideration for commercial objectives.

To maximise the impact and scientific validity of the Trial, data shall be consolidated over the duration of the trial, reviewed internally among all investigators and not be submitted for publication prematurely. Lead in any publications arising from the Trial shall lie with the Sponsor in the first instance.

**Before the official completion of the Trial,**

All publications during this period are subject to permission by the Sponsor. If an investigator wishes to publish a sub-set of data without permission by the Sponsor during this period, the **Steering Committee/the Funder** shall have the final say.

Exempt from this requirement are student theses that can be submitted for confidential evaluation but are subject to embargo for a period not shorter than the anticipated remaining duration of the trial.

**Up to 180 days after the official completion of the Trial**

During this period the Chief Investigator shall liaise with all investigators and strive to consolidate data and results and submit a manuscript for peer-review with a view to publication in a reputable academic journal or similar outlet as the Main Publication.

- The Chief Investigator shall be senior and corresponding author of the Main Publication.
- Insofar as compatible with the policies of the publication outlet and good academic practice, the other Investigators shall be listed in alphabetic order.
- Providers of analytical or technical services shall be acknowledged, but will only be listed as co-authors if their services were provided in a non-routine manner as part of a scientific collaboration.
- Members of the Steering Group shall only be acknowledged as co-authors if they contributed in other capacities as well.
- If there are disagreements about the substance, content, style, conclusions, or author list of the Main Publication, the Chief Investigator shall ask the Steering Group to arbitrate.

**Beyond 180 days after the official completion of the Trial**

After the Main Publication or after 180 days from Trial end date any Investigator or group of investigators may prepare further publications. In order to ensure that the Sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the Sponsor for review at least sixty (60) days prior to submission for publication, public dissemination, or review by a publication committee. Sponsor's reasonable comments shall be reflected. All publications related to the Trial shall credit the Chief and Co-Investigators as co-authors where this would be in accordance with normal academic practice and shall acknowledge the Sponsor and the Funders.

### 9.2 Archiving Arrangements

Each site will be responsible for their onsite level study archiving. The trial essential TMF along with any central trial database will be archived in accordance with the sponsor SOP.

## 10 REFERENCES


1 Johns Hopkins University. COVID-19 Tracker map.

2 Allotey J, Stallings E, Bonet M, *et al.* Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: living systematic review and meta-analysis. *BMJ* Published Online First: 2020. doi:10.1136/bmj.m3320

3 Ripe Tomato.

4 Dean A. Blumberg, Mark A. Underwood, Herman L. Hedriana SL. Vertical Transmission of SARS-CoV-2: What is the Optimal Definition? *Am J Perinatol* 2020;**37**:769–72.

5 Assiri A, Abedi GR, Al Masri M, *et al.* Middle East Respiratory Syndrome Coronavirus Infection during Pregnancy: A Report of 5 Cases from Saudi Arabia. *Clin Infect Dis* Published Online First: 2016. doi:10.1093/cid/ciw412

6 Di Mascio D, Khalil A, Saccone G, *et al.* Outcome of coronavirus spectrum infections (SARS, MERS, COVID-19) during pregnancy: a systematic review and meta-analysis. *Am J Obstet Gynecol MFM* Published Online First: 2020. doi:10.1016/j.ajogmf.2020.100107

7 Pierce M, Kurinczuk JJ, Spark P, *et al.* Perinatal outcomes after maternal 2009/H1N1 infection: National cohort study. *BMJ* Published Online First: 2011. doi:10.1136/bmj.d3214

8 Jamieson DJ, Honein MA, Rasmussen SA, *et al.* H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet* Published Online First: 2009. doi:10.1016/S0140-6736(09)61304-0

9 COVID-19. DMDW (The WA of PM working group on. Maternal and Perinatal Outcomes of Pregnant Women with SARS-COV-2 infection. *Ultrasound Obs Gynecol* 2020.

10 Khalil A, Kalafat E, Benlioglu C, *et al.* SARS-CoV-2 infection in pregnancy: A systematic review and meta-analysis of clinical features and pregnancy outcomes. *EClinicalMedicine* Published Online First: 2020. doi:10.1016/j.eclinm.2020.100446

11 PREGCOV.

12 Gajbhiye R, Modi D, Mahale S. Pregnancy outcomes, Newborn complications and Maternal-Fetal Transmission of SARS-CoV-2 in women with COVID-19: A systematic review. *medRxiv* Published Online First: 2020. doi:10.1101/2020.04.11.20062356

13 Chen H, Guo J, Wang C, *et al.* Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet* Published Online First: 2020. doi:10.1016/S0140-6736(20)30360-3

14 Facchetti F, Bugatti M, Drera E, *et al.* SARS-CoV2 vertical transmission with adverse effects on the newborn revealed through integrated immunohistochemical, electron microscopy and molecular analyses of Placenta. *EBioMedicine* 2020;**59**:102951. doi:10.1016/j.ebiom.2020.102951

15 Sisman J, Jaleel MA, Moreno W, *et al.* Intrauterine Transmission of SARS-CoV-2 infection in a pretern infant. *Pediatr Infect Dis J* 2020;**Publish Ah**. doi:10.1097/INF.0000000000002815

16 Overview of the UK population - Office for National Statistics.

17 Khalil A, Hill R, Ladhani S, *et al.* SARS-CoV-2 in pregnancy: symptomatic pregnant women are only the tip of the iceberg. *Am J Obstet Gynecol* Published Online First: 2020. doi:10.1016/j.ajog.2020.05.005

18 Sutton D, Fuchs K, D'Alton M, *et al.* Universal screening for SARS-CoV-2 in women admitted for delivery. *N Engl J Med* 2020;**382**:2163–4. doi:10.1056/NEJMc2009316

19 Knight M, Bunch K, Vousden N, *et al.* Characteristics and outcomes of pregnant women admitted to hospital with confirmed SARS-CoV-2 infection in UK: national population based cohort study. *BMJ* Published Online First: 2020. doi:10.1136/bmj.m2107

20 Marchant A, Sadarangani M, Garand M, *et al.* Maternal immunisation: collaborating with mother nature. Lancet Infect. Dis. 2017. doi:10.1016/S1473-3099(17)30229-3

21 Blencowe H, Lawn J, Vandelaer J, *et al.* Tetanus toxoid immunization to reduce mortality from

neonatal tetanus. *Int J Epidemiol* Published Online First: 2010. doi:10.1093/ije/dyq027
22 Benowitz I, Esposito DB, Gracey KD, *et al.* Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants. *Clin Infect Dis* Published Online First: 2010. doi:10.1086/657309
23 Nunes MC, Cutland CL, Jones S, *et al.* Duration of infant protection against influenza illness conferred by maternal immunization secondary analysis of a randomized clinical trial. *JAMA Pediatr* Published Online First: 2016. doi:10.1001/jamapediatrics.2016.0921
24 COVID-19 vaccine tracker.
25 Heath PT, Le Doare K, Khalil A. Inclusion of pregnant women in COVID-19 vaccine development. Lancet Infect. Dis. 2020. doi:10.1016/S1473-3099(20)30638-1
26 NHS England. Guidance and Standard Operating ProcedureCOVID-19 Virus Testing in NHS Laboratories. 2020.
27 Ladhani SN, Jeffery-Smith AJ, Patel M, *et al.* High prevalence of SARS-CoV-2 antibodies in care homes affected by COVID-19 a prospective cohort study in England. *Medrxiv* Published Online First: 2020. doi:10.1101/2020.08.10.20171413

## 11. APPENDICIES

### 11.1 Appendix 1 – Amendment Log

| Amendment Log | | | | |
|---|---|---|---|---|
| **Amendment No.** | **Protocol version no.** | **Date issued** | **Author(s) of changes** | **Details of changes made** |
| 1 | V1.1 | 21.1.21 | Sarah Sturrock | -Updated flow chart consistent with protocol submitted to IRAS<br>-Details of AMR funding added<br>-Added infant seroepidemiology into primary objective in line with IRAS form<br>-Streamlined sample list<br>-Added information regarding samples requested from vaccinated women<br>- Added process for obtaining consent by post/telephone |