FULL/LONG TITLE OF THE STUDY	A Phase II, randomised, single-blind, platform trial to assess safety, reactogenicity and immunogenicity of COVID-19 vaccines in pregnant women in the United Kingdom
SHORT STUDY TITLE / ACRONYM	Preg-CoV (COVID-19 vaccines in pregnancy)
PROTOCOL VERSION NUMBER AND DATE	V5.0, 23-July-2021
Study Type / Phase:	Randomised clinical trial to compare interventions in clinical practice
IRAS Number:	301115
EudraCT Number:	2021-003073-60
Clinical Studies registry number (ISRCTN Number / Clinical trials.gov Number):	
JRES (sponsor) Reference Number	2021.0144
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 trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

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 clinical investigation without the prior written consent of the Sponsor

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

For and on behalf of the Trial Sponsor:

Signature: 

Date: 23/07/2021

Name (please print): Subhir Bedi

Position: Head of Research Governance and Delivery

Chief Investigator:

Signature: 

Date: 23/07/2021

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ii. LIST OF ABBREVIATIONS	
AE	Adverse Events
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File (This forms part of the TMF)
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
NHS R&D	National Health Service Research & Development

NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
PIC	Participant Identification Centre
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSI	Site Specific Information
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

TRIAL SUMMARY	
Trial Title	A Phase II, randomised, single-blind, platform trial to assess safety, reactogenicity and immunogenicity of COVID-19 vaccines in pregnant women in the United Kingdom
Clinical Phase	Phase II
Trial Design	Randomised clinical trial to compare interventions in clinical practice
Trial Participant Population	Main cohort: pregnant women aged 18 - 45 years who have not yet received a COVID-19 vaccine Sub-study: pregnant women aged 18 - 45 years who have received one dose of a COVID-19 vaccine prior to this pregnancy
Eligibility Criteria: (maternal)	Inclusion: 1. Healthy women, or women with stable underlying medical conditions, 18 - 45 years of age, between 13 0/7 and 34 0/7 weeks' gestation on the day of planned vaccination, with an uncomplicated, singleton pregnancy, and who are at no known increased risk of severe COVID-19 or obstetric complications 2. Able and willing (in the investigator's opinion) to comply with all study requirements 3. Willing to allow the investigators to discuss the volunteer's medical history with their General Practitioner and access all medical records when relevant to study procedures 4. Willing and able to give informed consent prior to study enrolment 5. No contraindication to the specific vaccine to be administered in the study, according to the Green Book.
	Exclusion: 1. Previous microbiological (based on a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19 2. Administration of immunoglobulins and/or any blood products within the 3 months preceding the planned administration of the study vaccine candidate (with the exception of anti-D immunoglobulin) 3. Previous vaccination with any COVID-19 vaccine (main cohort); prior receipt of one dose of a COVID-19 vaccine is permitted (sub-study) 4. Any confirmed or suspected immunosuppressive or immunodeficient state; chronic administration (defined as more than 14 continuous days) of immunosuppressant medication within the past 3 months, except topical steroids or short-term oral steroids (course lasting ≤ 14 days). 5. Any contraindication to the specific vaccine to be administered in the study, according to the Green

	Book or to the Summary of Product Characteristics for a specific vaccine 6. Current major illness of the mother or conditions of the fetus that, in the investigator's judgment, will substantially increase the risk associated with the participant's participation in, and completion of, the study or could preclude the evaluation of the participant's response, including but not limited to the following: • Uncontrolled gestational hypertension • Preeclampsia-eclampsia • Placental abnormality • Polyhydramnios or oligohydramnios • Significant bleeding or blood clotting disorder • Uncontrolled gestational diabetes • Any signs of premature labor with the current pregnancy or having ongoing intervention (medical/surgical) in the current pregnancy to prevent preterm birth • Prior stillbirth or neonatal death, preterm delivery (≤34 weeks), or previous infant with a known genetic disorder or major congenital anomaly.	
Eligibility Criteria: (infant)	1. Evidence of a signed and dated informed consent form signed by the parent(s) 2. Parent(s) willing and able to comply with scheduled visits and other study procedures	
Planned Sample Size/Target	200 participants for each COVID-19 vaccine included 100 participants for each sub-study	
Treatment duration	2 doses of vaccine, to be administered on Days 0 and at short or long intervals (main cohort); 1 dose of vaccine administered at Day 0 (sub-study)	
Follow up duration	Participants will be followed up until 12 months after delivery of their infant. Infants of participants will be followed up from birth through to 12 months of age.	
Planned Trial Period	June 2021 – June 2023	
Objectives		Outcome Measures
Primary (maternal)	• To determine whether the immune response, in COVID-19 seronegative participants, to immunisation with COVID-19 vaccines according to "long" dosing intervals is superior to that observed following immunisation according to "short" dosing intervals.	• SARS-COV-2 IgG-specific antibody concentrations measured on blood samples collected from vaccinated maternal subjects at delivery.

	• To evaluate the reactogenicity of COVID-19 vaccines, when given as 1- or 2-dose vaccination regimens, in pregnant participants.	• Occurrence of solicited local and general adverse events (AE) that occur during a 7-day follow-up period after each vaccination (i.e., the day of vaccination and 6 subsequent days) • Occurrence of unsolicited AEs that occur during a 30-day follow-up period after vaccination (i.e., the day of vaccination and 29 subsequent days)
Secondary (maternal)	• To describe pregnancy outcomes in women who receive COVID-19 vaccine(s) during pregnancy.	• Pregnancy outcomes from Visit 1 up to 6 weeks after delivery. These include live birth with congenital anomalies, miscarriage, fetal death/stillbirth (antepartum or intrapartum), mode of delivery, elective/therapeutic termination.
	• To evaluate safety in terms of SAEs and medically attended adverse events (MAAEs) in women who receive COVID-19 vaccine(s) during pregnancy.	• Occurrence of serious adverse events (SAEs), AEs leading to study withdrawal, and MAAEs from Visit 1 (Day 0) up to 6 weeks after delivery
	• To evaluate safety in terms of AESI (including potential immune-mediated medical conditions (PIMMCs)) relevant to COVID-19, including possible vaccine-enhanced disease, in all women at any time after the first dose of a COVID-19 vaccine	• AESI from Visit 1 up to 6 weeks after delivery. These include but are not limited to maternal death, hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia, pre-eclampsia with severe features including eclampsia), antenatal bleeding (morbidly adherent placenta, placental abruption, caesarean scar pregnancy, uterine rupture), postpartum haemorrhage, fetal growth restriction, gestational diabetes mellitus, non-reassuring fetal status, pathways to preterm birth (premature preterm rupture of membranes, preterm labour, iatrogenic preterm birth), chorioamnionitis, oligohydramnios,

		polyhydramnios, gestational liver disease (intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy), maternal sepsis.
	• To evaluate the immunogenicity of COVID-19 vaccines, when given as 1- or 2-dose vaccination regimens, in serologically negative (to SARS-CoV-2) pregnant participants.	• SARS-COV-2 IgG-specific antibody concentrations, (and neutralizing antibody titres and cellular immune responses in subsets) measured on blood samples collected from vaccinated maternal subjects at Day 0 (before vaccination), Day 28-42, Day 56-84, Day 84-112, Day 112-140, at delivery, between 4 weeks and 12 weeks, and at 12 months after delivery
	• To evaluate the immunogenicity of COVID-19 vaccines, when given as 1- or 2-dose vaccination regimens, in pregnant participants (regardless of serostatus as baseline)	• SARS-COV-2 IgG-specific antibody concentrations, (and neutralizing antibody titres and cellular immune responses in subsets) measured on blood samples collected from vaccinated maternal subjects at Day 0 (before vaccination), Day 28-42, Day 56-84, Day 84-112, Day 112-140, at delivery, between 4 weeks and 12 weeks, and at 12 months after delivery
Secondary (infant)	• To evaluate the safety of infants born to women vaccinated with COVID-19 vaccine(s) up to 12 months after birth.	• From birth through 6 weeks after birth, occurrences of SAEs, AEs leading to study withdrawal, and MAAEs • Occurrence of neonatal AEs of special interest (up to 6 weeks after birth). These include but are not limited to small for gestational age, low birth weight including very low birth weight, neonatal encephalopathy, congenital microcephaly (postnatally or prenatally diagnosed), congenital anomalies (major external structural defects,

		internal structural defects, functional defects), neonatal death (in a preterm live birth or in a term live birth), neonatal infections (blood stream infections, meningitis, respiratory infection), respiratory distress in the neonate, preterm birth, failure to thrive, large for gestational age, macrosomia • Developmental status at 12 months of age
	• To evaluate the transfer of SARS-CoV-2 specific antibodies from mothers vaccinated with COVID-19 vaccine(s), according to different regimens, to their infants at the time of delivery	• SARS-COV-2 IgG-specific antibody concentration, (and neutralizing antibody titres in a subset) against SARS-COV-2 measured on the cord blood sample collected at delivery, or on a blood sample collected from the infant within 3 days after birth (if no cord blood sample can be obtained) • The ratio between cord blood and maternal SARS-COV-2 IgG-specific antibody concentrations or an infant blood sample collected within 72 hours after birth (if no cord blood sample can be obtained)
	• To evaluate the kinetics of SARS-CoV-2 specific maternal antibodies in infants born to mothers vaccinated with COVID-19 vaccine(s), up to 3 months after birth	• SARS-COV-2 IgG-specific antibody concentrations and Neutralizing antibody titres against SARS-COV-2 in infants born to vaccinated mothers at Day 28 to 42 or Day 70 to 84 post- delivery
	• To assess the effect of gestational age at vaccination, interval between vaccination and delivery, maternal age, health status, vaccine type and schedule on immune responses and duration of immune responses in vaccinated women and on placental	• SARS-COV-2 IgG-specific antibody concentration, (and neutralizing antibody titres in a subset) against SARS-COV-2 measured on the cord blood sample collected at delivery, or on a blood sample collected from the infant within 3 days after birth (if no cord blood sample can be obtained)

	transfer and antibody kinetics in their infants	• The ratio between cord blood and maternal SARS-COV-2 IgG-specific antibody concentrations or an infant blood sample collected within 72 hours after birth (if no cord blood sample can be obtained) • SARS-COV-2 IgG-specific antibody concentrations and Neutralizing antibody titres against SARS-COV-2 in infants born to vaccinated mothers at Day 28 to 42 or Day 70 to 84 post- delivery
Exploratory (maternal)	• To describe SARS-COV-2 antibodies in breast milk of mothers who receive COVID-19 vaccine in pregnancy	• Levels of maternal IgA and/or IgG (and subtypes) against SARS-CoV-2 in colostrum and breast milk within 3 days and 14 days where possible
	• To describe the effectiveness of COVID-19 vaccines in pregnancy against maternal COVID-19 in pregnancy or post-partum	• Occurrence of COVID-19 up to 12 months post-delivery (mother)
	• To evaluate the immunogenicity of a COVID-19 vaccine when given as a booster dose, in pregnant participants who have received one dose of a COVID-19 vaccine before pregnancy	• SARS-COV-2 IgG-specific antibody concentrations, (and neutralizing antibody titres and cellular immune responses in subsets) measured on blood samples collected from vaccinated maternal subjects at Day 0 (before booster vaccination), Day 28-42, Day 56-84, Day 84-112, Day 112-140, at delivery, between 4 weeks and 12 weeks, and at 12 months after delivery
	• To compare the immunogenicity of a COVID-19 vaccine, when given as a booster dose to pregnant participants of 28-34 weeks' gestation who have received a prime dose of a COVID-19 vaccine before pregnancy, with the immunogenicity of a COVID-19 vaccine when	• SARS-COV-2 IgG-specific antibody concentrations, (and neutralizing antibody titres and cellular immune responses in subsets) measured on blood samples collected from vaccinated maternal subjects at Day 0 (before vaccination), Day 28-42, Day 56-84, Day 84-112,

	given as a prime dose to pregnant participants of 28-34 weeks' gestation who have not received a dose of a COVID-19 vaccine previously	Day 112-140, at delivery, between 4 weeks and 12 weeks, and at 12 months after delivery
	• To assess the impact of prime- boost interval on immunogenicity when a booster dose is given to pregnant participants of 28-34 weeks' gestation who have received a prime dose of COVID-19 vaccine before pregnancy	• SARS-COV-2 IgG-specific antibody concentrations, (and neutralizing antibody titres and cellular immune responses in subsets) measured on blood samples collected from vaccinated maternal subjects at Day 0 (before vaccination), Day 28-42, Day 56-84, Day 84-112, Day 112-140, at delivery, between 4 weeks and 12 weeks, and at 12 months after delivery
Exploratory (infant)	• To describe the effectiveness of maternal antibodies against SARS-CoV-2 to protect against COVID-19 / symptomatic disease / severity in infants in the first 12 months of life	• Occurrence of COVID-19 up to 12 months post-delivery (infant)
	• To describe the effectiveness of breast milk antibodies against SARS-CoV-2 to protect against COVID-19 / symptomatic disease / severity in infants in the first 12 months of life	• Occurrence of COVID-19 up to 12 months post-delivery (infant)
Investigational Medicinal Product(s) Or Device Name	1. Pfizer / BioNTech COVID-19 mRNA Vaccine BNT162b2 2. Moderna COVID-19 mRNA-1273 vaccine 3. *Novavax NVX-CoV2373 COVID-19 vaccine** 4. AstraZeneca COVID-19 vaccine (ChAdOx1 nCOV-19) (pre-pregnancy sub-study) 5. *Other approved vaccines as per MHRA / JCVI guidance** **pending approval*	
Formulation, Dose, Route of Administration	Pfizer / BioNTech COVID-19 mRNA Vaccine BNT162b2 0.3ml, IM injection	
	Moderna COVID-19 mRNA-1273 vaccine 0.5ml, IM injection	

	<u>AstraZeneca COVID-19 vaccine (ChAdOx1 nCOV-19)</u> 0.5ml, IM injection
	*Novavax NVX-CoV2373 COVID-19 vaccine** *0.5ml, IM injection* **pending approval*

iv. FUNDING

This study is funded by the UK Vaccine Task Force.

v. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES / GROUPS & INDIVIDUALS

- Trial Steering Committee

A Trial Steering Committee will be formed to oversee the study and advise the Study Management Committee on key issues of study conduct, including, but not limited to, study pauses due to safety concerns on the advice of the DSMB.

- Data Monitoring (and ethics) Committee

A Data Safety Monitoring Board (DSMB) will be convened. The DSMB will evaluate frequency of events, safety and efficacy data as specified in the DSMB charter. The DSMB will make recommendations concerning the conduct, continuation or modification of the study for safety reasons to the Trial Steering Committee.

The DSMB will review SAEs or AESIs deemed possibly, probably or definitively related to study interventions. The DSMB will be notified within 24 hours of the Investigators' being aware of their occurrence. The DSMB can recommend placing the study on hold if deemed necessary following a study intervention-related SAE.

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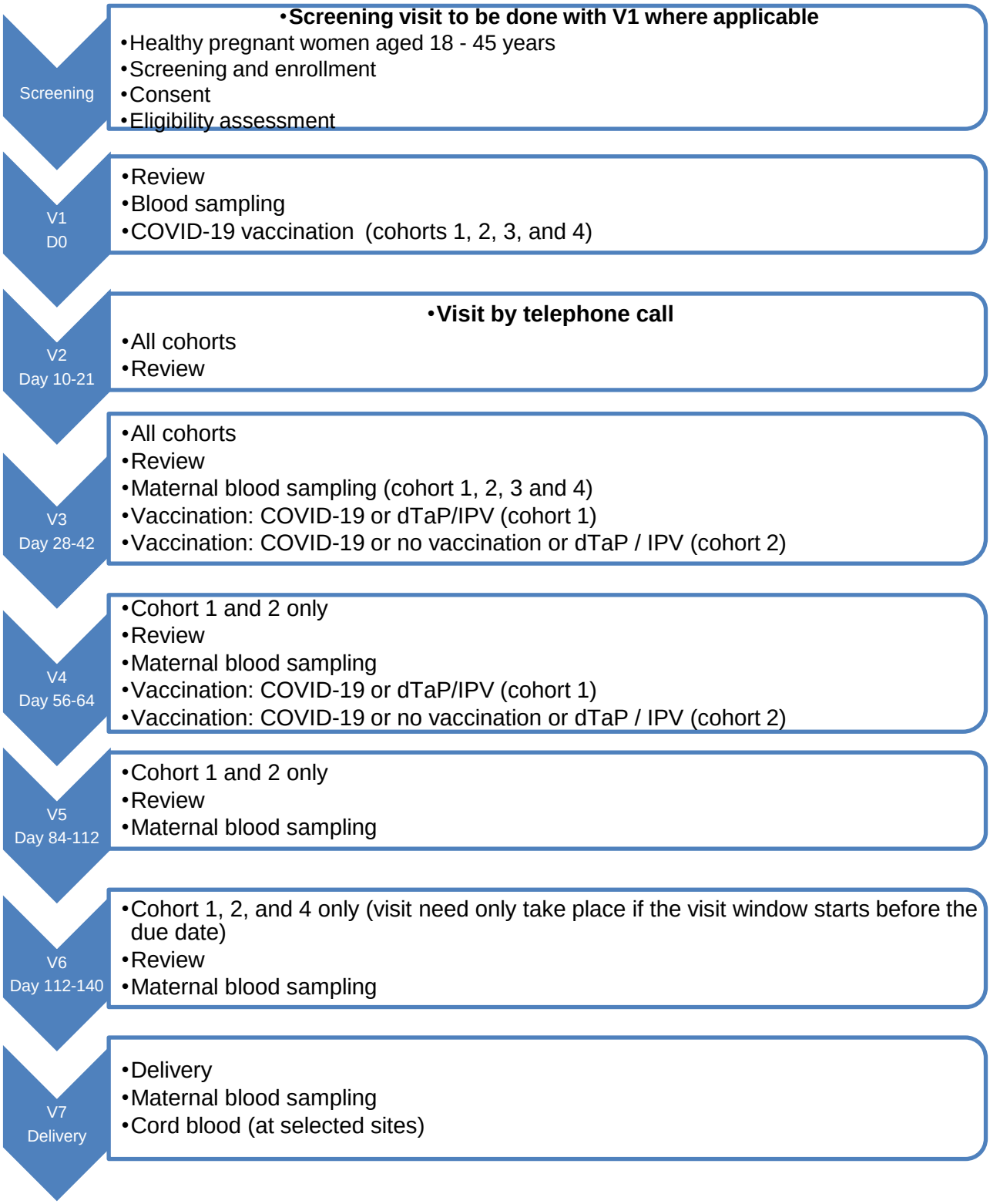
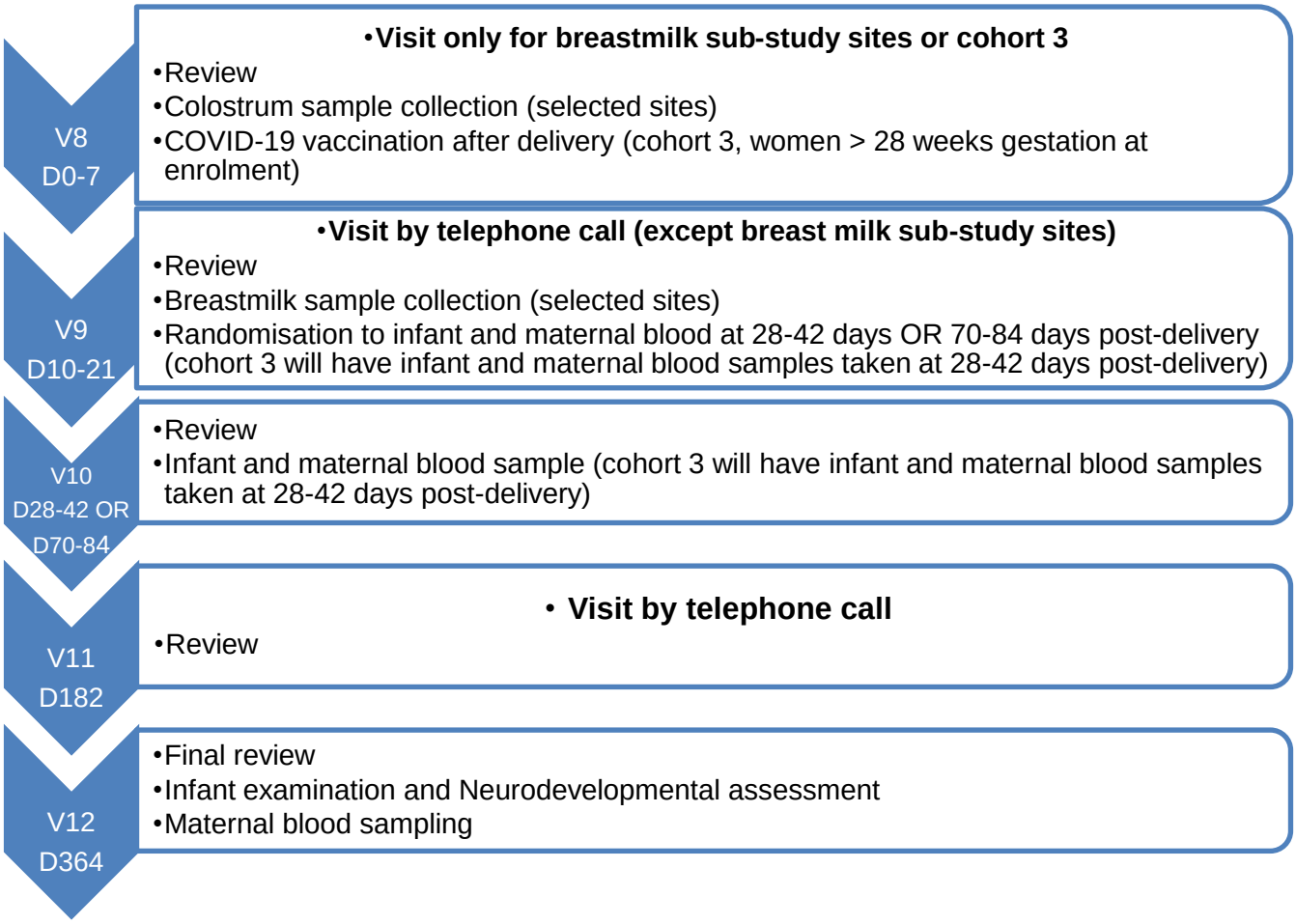
vi. Protocol contributors

Paul Heath and Eva Galiza wrote the protocol with input from study teams at participating sites, Kirsty Le Doare, Asma Khalil, Chrissie Jones, Nigel Simpson, Lucy Chappell, Asma Khalil, Hana Tabusa, Tatiana Munera Huertas. The study design and aspects of the protocol have been discussed with the maternal and paediatric infections patient and public involvement (PPI) group based at St George's, University of London.

vii. TRIAL FLOW CHART (Prenatal)



vii. TRIAL FLOW CHART (Postnatal)



1 BACKGROUND

The risk to pregnant women and neonates following COVID-19 infection is generally low and more than half of pregnant women who test positive for SARS-CoV-2 are asymptomatic (Allotey et al, 2021). Whether SARS-CoV-2 can be transmitted vertically is unclear. A national cohort study using the UK Obstetric Surveillance System showed that only about 2% of neonates born to COVID-positive mothers in the UK tested positive for SARS-CoV-2 in the first 12 hours of life (Vousden et al, 2021). However, there is a two to threefold increased risk of preterm birth for women with symptomatic COVID-19 (Vousden et al, 2021), possibly resulting from a medical recommendation to deliver early to improve maternal oxygenation (NICE guideline 25, 2019 https://www.nice.org.uk/guidance/ng25). In addition, analysis of a large registry indicated that pregnant women are more likely to be admitted to the intensive care unit with COVID-19 than age-matched non-pregnant women (Mullins et al, 2021). This has been recognised in the UK as well (https://www.icnarc.org/Our-Audit/Audits/Cmp/Reports).

Risk factors for severe COVID-19 infection in pregnant women include being overweight or obese, of black and asian minority ethnic background, with co-morbidities such as diabetes, hypertension and asthma, or being 35 years old or older (Vousden et al, 2021, Allotey et al, 2021).

UK recommendations for COVID-19 vaccines in pregnancy:

The current advice (April 16, 2021) from the Joint Committee on Vaccination and Immunisation (JCVI) is that COVID-19 vaccines should be offered to pregnant women at the same time as the rest of the population, based on their age and clinical risk group. Women should discuss the benefits and risks of having the vaccine with their healthcare professional and reach a joint decision based on individual circumstances.

Currently, as of May 2021, COVID-19 vaccination in the UK is therefore offered to the following groups of pregnant women:

- those with high-risk medical conditions who have a greater risk of severe illness from COVID-19
- health or social care workers - who are at very high risk of catching COVID-19
- individuals considered at high risk of COVID-19 because of health and personal factors that include age ethnicity, BMI and underlying health conditions (this includes pregnant women in priority group 6- considered at risk and adults who live with those who are immunosuppressed)
- women diagnosed with gestational diabetes in pregnancy or pregnant women with a BMI of more than over 40
- individuals aged 45 or over.

It is anticipated that the age threshold will reduce in line with that for the national roll-out of COVID-19 vaccines.

With regard to breastfeeding women, the JCVI advice is that there is no known risk in giving available COVID-19 vaccines and so they should be offered vaccination at the time when they otherwise become eligible (JCVI, Dec 2020).

Available vaccines

At this time three COVID-19 vaccines have been implemented in the UK, BioNTech / Pfizer (BNT162b2; mRNA), Oxford-AstraZeneca (AZD1222; Adenovirus-vector) and Moderna vaccine (mRNA). It is anticipated that the Novavax vaccine (subunit protein-adjuvant) will be approved shortly.

For all vaccines (preliminary) animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryofetal development, parturition, or post-natal development.

The Phase 3 trials of these vaccines excluded pregnant women. Reports suggest that a relatively small number of women in these trials were pregnant at the time of vaccination; safety data from these pregnancies are still pending but, as yet no significant adverse effects have been reported. Following implementation of these vaccines in different populations many thousands of pregnant women have now received COVID-19 vaccines and to date there have been no concerning 'red flags' (Shimbukuro 2021).

Ongoing pregnancy studies

Company-sponsored pregnancy studies with Janssen (April 2021, n=52, no placebo) and BioNTech/Pfizer (June 2021, n= 235, saline placebo) COVID-19 vaccines are due to start in the UK shortly. The latter study is a double-blind placebo-controlled trial (with cross-over after delivery) in pregnant women 24-34 weeks' gestation, with the vaccine administered at an interval of 3 weeks. A study with the AZ vaccine is proposed (no further details available) but there are no current plans for pregnancy studies with the Moderna and Novavax vaccines.

Potential vaccine schedules in pregnancy

Different schedules have been used in the Phase 3 trials (AZ: 4-12 weeks; Pfizer: 3 weeks; Moderna: 4 weeks; Novavax: 3 weeks). However, for operational reasons the current Green Book guidance is that the second dose of all vaccines should be routinely scheduled between four and 12 weeks after the first dose.

This trial aims to assess the safety, reactogenicity and immunogenicity of available COVID-19 vaccines in pregnant women in the United Kingdom and to provide data to inform national guidance for COVID-19 vaccination in pregnancy.

2 RATIONALE

Pregnant women should be provided with a balanced and clear assessment of their risk of COVID-19 in pregnancy, taking into account their individual circumstances, local practices and available evidence. They should also be counselled with a balanced summary of the potential direct and indirect benefits of COVID-19 vaccines, and the current lack of safety data should be acknowledged. COVID-19 vaccination should not be withheld from women who have received adequate counselling and understand the uncertainties, potential harms, and potential benefits of these vaccines. However, there are important unanswered questions regarding the reactogenicity, safety, immunogenicity, and persistence of immunity in the mother and infant, as well as the efficiency of placental transfer of antibodies and the optimal schedule for pregnant women, it is important that such data are gathered in a systematic and controlled manner. İn doing so, evidence based guidelines can be developed which will then benefit all pregnant women.

There is a widespread call to gather such evidence for use of COVID-19 vaccines in pregnant women; however, it is possible that the window of opportunity for doing this is closing as more women receive vaccine routinely. A number of advantages therefore exist in recruiting pregnant women into a pragmatic clinical trial in which they all receive a COVID-19 vaccine (rather than a placebo).

Using a platform design Preg-CoV will allow inclusion of new COVID-19 vaccines as they become licensed, as well as rapidly address new questions of relevance to the vaccine programme as they arise (different intervals, one dose schedules etc).

Vaccine schedules in pregnancy.

Despite the use of shorter intervals in the phase 3 trials (e.g. 3 weeks for Pfizer), the UK introduction has permitted a schedule of up to 12 weeks between doses in order to allow more people to benefit from the protection provided from the first dose during this roll out phase. However, pregnant women have a unique requirement to achieve maximal protection by the 3rd trimester of pregnancy, as this is when more severe disease is seen (Knight et al. 2020). There are no data in pregnant women as to whether this is best achieved by 2 doses administered at a short interval (which is the interval used in all the phase 3 trials of the COVID-19 vaccines to be used in Preg-CoV) or 2 doses administered at a long interval (8-12 weeks), or indeed whether these are equivalent. However, (non-trial) data from non-pregnant populations suggest that longer intervals between doses may result in improved antibody responses (Parry et al. 2021; Voysey et al. 2021). Of note, however, this may be at the expense of optimal cellular immune responses (Parry et al. 2021). The balance between these two aspects of immunity is particularly relevant when considering pregnant women because the cellular immune mechanisms required to promote maternal–fetal tolerance (e.g. Th1–Th2 shift) might also impact on responses to vaccines. This issue therefore needs to be addressed specifically for pregnant women. It

will be of particular relevance for those vaccinated in the second trimester of pregnancy (13-27+6 weeks). For those vaccinated in the third trimester (28 weeks-) it may be that one dose will be sufficient, with the second dose administered after delivery (and still within 12 weeks). This option will therefore be assessed and will be of value when considering implementation strategies. Additionally, a rapidly emerging question is the optimal vaccination schedule for women who have received one dose of a COVID-19 vaccine prior to pregnancy. This can also be addressed in Preg-CoV.

Gestational age at vaccination.

Although there is no minimum gestational age for receipt of a COVID-19 vaccine in pregnancy, it is recognised that COVID-19 has more serious complications in later pregnancy (Knight et al. 2020) and so maximal protection should be provided by the third trimester. Additionally, women may prefer to avoid vaccination in the first trimester (when fetal development is greatest). The ideal window for vaccination may therefore be between 13 and 27+6 weeks gestation, although it is recognised that in a vaccine programme some women may present later than this and still require protection against COVID-19. A maximal gestational age of 36 weeks for a second dose of vaccine is therefore proposed. A trial primary endpoint of delivery anti-S antibody concentrations has been chosen as a "fixed point" to correspond with the primary objective of maximal protection in the 3rd trimester of pregnancy.

Pertussis-containing vaccine in pregnancy.

A single dose of a pertussis containing vaccine (dTaP/IPV) is routinely recommended in each pregnancy. This can be offered from 16 weeks' gestation, although in practice is often given after the routine anomaly scan at 20 weeks' gestation. It is ideally administered by 32 weeks' gestation. Women may find it helpful to receive this vaccine as part of this trial, so it is therefore incorporated into the schedules.

Study design.

In order to incorporate the considerations around intervals between doses, gestational age at vaccination and achieving maximal protection against COVID-19 in the third trimester, as well as offering the opportunity to receive the pertussis-containing vaccine, the trial will need to include several schedules (cohorts, see below). The inclusion of the pertussis-containing vaccine will additionally allow convenient "blinding" of the schedule of COVID-19 vaccines received.

Cohorts 1 and 2 will be main study cohorts on which the sample size calculation is based on.

Cohorts 3 and 4 will be the sub-study cohorts.

Table 1. Cohort 1.

Recruitment window (wk)	**Total n=200 for each vaccine for cohort 1 + cohort 2**	**Day 0**	**Short 4-6 wk**	**Long 8-12 wk***
13 0/7 – 23 6/7		Vaccine A	dTaP/IPV	Vaccine A
		Vaccine A	Vaccine A	dTaP/IPV
		Vaccine B	dTaP/IPV	Vaccine B
		Vaccine B	Vaccine B	dTaP/IPV
		Vaccine C	dTaP/IPV	Vaccine C
		Vaccine C	Vaccine C	dTaP/IPV

* "Long" dose must be given by 32 weeks' gestation i.e. if recruited between 21 to 23+6 weeks gestational age, long dose should be given 8 weeks later.

Table 2. Cohort 2.

Recruitment window (wk)	**Total n=200 for each vaccine for cohort 1 + cohort 2**	**Day 0**	**Short 4-6 wk**	**Long 8 wk-12wks***
24 0/7 – 27 6/7		Vaccine A	- **	Vaccine A
		Vaccine A	Vaccine A	- **
		Vaccine B	- **	Vaccine B
		Vaccine B	Vaccine B	- **
		Vaccine C	- **	Vaccine C
		Vaccine C	Vaccine C	- **

* "Long" dose must be given by 36 weeks' gestation

** dTaP/IPV should be given by 32 weeks' gestation with an interval of at least 1 week before / after receipt of COVID-19 vaccine

Table 3. Cohort 3.

Recruitment window (wk)	Total n=100	Day 0	Post delivery (4-12 weeks but given after delivery)*
28 0/7 – 34 0/7		Vaccine A	Vaccine A
		Vaccine B	Vaccine B
		Vaccine C	Vaccine C

* Booster dose should be given as soon as possible after delivery

** if require dTaP/IPV, it should be given by 32 weeks' gestation and with an interval of at least 1 week before / after receipt of COVID-19 vaccine

Table 4. Cohort 4.

Recruitment window (wk)	Total n= 100	Boost dose <26 weeks	Boost dose ≥26 weeks
13 0/7 – 34 0/7		Vaccine A/B/C/D*	Vaccine A/B/C/D*

*Same vaccine as given pre-pregnancy / first trimester (0 0/7 – 12 6/7 gestational weeks)

** if require dTaP/IPV, it should be given by 32 weeks' gestation and with an interval of at least 1 week before / after receipt of COVID-19 vaccine

2.1 Assessment and management of risk

This study involves vaccinating pregnant women with COVID-19 vaccines within a time period in the UK. There is a small risk of adverse reaction to any vaccine, but this risk is low and is no higher in this study than in routine practice. All staff administering vaccines in this study will be appropriately trained in vaccine administration and in managing any side effects from this and all vaccines will be given in an environment where emergency equipment is available.

This trial is categorised as:

- Type A = No higher than the risk of standard medical care

In the context of the current global pandemic of COVID-19 it is important that measures are taken to protect participants and staff from infection. All participating institutions should have an SOP or risk assessment for the conduct of study visits during this period and this must be available before visits recommence. If at any point a participant or a household contact of a participant is found to be experiencing any symptoms of COVID-19, the visit should not take place and they should be advised to follow the national public health guidance.

Benefit-risk assessment for trial participants in the Oxford/AstraZeneca cohort of Preg-CoV

This issue applies only to those pregnant women who have had one dose of the Oxford / Astra Zeneca (AZ) COVID-19 vaccine previously, with no serious side effects. For these individuals only, the benefits and risks of a second dose of the AZ COVID-19 vaccine will be discussed.
It is recognised that there is an increased risk of thromboembolic events with low platelets after a first (or unknown) doses of the AZ COVID-19 vaccine, with an overall incidence of 13.6 per million doses. No specific risk factors for this adverse event have been identified to this time. The incidence following a 2nd dose is reported to be 1.3 per million doses, with all cases reported being over the age of 50 years (MHRA Yellow Card reporting as of 26 May 2021).

Although pregnancy itself is associated with an increased risk of thrombosis, there is no evidence to suggest that pregnancy itself is a specific risk factor for the thromboembolic events described above. It should be acknowledged however, that there are very little data on the use of the AZ COVID-19 vaccine in pregnancy.

Conversely, there is an increased risk of severe illness from COVID-19 in pregnant women compared to non-pregnant women, particularly in the third trimester and that COVID-19 vaccines, especially 2 doses, are likely to significantly reduce this risk. Risk factors for COVID-19 in pregnancy include Black, Asian and minority ethnic background, increased BMI, pre-pregnancy co-morbidity (such as pre-existing diabetes and chronic hypertension), maternal age 35 years or older, living in areas or households of increased socioeconomic deprivation. Therefore, discussions on the benefit-risk of COVID-19 vaccines in pregnant women in general, as well of a 2nd dose of AZ vaccine, would be additionally informed by the presence or absence of these risk factors.

The following guidance from the RCOG additionally refers to statements from the JCVI and MHRA and serves as a useful text for discussions with relevant pregnant women.

RCOG (Royal College of Obstetricians and Gynaecologists) guidance (May 2021)
'If you have received a first dose of AstraZeneca vaccine, and subsequently become pregnant, you should be given the opportunity to discuss with your obstetrician, midwife or GP, your decision on whether to have your second dose. On 7 April 2021, the JCVI stated: 'To date, there are no reports of the extremely rare thrombosis/thrombocytopenia events following receipt of the second dose of the AstraZeneca COVID-19 vaccine. All those who have received a first dose of the AstraZeneca COVID-19 vaccine should continue to be offered a second dose of AstraZeneca COVID-19 vaccine, irrespective of age. The second dose will be important for longer lasting protection against COVID-19.'

Since then, there have been very rare reports of serious blood clots after a second dose of the AstraZeneca vaccine. As of 19 May 2021, 34.9 million doses of the AstraZeneca vaccine have been given in the UK. There have been 17 cases of serious blood clots following the second dose of the vaccine, compared to 315 cases after a first dose of the vaccine. The official national publication on vaccines (the Green book) advised on 7 May 2021 that: "Pfizer and Moderna vaccines are the preferred vaccines for eligible pregnant women of any age, because of more extensive experience of their use in pregnancy. Pregnant women who commenced vaccination with AstraZeneca, however, are advised to complete with the same vaccine".

Additionally, monitoring and reporting of safety events in Preg-CoV is clearly defined in Preg-CoV participant documents. Women receiving a 2nd dose of AZ will be specifically informed of the symptoms of possible thrombotic events and the need to seek urgent medical attention if any of them occur (see "What to look out for after vaccination" https://www.gov.uk/government/publications/covid-19-vaccination-and-blood-clotting/covid-19-vaccination-and-blood-clotting).

3 OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

3.1 Primary objective

Maternal

- To determine whether the immune response, in COVID-19 seronegative participants, to immunisation with COVID-19 vaccines according to "long" dosing intervals is superior to that observed following immunisation according to "short" dosing intervals.
- To evaluate the reactogenicity of COVID-19 vaccines, when given as 1- or 2-dose vaccination regimens, in pregnant participants.

3.2 Secondary objectives

Maternal

- To describe pregnancy outcomes in women who receive COVID-19 vaccine(s) during pregnancy.
- To evaluate safety in terms of SAEs and medically attended adverse events (MAAEs) in women who receive COVID-19 vaccines during pregnancy.
- To evaluate safety in terms of AESI (including potential immune-mediated medical conditions (PIMMCs)) relevant to COVID-19, including possible vaccine-enhanced disease, in all women at any time after the first dose of a COVID-19 vaccine.
- To evaluate the immunogenicity of COVID-19 vaccines, when given as 1- or 2-dose vaccination regimens, in serologically negative (to SARS-CoV-2) pregnant participants.
- To evaluate the immunogenicity of COVID-19 vaccines, when given as 1- or 2-dose vaccination regimens, in pregnant participants (regardless of serostatus as baseline).

Infant

- To evaluate the safety of infants born to women vaccinated with COVID-19 vaccine(s) up to 12 months after birth.
- To evaluate the transfer of SARS-CoV-2 specific antibodies from mothers vaccinated with COVID-19 vaccine(s), according to different regimens, to their infants at the time of delivery
- To evaluate the kinetics of SARS-CoV-2 specific maternal antibodies in infants born to mothers vaccinated with COVID-19 vaccine(s), up to 3 months after birth
- To assess the effect of gestational age at vaccination, interval between vaccination and delivery, maternal age, health status, vaccine type and schedule on immune responses and duration of immune responses in vaccinated women and on placental transfer and antibody kinetics in their infants

3.2.1 Exploratory objectives

Maternal

- To describe SARS-COV-2 antibodies in breast milk of mothers who receive COVID-19 vaccine in pregnancy
- To describe the effectiveness of COVID-19 vaccines in pregnancy against maternal COVID-19 in pregnancy or post-partum
- To evaluate the immunogenicity of a COVID-19 vaccine when given as a booster dose, in pregnant participants who have received one dose of a COVID-19 vaccine before pregnancy

- To compare the immunogenicity of a COVID-19 vaccine, when given as a booster dose to pregnant participants of 28-34 weeks' gestation who have received a prime dose of a COVID-19 vaccine before pregnancy, with the immunogenicity of a COVID-19 vaccine when given as a prime dose to pregnant participants of 28-34 weeks' gestation who have not received a dose of a COVID-19 vaccine previously
- To assess the impact of prime- boost interval on immunogenicity when a booster dose is given to pregnant participants of 28-34 weeks' gestation who have received a prime dose of COVID-19 vaccine before pregnancy

Infant

- To describe the effectiveness of maternal antibodies against SARS-CoV-2 to protect against COVID-19 / symptomatic disease / severity in infants in the first 12 months of life
- To describe the effectiveness of breast milk antibodies against SARS-CoV-2 to protect against COVID-19 / symptomatic disease / severity in infants in the first 12 months of life

3.3 Outcome measures/endpoints

Described in section 3.4, 3.5, 3.6.

3.4 Primary endpoint/outcome

- SARS-COV-2 IgG-specific antibody concentrations measured on blood samples collected from vaccinated maternal subjects at delivery.
- Occurrence of solicited local and general adverse events (AE) that occur during a 7-day follow-up period after each vaccination (i.e., the day of vaccination and 6 subsequent days)
- Occurrence of unsolicited AEs that occur during a 30-day follow-up period after vaccination (i.e., the day of vaccination and 29 subsequent days)

3.5 Secondary endpoints/outcomes

Maternal

- Pregnancy outcomes from Visit 1 up to 6 weeks after delivery. These include live birth with congenital anomalies, miscarriage, fetal death/still birth (antepartum or intrapartum), mode of delivery, elective/therapeutic termination.
- Occurrence of serious adverse events (SAEs), AEs leading to study withdrawal, and MAAEs from Visit 1 (Day 0) up to 6 weeks / 6 months after delivery

- AESI from Visit 1 up to 6 weeks after delivery. These include but are not limited to maternal death, hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia, pre-eclampsia with severe features including eclampsia), antenatal bleeding (morbidly adherent placenta, placental abruption, caesarean scar pregnancy, uterine rupture), postpartum haemorrhage, fetal growth restriction, gestational diabetes mellitus, non-reassuring fetal status, pathways to preterm birth (premature preterm rupture of membranes, preterm labour, iatrogenic preterm birth), chorioamnionitis, oligohydramnios, polyhydramnios, gestational liver disease (intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy), maternal sepsis.
- SARS-COV-2 IgG-specific antibody concentrations, (and neutralizing antibody titres and cellular immune responses in subsets) measured on blood samples collected from vaccinated maternal subjects at Day 0 (before vaccination), Day 28-42, Day 56-84, Day 84-112, Day 112-140, at delivery, between 4 weeks and 12 weeks, and at 12 months after delivery

Infant

- From birth through 6 weeks after birth, occurrences of SAEs, AEs leading to study withdrawal, and MAAEs
- Occurrence of neonatal AEs of special interest (up to 6 weeks after birth). These include but are not limited to small for gestational age, low birth weight including very low birth weight, neonatal encephalopathy, congenital microcephaly (postnatally or prenatally diagnosed), congenital anomalies (major external structural defects, internal structural defects, functional defects), neonatal death (in a preterm live birth or in a term live birth), neonatal infections (blood stream infections, meningitis, respiratory infection), respiratory distress in the neonate, preterm birth, failure to thrive, large for gestational age, macrosomia
- Developmental status at 12 months of age
- SARS-COV-2 IgG-specific antibody concentration, (and neutralizing antibody titres in a subset) against SARS-COV-2 measured on the cord blood sample collected at delivery, or on a blood sample collected from the infant within 3 days after birth (if no cord blood sample can be obtained)
- The ratio between cord blood and maternal SARS-COV-2 IgG-specific antibody concentrations or an infant blood sample collected within 72 hours after birth (if no cord blood sample can be obtained)
- SARS-COV-2 IgG-specific antibody concentrations and Neutralizing antibody titres against SARS-COV-2 in infants born to vaccinated mothers at Day 28 to 42 or Day 70 to 84 post-delivery.

3.6 Exploratory endpoints/outcomes

Maternal

- Levels of maternal IgA and/or other IgG (and subtypes) against SARS-CoV-2 in colostrum and breast milk within 3 days and 14 days where possible
- Occurrence of COVID-19 up to 12 months post-delivery

- SARS-COV-2 IgG-specific antibody concentrations, (and neutralizing antibody titres and cellular immune responses in subsets) measured on blood samples collected from vaccinated maternal subjects at Day 0 (before booster vaccination), Day 28-42, Day 56-84, Day 84-112, Day 112-140, at delivery, between 4 weeks and 12 weeks, and at 12 months after delivery

- SARS-COV-2 IgG-specific antibody concentrations, (and neutralizing antibody titres and cellular immune responses in subsets) measured on blood samples collected from vaccinated maternal subjects at Day 0 (before vaccination), Day 28-42, Day 56-84, Day 84-112, Day 112-140, at delivery, between 4 weeks and 12 weeks, and at 12 months after delivery

Infant

- Occurrence of COVID-19 up to 12 months post-delivery (infant)

3.7 Table of endpoints/outcomes

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure (if applicable)
Primary **(maternal)** • To determine whether the immune response, in COVID-19 seronegative participants, to immunisation with COVID-19 vaccines according to "long" dosing intervals is superior to that observed following immunisation according to "short" dosing intervals.	• SARS-COV-2 IgG-specific antibody concentrations measured on blood samples collected from vaccinated maternal subjects at delivery.	Maternal blood sampling at delivery
• To evaluate the reactogenicity of COVID-19 vaccines, when given as 1- or 2-dose vaccination regimens, in pregnant participants.	• Occurrence of solicited local and general adverse events (AE) that occur during a 7-day follow-up period after each vaccination (i.e., the day of vaccination and 6 subsequent days)	Diary data entry (solicited AE) from Day 0 to Day 6.
	• Occurrence of unsolicited AEs that occur during a 30-day follow-up period after vaccination (i.e., the day of vaccination and 29 subsequent days)	Diary data entry (unsolicited AE) from Day 0 to Day 29.
Secondary Objectives **Maternal** • To describe pregnancy outcomes in women who receive COVID-19 vaccine(s) during pregnancy.	• Pregnancy outcomes from Visit 1 up to 6 weeks after delivery. These include live birth with congenital anomalies, miscarriage, fetal death/still birth (antepartum or intrapartum), mode of delivery, elective/therapeutic termination.	Review at delivery and at 3 days, 14 days, and 42-48 days after delivery.
• To evaluate safety in terms of SAEs and medically attended adverse events (MAAEs) in women who receive COVID-19 vaccines during pregnancy.	• Occurrence of serious adverse events (SAEs), AEs leading to study withdrawal, and MAAEs from Visit 1 (Day 0) up to 6 weeks after delivery	Notification of SAE / AE / MAAE to site by participant from enrolment to 1 year after delivery / birth.

• To evaluate safety in terms of AESI (including potential immune-mediated medical conditions (PIMMCs)) relevant to COVID-19, including possible vaccine-enhanced disease, in all women at any time after the first dose of a COVID-19 vaccine.	• AESI from Visit 1 up to 6 weeks after delivery (Day 42 post-delivery). These include but are not limited to maternal death, hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia, pre-eclampsia with severe features including eclampsia), antenatal bleeding (morbidly adherent placenta, placental abruption, caesarean scar pregnancy, uterine rupture), postpartum haemorrhage, fetal growth restriction, gestational diabetes mellitus, non-reassuring fetal status, pathways to preterm birth (premature preterm rupture of membranes, preterm labour, provider-initiated preterm birth), chorioamnionitis, oligohydramnios, polyhydramnios, gestational liver disease (intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy), maternal sepsis.	Notification of AESI to site by participant from enrolment to 6 weeks after delivery for the mother and up to 6 weeks after birth for the infant.
• To evaluate the immunogenicity of COVID-19 vaccines, when given as 1- or 2-dose vaccination regimens, in serologically negative (to SARS-CoV-2) pregnant participants.	• SARS-COV-2 IgG-specific antibody concentrations, (and neutralizing antibody titres and cellular immune responses in subsets) measured on blood samples collected from vaccinated maternal subjects at Day 0 (before vaccination), Day 28-42, Day 56-84, Day 84-112, Day 112-140, at delivery, between 4 weeks and 12 weeks, and at 12 months after delivery	Maternal blood sampling at Day 0 (before vaccination), Day 28-42, Day 56-84, Day 84-112, Day112-140, at delivery, between 4 weeks and 12 weeks, and at 12 months after delivery

• To evaluate the immunogenicity of COVID-19 vaccines, when given as 1- or 2-dose vaccination regimens, in pregnant participants (regardless of serostatus as baseline).	• SARS-COV-2 IgG-specific antibody concentrations, (and neutralizing antibody titres and cellular immune responses in subsets) measured on blood samples collected from vaccinated maternal subjects at Day 0 (before vaccination), Day 28-42, Day 56-84, Day 84-112, Day 112-140, at delivery, between 4 weeks and 12 weeks, and at 12 months after delivery	Maternal blood sampling at Day 0 (before vaccination), Day 28-42, Day 56-84, Day 84-112, Day112-140, at delivery, between 4 weeks and 12 weeks, and at 12 months after delivery
Secondary Objectives **Infant** • To evaluate the safety of infants born to women vaccinated with COVID-19 vaccine(s) up to 12 months after birth.	• From birth through 6 weeks after birth, occurrences of SAEs, AEs leading to study withdrawal, and MAAEs.	Review of SAEs, AEs leading to study withdrawal, and MAAEs at delivery and at 3 days, 14 days, and 42-48 days after delivery, and at 6 months and 12 months.
	• Occurrence of neonatal AEs of special interest (up to 6 weeks after birth). These include but are not limited to small for gestational age, low birth weight including very low birth weight, neonatal encephalopathy, congenital microcephaly (postnatally or prenatally diagnosed), congenital anomalies (major external structural defects, internal structural defects, functional defects), neonatal death (in a preterm live birth or in a term live birth), neonatal infections (blood stream infections, meningitis, respiratory infection), respiratory distress in the neonate, preterm birth, failure to thrive, large for gestational age, macrosomia	Review of neonatal AESIs at delivery and at 3 days, 14 days, and 42-48 days after delivery, and at 6 months and 12 months.
	• Developmental status at 12 months of age	Perform neurodevelopmental assessment at 12 months of age

• To evaluate the transfer of SARS-CoV-2 specific antibodies from mothers vaccinated with COVID-19 vaccines, according to different regimens, to their infants at the time of delivery	• SARS-COV-2 IgG-specific antibody concentration, (and neutralizing antibody titres in a subset) against SARS-COV-2 measured on the cord blood sample collected at delivery, or on a blood sample collected from the infant within 3 days after birth (if no cord blood sample can be obtained)	Cord blood sample taken at delivery or infant blood sample taken within 3 days of life (if no cord blood sample can be obtained).
	• The ratio between cord blood and maternal SARS-COV-2 IgG-specific antibody concentrations or an infant blood sample collected within 72 hours after birth (if no cord blood sample can be obtained)	
• To evaluate the kinetics of SARS-CoV-2 specific maternal antibodies in infants born to mothers vaccinated with COVID-19 vaccine(s), up to 3 months after birth	• SARS-COV-2 IgG-specific antibody concentrations and Neutralizing antibody titres against SARS-COV-2 in infants born to vaccinated mothers at Day 28 to 42 or Day 70 to 84 post- delivery	Infant blood sampling between day 42 and day 84 post-delivery
• To assess the effect of gestational age at vaccination, interval between vaccination and delivery, maternal age, health status, vaccine type and schedule on immune responses and duration of immune responses in vaccinated women and on placental transfer and antibody kinetics in their infants	• SARS-COV-2 IgG-specific antibody concentration, (and neutralizing antibody titres in a subset) against SARS-COV-2 measured on the cord blood sample collected at delivery, or on a blood sample collected from the infant within 3 days after birth (if no cord blood sample can be obtained) • The ratio between cord blood and maternal SARS-COV-2 IgG-specific antibody concentrations or an infant blood sample collected within 72 hours after birth (if no cord blood sample can be obtained)	Maternal blood sample taken at delivery and cord blood sample taken at delivery or infant blood sample taken within 3 days of life (if no cord blood sample can be obtained).
	• SARS-COV-2 IgG-specific antibody concentrations and Neutralizing antibody titres against SARS-COV-2 in infants born to vaccinated mothers at Day 28 to 42 or Day 70 to 84 post- delivery	Infant blood sampling between day 28 and day 84 post-delivery

Exploratory Objectives **Maternal** • To describe SARS-COV-2 antibodies in breast milk of mothers who receive COVID-19 vaccine in pregnancy	• Levels of maternal IgA and/or IgG (and subtypes) against SARS-CoV-2 in colostrum and breast milk within 3 days and 14 days where possible	Collection of colostrum and breast milk sample at 3 days and 14 days post-delivery.
• To describe the effectiveness of COVID-19 vaccines in pregnancy against maternal COVID-19 in pregnancy or post-partum	• Occurrence of COVID-19 up to 12 months post-delivery (mother)	Identification and laboratory confirmation of SARS-CoV-2 infection and symptomatic COVID-19 throughout the study.
• To evaluate the immunogenicity of a COVID-19 vaccine when given as a booster dose, in pregnant participants who have received one dose of a COVID-19 vaccine before pregnancy	• SARS-COV-2 IgG-specific antibody concentrations, (and neutralizing antibody titres and cellular immune responses in subsets) measured on blood samples collected from vaccinated maternal subjects at Day 0 (before booster vaccination), Day 28-42, Day 56-84, Day 84-112, Day 112-140, at delivery, between 4 weeks and 12 weeks, and at 12 months after delivery	Maternal blood sampling at Day 0 (before vaccination), Day 28-42, Day 56-84, Day 84-112, Day 112-140, at delivery, between 4 weeks and 12 weeks, and at 12 months after delivery
• To compare the immunogenicity of a COVID-19 vaccine, when given as a booster dose to pregnant participants of 28-34 weeks' gestation who have received a prime dose of a COVID-19 vaccine before pregnancy, with the immunogenicity of a COVID-19 vaccine when given as a prime dose to pregnant participants of 28-34 weeks' gestation who have not received a dose of a COVID-19 vaccine previously	• SARS-COV-2 IgG-specific antibody concentrations, (and neutralizing antibody titres and cellular immune responses in subsets) measured on blood samples collected from vaccinated maternal subjects at Day 0 (before vaccination), Day 28-42, Day 56-84, Day 84-112, Day 112-140, at delivery, between 4 weeks and 12 weeks, and at 12 months after delivery	Maternal blood sampling at Day 0 (before vaccination), Day 28-42, Day 56-84, Day 84-112, Day 112-140, at delivery, between 4 weeks and 12 weeks, and at 12 months after delivery
• To assess the impact of prime-boost interval on immunogenicity when a booster dose is given to pregnant participants of 28-34 weeks' gestation who have received a prime dose of COVID-19 vaccine before pregnancy	• SARS-COV-2 IgG-specific antibody concentrations, (and neutralizing antibody titres and cellular immune responses in subsets) measured on blood samples collected from vaccinated maternal subjects at Day 0 (before vaccination), Day 28-42, Day 56-84, Day 84-112, Day 112-140, at delivery,	Maternal blood sampling at Day 0 (before vaccination), Day 28-42, Day 56-84, Day 84-112, Day 112-140, at delivery, between 4 weeks and 12 weeks, and at 12 months after delivery

	between 4 weeks and 12 weeks, and at 12 months after delivery	
Exploratory Objectives **Infant** • To describe the effectiveness of maternal antibodies against SARS-CoV-2 to protect against COVID-19 / symptomatic disease / severity in infants in the first 12 months of life	• Occurrence of COVID-19 up to 12 months post-delivery (infant)	Identification and laboratory confirmation of SARS-CoV-2 infection and symptomatic COVID-19 throughout the study.
• To describe the effectiveness of breast milk antibodies against SARS-CoV-2 to protect against COVID-19 / symptomatic disease / severity in infants in the first 12 months of life	• Occurrence of COVID-19 up to 12 months post-delivery (infant)	Identification and laboratory confirmation of SARS-CoV-2 infection and symptomatic COVID-19 throughout the study.

4 TRIAL DESIGN

This is a Phase II, multi-centre, randomised, single-blind, platform study evaluating the safety, reactogenicity and immunogenicity of COVID-19 vaccines in pregnant women participants in the UK.

The design is “adaptive” in that new COVID-19 vaccines may be included as soon as they are approved, and new schedules may be assessed as they become relevant or considered for implementation (e.g., one dose schedules in which the single dose is given earlier than 28 weeks’ gestation, etc).

Potential participants will be recruited through academic and NIHR clinical trials sites.

After signing informed consent, participants may be screened and enrolled. During the screening period nose/throat samples may be taken to detect SARS-CoV-2 by PCR, if the participant has any COVID-19 symptoms or significant exposure history.

Approximately 800 pregnant participants are planned for the study, but this will be dictated by the number of vaccines being evaluated. An effort will be made to enrol groups that are most affected by COVID-19, including ethnic minorities.

As determined by their gestation at recruitment (and whether they had already received a single dose of COVID-19 vaccine pre-pregnancy), participants will then be randomised to receive 1 or 2 intramuscular (IM) injections of either vaccine A or B or C (etc.), at one of two dosing intervals (see tables 1- 4).

5 TRIAL SETTING

This is a multicentre study which will take place across approximately 15 sites in the UK.

It is possible that further sites will be opened. If this occurs these sites will be added to the protocol at the next protocol update, and this will not alone necessitate a protocol amendment.

Women may receive information about the study from community midwives under the management of a trial site, through the national NIHR vaccine registry or through national or local advertising.

6 PARTICIPANT ELIGIBILITY CRITERIA

6.1 Inclusion criteria (maternal)

- Healthy women, or women with stable underlying medical conditions, 18 - 45 years of age, between 13 0/7 and 34 0/7 weeks' gestation on the day of planned vaccination, with an uncomplicated, singleton pregnancy, and who are at no known increased risk of severe COVID-19 or obstetric complications
- Able and willing (in the investigator's opinion) to comply with all study requirements
- Willing to allow the investigators to discuss the volunteer's medical history with their General Practitioner and access all medical records when relevant to study procedures
- Willing and able to give informed consent prior to study enrolment
- No contraindication to the specific vaccine to be administered in the study, according to the Green Book.

6.2 Exclusion criteria (maternal)

- Previous microbiological (based on a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19
- Administration of immunoglobulins and/or any blood products within the 3 months preceding the planned administration of the study vaccine candidate (with the exception of anti-D immunoglobulin)
- Previous vaccination with any COVID-19 vaccine (main cohort); prior receipt of one dose of a COVID-19 vaccine is permitted (sub-study)
- Any confirmed or suspected immunosuppressive or immunodeficient state; chronic administration (defined as more than 14 continuous days) of immunosuppressant medication within the past 3 months, except topical steroids or short-term oral steroids (course lasting ≤ 14 days).
- Any contraindication to the specific vaccine to be administered in the study, according to the Green Book or to the Summary of Product Characteristics for a specific vaccine.
- Current major illness of the mother or conditions of the fetus that, in the investigator's judgment, will substantially increase the risk associated with the participant's participation in, and completion of, the study or could preclude the evaluation of the participant's response, including but not limited to the following:
    - Uncontrolled gestational hypertension

- Preeclampsia-eclampsia
- Placental abnormality
- Polyhydramnios or oligohydramnios
- Significant bleeding or blood clotting disorder
- Uncontrolled gestational diabetes
- Any signs of premature labor with the current pregnancy or having ongoing intervention (medical/surgical) in the current pregnancy to prevent preterm birth
- Prior stillbirth or neonatal death, preterm delivery (≤34 weeks), or previous infant with a known genetic disorder or major congenital anomaly.

6.3 Eligibility Criteria (infant)

- Evidence of a signed and dated informed consent form signed by the parent(s)
- Parent(s) willing and able to comply with scheduled visits and other study procedures

6.4 Other considerations (maternal vaccination)

- Clinically significant pregnancy-related conditions according to medical judgement
- Clinically significant acute illness at the time of vaccination (cardiovascular, endocrine, gastrointestinal, hepatic, renal, neurological, respiratory, or other medical disorders) that is actively causing symptoms that could, in the opinion of the investigator, impact the assessment of reactogenicity or other study assessments. Participants may have planned study vaccination deferred for a later date, but these criteria are not exclusionary for study enrolment. Participant may be vaccinated once symptoms have resolved or are stabilised for > 3 days. Out-of-window study vaccination is allowed for this reason.
- Fever (body temperature ≥38.0ºC [100.4ºF]) within 24 hours prior to the planned vaccination. Participants may be vaccinated once the fever has resolved and there has not been any temperature measured as being > 38°C for > 3 days. Out-of-window study vaccination is allowed for this reason.

7 TRIAL PROCEDURES

Screening + study visit 1 (Maternal)

This visit will take place between 13 0/7 – 27 6/7 gestational weeks (for the earlier gestational weeks group) or between 28 0/7 – 34 0/7 gestational weeks (for the later gestational weeks group) at the participating institution. Eligibility will be confirmed, the study will be discussed in more detail and women will be asked to sign a consent form. They will then be asked about demographic details (including NHS number), past medical history, receipt of any prior dose of a COVID-19 vaccine, details of the current pregnancy including the results of antenatal screening and scans to ensure that they are eligible for the study. The participant's antenatal medical notes will be reviewed. Details will be collected about concomitant medication. A physical examination will be performed, and vital signs, height and weight will be recorded. Immunogenicity blood samples will be obtained.

Cohort 1, 2, 3: Participants will be randomised to a single group to receive one type of COVID-19 vaccine with the first dose to be given at visit 1.

Cohort 4: Participants will receive the same vaccine as given pre-pregnancy or during their first trimester (0 0/7 – 12 6/7 gestational weeks) and randomised to either receiving the booster dose before or after 26 weeks' gestation.

Vaccination will be given by members of the study team who are trained and experienced in vaccine administration and in emergency procedures in the event of an allergic reaction. They will have access to emergency medication and equipment. The vaccinations will be given according to the advice in the "Green Book" and the Summary of Product Characteristics (SmPC). An eDiary will be set up for the participant and they will be given instructions to complete the diary regularly for 28 days following vaccination. The participant will be observed for a period of 20 minutes following vaccination to assess for allergic adverse events.

Study visit 2 (Maternal) all cohorts

14 days (10 days – 21 days) after first vaccination review by telephone call.

- SAE / AESI / MAAE check
- Concomitant medication check
- eDiary review

Study visit 3 (Maternal) all cohorts

Day 28-42 following the first vaccination at the participating institution.

- SAE / AESI / MAAE check
- Concomitant medication check
- eDiary review
- Targeted physical examination if indicated
- Immunogenicity blood samples will be collected
- **Cohort 1.**
    - Vital signs pre-vaccination
    - **Vaccination with COVID-19 vaccine if randomised to the short interval boost or dTaP/IPV if randomised to the long boost arm and has not previously received pertussis vaccine.**
    - Observation period post-vaccination for 20 minutes
- **Cohort 2.**
    - Vital signs pre-vaccination

- **Vaccination with COVID-19 vaccine if randomised to the short interval boost or no vaccine or dTaP/IPV if randomised to the long interval boost arm and has not previously received pertussis vaccine. If dTaP/IPV vaccination is requested, it should be given by 32 weeks' gestation and with an interval of at least 1 week before / after receipt of COVID-19 vaccine.**
- Observation period post-vaccination for 20 minutes

- **No vaccination for cohort 3 (28 0/7 – 34 0/7 gestational weeks at recruitment) and cohort 4 (COVID-19 vaccine received pre-pregnancy / first trimester (0 0/7 – 12 6/7 gestational weeks)).**

Study visit 4 (Maternal) Cohort 1 and 2 only

Day 56-84 following the first vaccination (or 28-42 days post-short interval boost dose) at the participating institution.

- SAE / AESI / MAAE check
- Concomitant medication check
- Diary card review if applicable
- Targeted physical examination if indicated
- Immunogenicity blood samples will be collected

- **Cohort 1.**
  - Vital signs pre-vaccination
  - **Vaccination with COVID-19 vaccine if randomised to the long interval boost or dTaP if randomised to the short interval boost arm and has not previously received the pertussis vaccine**
  - Observation period post-vaccination for 20 minutes
  - eDiary review
- **Cohort 2.**
  - Vital signs pre-vaccination
  - **Vaccination with COVID-19 vaccine if randomised to the long interval boost or no vaccine or dTaP/IPV if randomised to the short interval boost arm and has not previously received pertussis vaccine. If dTaP/IPV vaccination is requested, it should be given by 32 weeks' gestation and with an interval of at least 1 week before / after receipt of COVID-19 vaccine.**
  - Observation period post-vaccination for 20 minutes
  - eDiary review

- **No visit 4 for cohort 3 (28 0/7 – 34 0/7 gestational weeks at recruitment) and cohort 4 (COVID-19 vaccine received pre-pregnancy / first trimester (0 0/7 – 12 6/7 gestational weeks)).**

Study visit 5 (Maternal) Cohort 1 and 2 only

Day 84-112 following the first vaccination (or 28-42 days post-long boost dose) at the participating institution / participant home.

- SAE / AESI / MAAE check
- Concomitant medication check
- eDiary review if applicable
- Targeted physical examination if indicated
- Immunogenicity blood samples will be collected
- **No visit 5 for cohort 3 (28 0/7 - 34 0/7 gestational weeks at recruitment) and cohort 4 (COVID-19 vaccine received pre-pregnancy / first trimester (0 0/7 – 12 6/7 gestational weeks)).**

Study visit 6 (Maternal) Cohort 1, 2 and 4 only

Day 112-140 following the first vaccination (or 56-84 days post second COVID-19 vaccine dose at the participating institution / participant home. This visit need only take place if the visit window starts before the due date.

- SAE / AESI / MAAE check
- Concomitant medication check
- eDiary review if applicable
- Targeted physical examination if indicated
- Immunogenicity blood samples will be collected
- **No visit 6 for cohort 3 (28 0/7 – 34 0/7 gestational weeks at recruitment).**

Study visit 7 (Delivery, maternal / infant)

Delivery at the participating institution.

- Targeted physical examination if indicated
- Immunogenicity maternal blood samples will be collected. These samples can be obtained by a member of the study team or a clinical member of staff. If blood sampling is not performed at delivery, women will be asked if a blood sample can be obtained from them within the first week following delivery and if a cord sample is not obtained parents will be asked if we can take a blood sample from the infant within the first week following delivery.
- Cord blood sample taken (at selected sites)

- Infant examination by clinical team

Study visit 8 (postnatal) only for participants in cohort 3 and / or in the breast milk sub-study

0 – 7 days post delivery where possible at the participating institution for those in the breast milk sub-study group and those due vaccination in cohort 3.

- SAE / AESI / MAAE check
- Concomitant medication check
- Targeted maternal physical examination for participants in cohort 3 only
- Colostrum sample collection (at selected sites). Participants who have agreed to take part in the breast milk sub-study will be asked if they still plan to breastfeed and if they are happy to provide a sample of colostrum. If women are still willing to take part in the study, they will be provided with information about colostrum sampling and containers and instructions for the collection of the sample.
- Participants who are taking part in the breast milk sub-study will hand express a sample of colostrum from each breast. Participants will be provided with containers and instructions for the collection of subsequent samples
- Vital signs pre-vaccination
- **Vaccination with COVID-19 vaccine for those in cohort 3 (28 0/7 – 34 0/7 gestational weeks at recruitment)**
- Observation period post-vaccination for 20 minutes
- eDiary set up for those receiving a vaccine

Study visit 9 (postnatal)

12 - 16 days post delivery where possible at the participating institution for those in the breast milk sub-study group. All other participants can be reviewed at this visit by a telephone call.

- SAE / AESI / MAAE check
- Concomitant medication check
- Breast milk sample collection (at selected sites). Women will be asked to provide a sample of breast milk from each breast. This sample can be collected by the woman in advance and collected by a member of the research team if this is a remote visit.
- There will be further randomisation to determine whether the infant bloods are taken at 4-6 weeks after birth or at 10-12 weeks after birth except cohort 3 (cohort 3 will have infant and maternal blood samples taken at **28-42 days** post-delivery).
- eDiary check for those who received a vaccine post-delivery (cohort 3)

Study visit 10 (postnatal)

28-42 days OR 70-84 days post delivery at the participating institution / participant home (cohort 3 will have infant and maternal blood samples taken at 28-42 days post-delivery).

- SAE / AESI / MAAE check
- Concomitant medication check
- Targeted maternal physical examination if indicated
- Maternal immunogenicity blood sample collection
- Infant blood sample collection This will be a venous sample where possible, taken by an experienced member of the research team.
- eDiary check for those who received a vaccine post-delivery (cohort 3)

Study visit 11 (postnatal)

182 days (-/+ 14 days) post delivery review by telephone call.

- SAE / AESI / MAAE check
- Concomitant medication check

Study visit 12 (postnatal)

364 days (-/+ 14 days) post delivery at the participating institution / participant home.

- SAE / AESI / MAAE check
- Concomitant medication check
- Immunogenicity blood sample collection
- Infant examination and neurodevelopmental assessment – "Ages and Stages" Questionnaire if not already completed by a healthcare professional during routine care.

Contraindications to vaccination

Clinically significant pregnancy-related conditions according to medical judgement

Clinically significant acute illness at the time of vaccination

Fever (body temperature ≥38.0^{o}C [100.4^{o}F]) within 24 hours prior to the planned vaccination

Symptomatic participants

Participants will be counselled at enrolment that should they receive a positive SARS-CoV-2 test (e.g. an antigen detection or nucleic acid amplification test, for example, via test and trace or occupational health services) they should contact the trial team on receipt of the positive result.

Once the participant has conveyed their result to the study team, and the study team confirm an appropriate test has been used (via verbal discussion with participant as to how testing was obtained). Confirmatory documentation may be sought from the participant (such as a forwarded email or a picture of a lateral flow assay result, but this is not essential). Cases of positive COVID-19 maternal infection will be noted.

Symptomatic infants will also receive an appropriate SARS-CoV-2 test and if positive an appointment will be arranged to review the participant at the relevant study site. At this visit blood samples for safety (FBC, Biochemistry, CRP and others if deemed clinically relevant) and immunology (PBMCs and serum for cellular and humoral immune responses) will be obtained. Vital signs and other clinical data will be recorded.

Participants (mothers/infants) will also be provided with a symptom diary to complete both solicited and unsolicited symptoms for at least 7 days and until symptom resolution (excepting persistent cough and anosmia/dysgeusia as these are recognised to be able to continue for extended periods). Additional visits on this pathway may be arranged at the clinical discretion of the investigator.

Lost to follow up

If contact with a participant is lost during the study, we will attempt to contact them by phone or email on three separate occasions. If we are unable to make contact using the information we have we will contact their GP to check if contact details have changed. We will specifically ask for consent from the pregnant woman to do this. We will ask for additional consent to use NHS number to trace the GP if the GP has changed since the start of the study. If there are new contact details, we will try again to make contact by phone or email on three separate occasions. If contact is still not possible or if the details we had been using previously were correct we will send a letter to the participant asking them to make contact with the research team. Participants will be considered lost to follow up if they have not made contact with the study team by two weeks following their estimated date of delivery.

7.1 Recruitment

Potential participants will be recruited through academic and NIHR clinical trials sites.

Information about the study will be disseminated as widely as possible amongst the potentially eligible population. Each site will record the number of mail out letters they send out and information will be collected on a pre-screening log about all women who are approached by a member of the research team to discuss the study. The information collected will include the date they were approached, their age and whether they are willing to consider participation in the study. If women are not willing to consider participation in the study the reason for this will be collected where possible.

7.1.1 Participant identification

Women may be identified in a number of ways according to local arrangements. Some may be identified when they attend hospital or community appointments and approached about the study, others may be identified from hospital lists of women due to attend for antenatal care and have information sent out to them. In the latter circumstance this identification will be performed by members of the clinical team - the research team will not have access to identifiable information without consent. After a woman has received information about the study at any point from the time of the booking appointment she may agree to being contacted by a member of the study team. This would require her to complete the information on the invitation letter and completion of this slip will be assumed to be consent to be contacted.

The following means of approaching women may be used at sites:

- Information sent through the post/email about the study
- Information provided directly when women attend for a community or hospital appointment
- Women seeing a leaflet or poster about the study when attending a hospital appointment
- Women seeing information about the study on an institutional website (both hospital and university), on social media or in a press release

Women who have signed up to the NIHR Vaccine registry may be approached directly about the study and provided with a link with further information.

Women who are potentially interested in participating in the study will be directed, via a link, to the trial website which will provide further information about the trial (including the participant information sheet and the inclusion and exclusion criteria).

7.1.2 Screening

The trial website will provide further information about the trial and direct potential participants to a series of screening questions. These questions will assess their suitability for inclusion (against the trial inclusion and exclusion criteria) as well as their geographic location. If they are deemed eligible for inclusion then the appropriate local recruitment site will be informed and will then make direct contact with the potential participant.

The eligibility of an individual to participate in this study will also be assessed by any appropriately trained and delegated member of the local research team. After signing the informed consent, participants may be screened and enrolled at Visit 1. During the screening period, nose/throat samples

may be taken to detect SARS-CoV-2 by PCR, if the participant has any COVID-19 symptoms or significant exposure history.

7.1.3 Expenses and Benefits

Volunteers will be compensated for their time, the inconvenience of having blood tests and procedures, and their travel expenses. The total amount compensated will depend on the exact number of visits, and whether any repeat or additional visits are necessary. For all trial visits compensation will be calculated according to the following:

- Travel expenses: £15 per visit (not applicable if home visit)
- Inconvenience of blood tests: £10 per blood donation
- Time required for visit: £20 per visit

7.2 Consent

The Principal Investigator (PI) retains overall responsibility for the conduct of research at their site, this includes the taking of informed consent of participants at their site. They must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki. If delegation of consent is acceptable then details should be provided.

Informed consent must be obtained prior to the participant undergoing procedures that are specifically for the purposes of the trial and are out-with standard routine care at the participating site (including the collection of identifiable participant data unless the trial has prior approval from the Confidentiality Advisory Group (CAG) and the Research Ethics Committee (REC))

The right of a participant to refuse participation without giving reasons must be respected.

The participant must remain free to withdraw at any time from the trial without giving reasons and without prejudicing her further treatment and must be provided with a contact point where she may obtain further information about the trial. Data and samples collected up to the point of withdrawal can only be used after withdrawal if the participant has consented for this. Any intention to utilise such data should be outlined in the consent literature. Where a participant is required to re-consent or new information is required to be provided to a participant it is the responsibility of the PI to ensure this is done in a timely manner.

The PI takes responsibility for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence.

The consent process will involve:

- discussion between the potential participant and a clinical member of the study team (research midwife / research nurse / research doctor) knowledgeable about the research, the nature and objectives of the trial and possible risks associated with their participation
- the presentation of written material (participant information leaflet (PIS) and consent document which is approved by the REC and in compliance with GCP, local regulatory requirements and legal requirements
- the opportunity for potential participants to ask questions
- assessment of capacity. Participants must be capable of giving consent for themselves. A capable person will:
    - understand the purpose and nature of the research
    - understand what the research involves, its benefits (or lack of benefits), risks and burdens
    - understand the alternatives to taking part
    - be able to retain the information long enough to make an effective decision.
    - be able to make a free choice
    - be capable of making this particular decision at the time it needs to be made

A copy of the signed Informed Consent Form (ICF) along with a copy of the most recent approved Patient Information Sheet (PIS) will be given to the study participant. An original signed and dated consent form will be placed in the participant's study folder and a copy will be sent to the GP. An entry will be made in the participant's handheld medical notes along with a copy of their signed consent form documenting her participation in the study.

7.2.1 Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Participants will be asked if they agree to sample collection (maternal and infant) and to the retention of any remaining samples for future related, ethically approved research. Consent to this will not be required for participation in the main study. With the participant's informed consent, any leftover samples will be frozen and transferred to St George's, University of London at the end of the study. If a subject elects not to permit this, all of that participant's leftover samples will be discarded at the end of the trial.

Participants at St George's University Hospitals NHS Foundation Trust and one other site (to be selected) will be asked if they are willing to take part in an additional study investigating functional immunity in breast milk following vaccination in pregnancy. If they are willing to participate in this aspect of the study, they will be asked to provide consent for this at the time of initial consent. Participation in this study is optional and not wishing to take part in this aspect of the study will not affect their participation in the rest of the study. Samples for this study will be identified with the study identification number. As with the main study participants will be informed that if they withdraw from the study their data and samples would continue to be used.

7.3 The randomisation scheme

7.3.1 Method of implementing the randomisation/allocation sequence

For the main study (cohort 1 and cohort 2), computer generated randomisation lists will be prepared by the study statistician. Participants will be randomised 1:1:1:1:1:1 for each of the vaccine groups (Pfizer / Moderna / Novavax) at "short" and "long" prime-boost intervals, using block randomisation. Random block sizes of 6 or 12 will be used. The randomisation will be stratified by the study cohort and study sites.

For the sub-study of cohort 3, participants will be randomised 1:1:1 to the study vaccines (Pfizer / Moderna / Novavax) using block randomisation. Random block sizes of 3 or 6 will be used, and the randomisation will be stratified by study sites. The sub-study of cohort 4 will be an open label study, women primed with a COVID-19 vaccine will be randomised to a boost vaccine (of the same type) before or after 26 weeks of gestational age on a 1:1 basis. Random block sizes of 2 or 4 will be used and stratified by study sites.

The study design is "adaptive" in that new COVID-19 vaccines may be included as soon as they are licensed. Randomisation will be adjusted accordingly. The allocation ratio will adaptively evolve over the course of the trial and will be fully described in the Interim Analysis.

7.4 Blinding

The study will be participant and laboratory blinded, i.e., while staff involved in study delivery will be aware of what vaccine schedule the participant is receiving, the participant themselves will remain blinded to which vaccine they receive. The "short" or "long" prime-boost interval allocation will be blinded to participant, where possible. This will be achieved in cohort 1, but in cohort 2, the pertussis-containing vaccine in the "long" prime-boost interval arm cannot be given at a COVID-19 vaccine visit (if after 32 weeks' gestation), and thus the whole cohort will be not blinded to "short" or "long" prime-boost intervals. During vaccination, the blind will be maintained by applying masking tape over the vaccine syringe. Laboratory staff will be blinded to both the randomised vaccines and the prime-boost intervals.

The timing of final unblinding of all trial participants will be after the creation of a locked analysis data set.

7.5 Emergency Unblinding

In this single-blinded study, if the clinical condition of a participant necessitates unblinding of the participant, this will be undertaken according to a trial specific working instruction. This will be done if unblinding is thought to be relevant and likely to change clinical management.

The trial code should only be broken for valid medical or safety reasons e.g. in the case of a serious adverse event where it is necessary for the treating health care professional to know which treatment the patient is receiving before the participant can be treated.

- if unblinding of a participant is required, a formal notification of unblinding will be made by the Investigator/treating health care professional to the CI or site PI
- if the person requiring the unblinding is not the CI/PI then that health care professional will notify the Investigating team that an unblinding is required for a trial participant and an assessment to unblind the participant should be made in consultation with the clinical and research teams
- on receipt of the treatment allocation details the site PI or treating health care professional will continue to deal with the participant's medical emergency as appropriate
- the PI documents the unblinding of the participant and the reasons for doing so on the CRF/data collection tool, in the site file and medical notes. It will also be documented at the end of the trial in any final trial report and/or statistical report
- the CI/PI will notify the Sponsor in writing as soon as possible following the unblinding process detailing the necessity of unblinding.
- the CI/Sponsor will also notify the relevant authorities if required
- The written information will be disseminated to the Data Safety Monitoring Committee for review in accordance with the DMC Charter. The responsibility for which should be assigned and documented
- As the investigator is responsible for the medical care of the individual trial participant (Declaration of Helsinki 3§ and ICH 4.3) emergency unblinding is permitted without prior discussion with the Sponsor.
- SUSARs are required to be reported unblinded

7.6 Baseline data

Baseline information collected about participants will include demographic details, NHS number, prior receipt of a COVID-19 vaccine, past medical history, details of the current pregnancy including the results of antenatal screening and scans, concomitant medication and a history of vaccinations received within the last five years and in all previous pregnancies.

7.7 Trial assessments

Blood samples will be obtained from women prior to vaccination, day 28-42, day 56-84, day 84-112, day 112-140 if not delivered already, at delivery, at 4-12 weeks after delivery, and at day 364 after delivery. A cord blood sample at selected sites will be obtained at delivery and if this is not collected a blood sample can be obtained from infant. All infants will have a blood sample taken at day 42 – 84 after birth. Colostrum samples will be obtained from women participating in the breastfeeding sub-study at 72 hours after delivery where possible and breast milk at day 14 after delivery where possible.

7.8 Long term follow-up assessments

A follow up assessment of infant development is planned at 12 months after birth using the “Ages and Stages” Questionnaire. Longer term follow up assessments for infants may be considered, but will be part of separate protocol and application.

7.9 Qualitative assessments

N/A

7.10 Withdrawal criteria

In consenting to the trial, participants are consenting to trial treatments, trial follow up and data collection. However, an individual participant may stop treatment early or be stopped early for any one of the following reasons:

- Having received vaccination outside of the study after randomisation, but before vaccination by the study team
- Any change in participant’s condition that in the investigator’s opinion justifies the discontinuation of follow up
- Withdrawal of consent by the participant

As participation in the trial is entirely voluntary, the participant may choose to discontinue treatment at any time without penalties or loss of benefits to which they may be entitled. Although not obliged to give a reason for discontinuing their trial treatment/ protocol inclusion a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights.

Participants who discontinue protocol treatment, for any of the above reasons, should remain in the trial for the purpose of follow up and data analysis.

However, if the participant confirms they do not wish to participate in the scheduled follow up data collection visits, then data that has already been collected should be kept and analysed according to the ITT principle, unless the participant specifically requests otherwise.

Participants who stop the trial follow up after receiving vaccination will not be replaced. Participants who withdraw prior to vaccination may be replaced.

If there is a change in the national recommendations or a safety signal is demonstrated the trial management group would consider if the study should be prematurely stopped.

7.11 Storage and analysis of clinical (biological) samples

7.11.1 Immunology blood tests (refer to the Laboratory Analysis Plan)

Immunogenicity will be assessed by a variety of immunological assays. Collaboration with other specialist laboratories in the UK, Europe and outside of Europe for further exploratory tests may occur. This would involve the transfer of serum, plasma, PBMC and/or other study samples to these laboratories, but these would remain anonymised. The analyses and which laboratories carry these out will be specified in the laboratory analysis plan.

Subjects will be informed that there may be leftover samples of their blood (after all testing for this study is completed), and that such samples may be stored indefinitely in the Infection and Immunity Biobank at St. George's, University of London for possible future ethically approved research. Subjects will be able to decide if they will permit such future use of any leftover samples. With the participants' informed consent, any leftover cells, serum/plasma or breast milk will be frozen indefinitely for future analysis of COVID-19 and other coronaviruses related diseases or pathogen-related immune responses. If a subject elects not to permit this, all of that participant's leftover samples will be discarded at the end of the trial.

Samples that are to be stored for future research will be transferred to the Infection and Immunity Biobank at St. George's, University of London.

7.11.2 Blood sampling (refer to the Laboratory Analysis Plan)

- Blood samples will be obtained by venepuncture by appropriately trained members of the research team. If it is not possible to obtain a venous sample from the infants, capillary blood sampling is acceptable although venous blood samples are preferable.
- Samples should be labelled with the participant number (prefixed with Preg-CoV), date of sampling and study visit number.
- Cord blood volumes. The required volume of cord blood is 30mls
- Maternal blood volumes. Refer to lab manual.
- Infant blood volumes. The required volume of infant blood is up to 5ml (no more than 1% of circulating blood volume)

7.11.3 Obtaining, labelling (colostrum/breast milk)

- Colostrum and breast milk samples will be collected by hand expression into a container after the breast and hands have been thoroughly cleaned with soap and water or a hygienic wipe.
- The samples will be taken immediately following a feed and will include colostrum/breast milk from both breasts
- Samples should be labelled with the participant number, date and time of sample collection, time since last feed and study visit number.
- Samples will be sent to the laboratory at St. George's, University of London on the same day if possible or kept in the fridge overnight if this is not possible. Samples may be frozen at -20C at the participant's home if it is not possible to transfer the breast milk to the laboratory within 48 hours of collection. Samples can be transferred in a cool box with ice packs by the study team who attend the woman's home.

7.11.4 Processing and storage (colostrum/breast milk) refer to the Laboratory Analysis Plan

- The colostrum/breast milk will be centrifuged and the lipid layer removed.
- The aqueous fraction will then be transferred to cryovials and frozen at -70°C.

7.11.5 Laboratory procedures (colostrum/breast milk) refer to the Laboratory Analysis Plan

- Multiplex immunoassays and functional assays will be performed on colostrum and breast milk at St George's, University of London.

It is the responsibility of the trial site to ensure that samples are appropriately labelled in accordance with the trial procedures to comply with the 2018 Data Protection Act. Biological samples collected from participants as part of this trial will be transported, stored, accessed, and processed in accordance with national legislation relating to the use and storage of human tissue for research purposes and such

activities shall at least meet the requirements as set out in the 2004 Human Tissue Act and the 2006 Human Tissue (Scotland) Act.

See appendix 4 – Schedule of Events / Procedures

7.12 End of trial

The end of the clinical phase of the study will be the last follow up visit of the last participant enrolled in the trial. The end of the study will be after the last sample has been assayed and analysed and database has been locked.

8 TRIAL TREATMENTS

8.1 Name and description of investigational medicinal product(s)

VACCINE A - Pfizer BioNTech (BNT162b2)

BNT162b2 is a lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine that encodes trimerised SARS-CoV-2 spike glycoprotein.

VACCINE B - COVID-19 Vaccine Moderna

COVID-19 Vaccine Moderna (mRNA-1273) encodes the S-2P antigen, consisting of the SARS-CoV-2 glycoprotein with a transmembrane anchor and an intact S1–S2 cleavage site. S-2P is stabilized in its prefusion conformation by two consecutive proline substitutions at amino acid positions 986 and 987, at the top of the central helix in the S2 subunit. The lipid nanoparticle capsule is composed of four lipids and formulated in a fixed ratio of mRNA and lipid.

VACCINE C - Novavax, NVX-CoV2373

Novavax, NVXCoV2373 is a nano-particle vaccine. It is constructed from the full-length wild-type (prototype Wuhan sequence) pre-fusion trimers of SARS-CoV2 spike glycoprotein. The native protein has been modified with several substitutions to limit protease cleavage and enhance thermal stability (the putative native furin cleavage site has been modified from RRAR to QQAQ and 2 proline substitutions (positions K986P and V987P) in the HR1 domain). It has also been optimised for expression in insect (Spodoptera frugiperda) Sf9 cells. The recombinant S-protein genes are cloned into

a baculovirus vector before being transferred into Sf9 cells. These cells then produce the protein which is extracted and purified. It is co-formulated with a saponin-based adjuvant, Matrix-M1™.

VACCINE D - AstraZeneca COVID-19 vaccine (ChAdOx1 nCOV-19) (*only for participants who have received one dose of this vaccine pre-pregnancy)

ChAdOx1 nCoV-19 is a recombinant replication-defective chimpanzee adenovirus expressing the SARS-CoV-2 spike (S) surface glycoprotein with a leading tissue plasminogen activator (TPA) signal sequence. S is a type I, trimeric, transmembrane protein located at the surface of the viral envelope, giving rise to spike shaped protrusions from the virion. The S proteins subunits are responsible for cellular receptor ACE-2 binding via the receptor-binding domain and fusion of virus and cell membranes, thereby mediating the entry of SARS-CoV-2 into the target cells. The S protein has an essential role in virus entry and determines tissue and cell tropism, as well as host range.

ChAdOx1 nCoV-19 expresses a codon-optimised coding sequence for Spike protein from the SARS-CoV-2 genome sequence accession MN908947. ChAd is a non-enveloped virus, and the glycoprotein antigen is not present in the vector but is only expressed once the genetic code within the vector enters the target cells. The vector genes are also modified to render the virus replication incompetent, and to enhance immunogenicity. Once the vector is in the nucleus, mRNA encoding the spike protein is produced that then enters the cytoplasm. This then leads to translation of the target protein which act as an intracellular antigen.

8.2 Regulatory status of the drug

VACCINE A – Pfizer BioNTech (BNT162b2)

The BNT162b2 vaccine received a conditional marketing authorisation from the European Medicines Agency on the 21st of December 2020.

VACCINE B – COVID-19 Vaccine Moderna

Approved for use under a temporary authorisation of the supply of an unlicensed vaccine; regulation 174 of the Human Medicines Regulations 2012.

VACCINE C- Novavax, NVX-CoV2373

No marketing authority or emergency use approval currently

VACCINE D - AstraZeneca COVID-19 vaccine (ChAdOx1 nCOV-19) (*only for participants who have received one dose of this vaccine pre-pregnancy)

Approved for use under a temporary authorisation of the supply of an unlicensed vaccine; regulation 174 of the Human Medicines Regulations 2012.

8.3 Product Characteristics

VACCINE A – Pfizer BioNTech (BNT162b2)

Refer to the Summary of Product Characteristics (SmPCs)

VACCINE B - Moderna

Refer to the Summary of Product Characteristics (SmPCs)

VACCINE C- Novavax, NVX-CoV2373

Refer to the Investigator Brochure

VACCINE D - AstraZeneca COVID-19 vaccine (ChAdOx1 nCOV-19) (*only for participants who have received one dose of this vaccine pre-pregnancy)

Refer to the Summary of Product Characteristics (SmPCs)

8.4 Drug storage and supply

Vaccines will be delivered to sites by Public Health England (PHE) and stored in accordance with manufacturers' recommendations.

All movements of the study vaccines will be documented in accordance with existing standard operating procedure (SOP). Vaccine accountability, storage, shipment and handling will be in accordance with relevant SOPs and forms. To allow for participants to receive the vaccine in a short time period, additional clinic locations may be used. In this instance vaccines will be transported in accordance with local SOP's and approvals as required.

VACCINE A – Pfizer BioNTech (BNT162b2)

The Pfizer BioNTech vaccine should be stored at -70°C +/- 10°C and has shelf life of 6 months. Once thawed, the vaccine may be stored for 31 days at 2-8°C. It should be used as soon as practically possible and within 6 hours of dilution.

VACCINE B – COVID-19 Vaccine Moderna

The COVID-19 Vaccine Moderna can be stored for 7 months at -25ºC to -15ºC. It should not be stored or transported on dry ice or below -40ºC. Once thawed it should not be re-frozen and may be stored refrigerated at 2°C to 8°C protected from light for up to 30 days if not used (needle-punctured). Chemical and physical stability of an unopened vial after removal from refrigerated conditions has been demonstrated for 12 hours at 8° to 25°C. Chemical and physical in-use stability has been demonstrated for 6 hours at 2 to 25ºC after first puncture. It should not be re-frozen once thawed.

VACCINE C- Novavax, NVX-CoV2373

SARS-CoV-2 rS and Matrix-M1 adjuvant should be stored at 2°C to 8°C and not frozen.

VACCINE D - AstraZeneca COVID-19 vaccine (ChAdOx1 nCOV-19) (*only for participants who have received one dose of this vaccine pre-pregnancy)

The AstraZeneca vaccine should be stored at +2ºC to +8ºC and has a shelf life of 6 months. The vaccine does not contain any preservative. After first opening the vial, it should be used within 6 hours when stored at room temperature (up to 30º C) or within 48 hours when stored in a refrigerator (2 to 8º C [36 to 46°F]). After this time, the vial must be discarded. The total cumulative storage time once opened must not exceed 48 hours.

8.5 Preparation and labelling of Investigational Medicinal Product

There will not be IMP labelling for this trial, products will be used as supplied by manufacturer (as for national supply) and blinding performed as per section 7.5.

8.6 Dosage schedules

VACCINE A – Pfizer BioNTech (BNT162b2)

The dose of Pfizer BioNTech COVID-19 vaccine is 30µg contained in 0.3ml of the diluted vaccine. Each pack of the Pfizer BioNTech vaccine contains 195 vials with 5 doses per vial (975 doses per pack). It is supplied with 0.9% sodium chloride diluent for injection plastic ampoules.

VACCINE B – COVID-19 Vaccine Moderna

COVID-19 Vaccine moderna (mRNA-1273) is packaged in multidose vials containing 10 doses of 0.5 mL. Vials are packaged in a carton containing a total of ten multidose vials per carton. One dose (0.5 mL) contains 0.10 mg of mRNA (embedded in lipid nanoparticles).

VACCINE C- Novavax, NVX-CoV2373

The dose of NVXCoV2373 is 5 µg recombinant spike protein with 50 µg Matrix-M1 adjuvant (0.5ml). The vaccine is supplied in 10 dose vials.

VACCINE D - AstraZeneca COVID-19 vaccine (ChAdOx1 nCOV-19) (*only for participants who have received one dose of this vaccine pre-pregnancy)

The dose of AstraZeneca COVID-19 vaccine is 0.5ml. The vaccine should be administered intramuscularly. The AstraZeneca vaccine is supplied in packs of 10 vials. Each vial contains 8 to 10 doses of vaccine, and is a colourless to slightly yellow, clear to slightly opaque liquid. Each dose is prepared by withdrawing 0.5 mL from a vial in a sterile 1 mL or equivalent syringe.

8.7 Dosage modifications

N/A

8.8 Known drug reactions and interaction with other therapies

There are currently no data on drug reactions and interactions with other therapies.

8.9 Concomitant medication

Women will not be recruited into the study if they are taking immunosuppressive medication other than inhaled or topical steroids. There are no other restrictions on medications which can be received by participants as part of participating in this study. Women should follow standard advice about the use of medication during pregnancy.

As set out by the exclusion criteria, volunteers may not enter the study if they have received: any other COVID-19 vaccine (with the exception of the sub-study participants), any investigational product within 30 days prior to enrolment or if receipt is planned during the study period, or if there is any use of immunosuppressant medication within 3 months prior to enrolment or if receipt is planned at any time during the study period (except topical steroids and short course of low dose steroids < 14 day). Concomitant medications taken at enrolment will be recorded, as will new medications taken within the 28 days after each immunisation. Subsequently only new medications taken in response to a medically attended adverse event up until 3 months post boost will be recorded. Women should follow standard advice about the use of medication during pregnancy.

8.10 Trial restrictions

Participants may take part in this study if they are already in involved in research providing that, in the opinion of the Principal Investigator, this involvement will not adversely affect the conduct or outcomes of the study.

8.11 Assessment of compliance with treatment

Solicited and unsolicited AEs will be reported by the participant using an online data capturing system. These data entries will be assessed on a daily basis by the study research team. Reminder notifications to complete these daily entries will be sent to the participants. Any non-compliance with this reporting will be noted and followed up by contacting the participant to prompt them to continue with the ediary entries.

8.12 Name and description of each Non-Investigational Medicinal Product (NIMP)

N/A

9 PHARMACOVIGILANCE

9.1

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative etiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: • in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within its licence. If it is being used off label an assessment of the SmPCs suitability will need to be undertaken. • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

9.2 Operational definitions for (S)AEs

We will not require SAE reporting for women being admitted to hospital for delivery, including those women who are admitted for induction of labour and caesarean section and neither instrumental delivery nor caesarean section would be reported as an SAE although the reasons for this may be, for example, if a caesarean section took place because of a significant antepartum haemorrhage the latter would be reported as an SAE although the caesarean section would not. Whether to report complications of delivery as an SAE should be decided at the discretion of the local PI with discussion with the Sponsor and CI as necessary.

9.3 Recording and reporting of SAEs, SARs AND SUSARs

Information about AEs and SAEs will be collected from the time of consent. Information about ARs, SARs and SUSARs will be collected from the time of administration of the vaccine. Information about SAEs will be collected for the duration of the study. Information about AEs will be enquired about at every study visit. AEs (apart from those which could reasonably be expected following vaccination- see section 9.2) will be recorded on the adverse event log for the period of 28 days following administration of the vaccine and medically attended adverse events which occur at any time in the study for the maternal participants will be collected. Medical attendance which is a routine part of antenatal care will not be considered an AE. Unscheduled medical attendances and events which meet the definition of an SAE should be recorded for the mother and infant.

Where a participant withdraws consent for further processing of data, this does not preclude the reporting of SARs and SUSARs which are required to continue being reported according to the protocol for regulatory purposes.

SAEs, SARs and SUSARs must be notified to the Sponsor immediately when the investigator becomes aware of the event (within 24 hours). Refer to JRESSOP0006 and ensure the completed SAE report form JRESDOC0012 is sent to the Sponsor by e-mail to adverseevents@sgul.ac.uk. All sites will correspond directly with the Sponsor, copying the CI into the correspondence.

We will not require SAE reporting for women being admitted to hospital for delivery, including those women who are admitted for induction of labour and caesarean section and neither instrumental delivery nor caesarean section would be reported as an SAE although the reasons for this may be, for example, if a caesarean section took place because of a significant antepartum haemorrhage the latter would be reported as an SAE although the caesarean section would not. Whether to report complications of delivery as an SAE should be decided at the discretion of the local PI with discussion with the Sponsor and CI as necessary.

For each SAE and SUSAR the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to trial drug / investigation), in the opinion of the investigator
- whether the event would be considered anticipated.

Any change of condition or other follow-up information should be emailed / faxed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached. Once all resulting queries have been resolved, the Sponsor will request the original form should also be posted to the Sponsor and a copy to be retained on site.

The collection of safety data in studies involving vaccination in pregnancy raises specific issues and it is important that the information collected about some outcomes of special interest is collected as consistently as possible (Jones, et al. 2016).

The Global Alignment of Immunization safety Assessment in pregnancy (GAIA) consortium have developed case definitions for a range of outcomes of interest. These should be used for the following events.

- Congenital microcephaly
- Failure to thrive
- Low birth weight
- Neonatal encephalopathy
- Respiratory distress in the newborn
- Small for gestational age
- Antenatal bleeding
- Dysfunctional labour
- Fetal growth restriction
- Gestational diabetes mellitus
- Congenital anomalies
- Neonatal death
- Neonatal infections
- Preterm birth
- Stillbirth

- Hypertensive disorders of pregnancy
- Maternal death
- Non-reassuring fetal status
- Post-partum haemorrhage

More details about these can be found via this link (http://gaia-consortium.net/outputs/)

All SAEs assigned by the PI or delegate (or following central review) as both suspected to be related to IMP-treatment and unexpected will be classified as SUSARs and will be subject to expedited reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA). The sponsor will inform the MHRA, the REC and Marketing Authorisation Holder (if not the sponsor) of SUSARs within the required expedited reporting timescales.

9.4 Responsibilities

Principal Investigator (PI):

Checking for AEs and ARs when participants attend for treatment / follow-up.

1. Using medical judgement in assigning seriousness, causality and whether the event/reaction was using the Reference Safety Information approved for the trial.
2. Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
3. Ensuring that AEs and ARs are recorded and reported to the sponsor in line with the requirements of the protocol.

Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning the SAEs seriousness, causality and whether the event was anticipated (in line with the Reference Safety Information) where it has not been possible to obtain local medical assessment.
3. Using medical judgement in assigning whether and event/reaction was anticipated or expectedness in line with the Reference Safety Information.

4. Immediate review of all SUSARs.
5. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
6. Assigning Medical Dictionary for Regulatory Activities (MedDRA) or Body System coding to all SAEs and SARs.
7. Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR).

Sponsor:

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
4. Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines.
5. Notifying Investigators of SUSARs that occur within the trial.
6. The unblinding of a participant for the purpose of expedited SUSAR reporting [For double blind trials only].
7. Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial.
8. Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC.

Trial Steering Committee (TSC):

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC):

In accordance with the Trial Terms of Reference for the DMC, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

9.5 Notification of deaths

All deaths, including deaths deemed unrelated to vaccination will be reported to the Sponsor within 48 hours of the investigator becoming aware of the death.

9.6 Overdose

This study involves administration of vaccines to participants. Women will be asked if they have received the whooping cough vaccination or COVID-19 vaccines previously in their pregnancy and if there is any uncertainty both the handheld notes and GP records will be consulted. It is extremely unlikely that a participant will receive an overdose of trial medication. If this happens, advice should be sought from the local Principal Investigator in discussion, if necessary, with the Chief Investigator.

9.7 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

9.8 The type and duration of the follow-up of participants after adverse reactions.

All vaccinations will be given by trained members of staff who are able to deal with an allergic reaction to the vaccine. All participants will be observed for 30 minutes following vaccine administration to ensure that they remain well. All participants will have access to contact details for the study team which they will be able to use if they have any concerns about adverse events following vaccine administration. These are licensed vaccines in adults so significant adverse reactions are extremely unlikely. All adverse events which occur within the 28 days after vaccine administration will be recorded on the AE log as well as all medically attended AE for the maternal participant which occur at any time during the study. Only events which meet the definition of an SAE should be recorded for the infant.

Any SUSAR will need to be reported to the Sponsor irrespective of how long after vaccine administration the reaction has occurred until resolved.

9.9 Development safety update reports

Where appropriate, the IMP manufacturer will submit Development Safety Update Reports (DSURs). These reports will be prepared by the sponsor (or delegate). In the absence of this, the CI will provide DSURs once a year throughout the clinical trial, or as necessary, to the Competent Authority (MHRA), where relevant the Research Ethics Committee and the sponsor.

The report will be submitted within 60 days of the Developmental International Birth Date (DIBD) of the trial each year until the trial is declared ended

10 STATISTICS AND DATA ANALYSIS

10.1 Sample size calculation

The primary analysis of this study will be a superiority test between the long and short prime-boost interval schedules within each group of COVID-19 vaccines.

The sample size calculation is based on the current available data from the ongoing ChAdOx1 nCoV-19 trial. The data suggests the standard devation of anti-spike IgG measured by standardised ELISA is 0.4 at D28 post boost. Though using a different validated assay, a study on immunogenicity among health care workers at 21 days after receiving two doses of ChAdOx1 nCoV-19 or BNT162b2 also reported a standard devation of anti-spike IgG between 0.3-0.5 (Eyre et al. 2021).

The sample calculation is based on the following assumptions:
1. The minimum clinical difference to detect is 1.75-fold difference in GMC between the long and short prime boost interval schedules, i.e. 0.243 on log scale (base 10).
2. The standard deviation of GMC on log scale (base 10) is 0.4.

Based on the above assumptions, the study will need to recruit 75 participants who are seronegative at baseline in each arm to achieve 90% of power at two-sided 1.67% significance level. Analysis will be performed separately for each group of COVID-19 vaccines. The significance level was adjusted for 3 comparisons using Bonferroni correction. We assume ~25% of study participants will be excluded from the primary analysis due to being seropositive at baseline or to loss of follow-up. Therefore, the sample size in

each arm will be expanded to 100 to give a total of 200 participants for each vaccine included. The total sample for 3 vaccines will be 600. Cohort 3 and cohort 4 will used for exploratory analyses to generate hypotheses, and thus no formal sample size calculation was carried out. We aim to recruit up to 100 pregnant women in each of these 2 cohorts. This sample size was chosen based on practical constraints.

10.2 Planned recruitment rate

It is hoped that recruitment will be completed within a 2 month period, although as with all studies recruiting in pregnancy, the recruitment rate can be unpredictable. The target recruitment number will be 800 to be recruited across 15 sites. It is expected that each site will recruit on average 24 participants per month.

10.3 Statistical analysis plan

A fully detailed statistical analysis plan will be prepared and will be signed off by the Chief Investigator prior to conducting any data analyses.

10.3.1 Summary of baseline data and flow of patients

At the end of the study, a flowchart will be used to summarise the number of women approached, consented, assigned to the different study arms, receiving vaccinations at the planned times, completing the study protocol and analysed for the primary outcome, as recommended by the CONSORT statement (http://www.consort-statement.org/). Baseline data will be summarised by study arms.

10.3.2 Primary outcome analysis

The immunogenicity data is expected to be highly skewed with possible censored data at the lower detection threshold. A value half the lower detection threshold will be used to impute the data, and the data will be log-transformed prior to analysis. The geometric mean concentration and associated 95% confidence interval will be summarised for each arm, by computing the anti-log of the mean of the log-transformed data.

The primary endpoint is anti-spike IgG at delivery. The geometric mean concentrations (GMC) of anti-spike IgG will be compared between “short” and “long” prime-boost interval arms for each of the COVID-19 vaccine groups under the hypothesis:

H0: GMC_{long} / GMC_{short} =1 or $log10$ GMC_{long} - $log10$ GMC_{short} = 0;

H1: GMC_{long} / GMC_{short} ≠1 or $log10$ GMC_{long} - $log10$ GMC_{short} ≠ 0.

For each vaccine groups (Pfizer / Moderna / Novavax / etc.), we will test the above hypothesis using a linear regression model adjusting for randomisation design variables. We will combine cohort 1 and cohort 2 in the primary analysis, and thus 3 regression models will be fitted. Sensitivity analysis will be carried out to further adjust for other covariates, which will be pre-specified in the statistical analysis plan. If a very high proportion (20%) of censored data are observed in the primary endpoint, then consideration will be made to use an alternative outcome as primary outcome, such as live neutralising antibodies against SARS-CoV-2.

The primary analysis will be conducted on the modified intent-to-treat basis, i.e. we will only include people who were seronegative at baseline and whose primary endpoint delivery is available. Because of the multiple comparisons in this trial, a p-value of two-sided 0.0167 will be considered as the threshold of statistical significance for the primary endpoint. Residual analysis will be used to check model fit. If model fit is not satisfactory specification of model covariates will be examined or an alternative model will be used.

10.3.3 Safety and Reactogenicity

The analysis population will be all randomised participants who received at least one study vaccine. Counts and percentages of each local and systemic solicited adverse reaction from diary cards, and all unsolicited AEs and SAEs will be presented by schedules of vaccine received.

10.4 Interim analysis and criteria for the premature termination of the trial

The interim analysis on immunogenicity will be carried out when the primary endpoint of anti-spike IgG data at delivery become available, while the interim analysis on reactogenicity will be conducted when the 7-day diary data become available for both the “short” and “long” prime-boost interval arms. The analysis will be carried out once the data is cleaned and the Study Analysis Plan is signed off. There will be no stopping rule for this interim analysis and the analysis will not affect the continuation of the trial.

10.8 Procedure(s) to account for missing or spurious data

The level and pattern of the missing data in the baseline variables and outcomes will be reported. The potential causes of any missing data will be investigated and documented as far as possible. Any missing data will be dealt with using methods appropriate to the conjectured missing mechanism and level of missing.

10.9 Economic evaluation

N/A

11 Data Management

11.1 Data collection tools and source document identification

The Chief Investigator will be responsible for all data that accrues from the study.

All study data including participant diary will be recorded directly into an EDC system (REDCap) or onto a paper source document for later entry into EDC if direct entry is not available. This includes safety, laboratory and outcome data. Any additional information that needs recording, but is not relevant for the eCRF (e.g signed consent forms) will be recorded on separate paper source documents. All documents will be stored safely and securely in confidential conditions. The EDC online data is stored on University of Oxford servers.

All participant reported adverse event data (both solicited & unsolicited) will be entered onto electronic diary cards (e-diaries) for a maximum of 28 days following administration of the IMP. The eDiary provides a full audit trial of edits and will be reviewed at time-points as indicated in the schedule of events. Any adverse event continuing beyond the period of the diary will be copied into the eCRF as required for safety review.

The participants will be identified by a unique trial specific number and code in any database. The name and any other identifying detail will NOT be included in any trial data electronic file, with the exception of the electronic diaries, for which consent will be obtained to store the participant email address for quality control purposes. Only site research staff and sponsor data managers have access to view the email address.

The EDC system (CRF data) uses a relational database (MySQL/ PostgreSQL) via a secure web interface with data checks applied during data entry to ensure data quality. The database includes a complete suite of features which are compliant with GCP, EU and UK regulations and Sponsor security policies, including a full audit trail, user-based privileges, and integration with the institutional LDAP server. The MySQL and PostgreSQL database and the webserver will both be housed on secure servers maintained by the University of Oxford IT personnel. The servers are in a physically secure location in Europe. Backups will be stored in accordance with the IT department schedule of daily, weekly, and monthly retained for one month, three months, and six months, respectively. The IT servers provide a stable, secure, well-maintained, and high capacity data storage environment. REDCap is a widely used, powerful, reliable, well-supported system. Access to the study's database will be restricted to members of the study team by username and password.

Source Data

Source Data and Case Report Forms (CRFs)

All protocol-required information will be collected in CRFs designed by the Investigator. All source documents will be filed in the participant file. Source documents are original documents, data, and records from which the participant CRF data are obtained. For this study, these will include, but are not limited to, volunteer consent form, blood results, GP response letters, laboratory records, diaries, medical records and correspondence. In the majority of cases, CRF entries will be considered source data as the CRF is the site of the original recording (i.e. there is no other written or electronic record of data). In this study this will include, but is not limited to medical history, medication records, vital signs, physical examination records, urine assessments, safety blood results, adverse event data and details of vaccinations. All source data and participant files will be stored securely.

To prevent withdrawal of a participant due to relocation, if there is a nearby participating site and with the consent of the participant, copies of relevant participant research records (such as ICF, paper source documents) will be transferred to the local site using secure email addresses such as nhs.net or by password protected sheets. The electronic research data stored on REDCap will also be transferred to the new site. The original records will be retained by the recruiting site.

11.2 Data handling and record keeping

The Investigators will maintain appropriate medical and research records for this trial, in compliance with GCP and regulatory and institutional requirements for the protection of confidentiality of volunteers. The Chief Investigator, co-Investigators and clinical research nurses will have access to records. The Investigators will permit authorised representatives of the Sponsor(s) and Host institution, as well as ethical and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

Identifiable information such as contact details will be stored for a minimum of 15 years from the end of the study. This includes storage of consent forms. Storage of these data will be reviewed every 15 years and files will be confidentially destroyed if storage is no longer required. Considerations at the time of this review will include the value of retaining this information for participant safety (e.g. to inform participants of unexpected safety signals emerging from post-licensing surveillance), as a resource for the participants (e.g. if they wish to check which vaccines they have received in the study) and any regulatory requirements. Financial information will be stored for 7 years. De-identified research data maybe be stored indefinitely. If volunteers consent to be contacted for future research, a record of this consent will be recorded, retained, and stored securely and separately from the research data. If

volunteers consent to have their samples stored and used in future research, information about their consent form will be retained and stored securely as per Biobanking procedures and SOP.

11.3 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits, and inspections- in line with participant consent.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorised third party, without prior written approval of the sponsor.

Data Quality

Data collection tools will undergo appropriate validation to ensure that data are collected accurately and completely. Datasets provided for analysis will be subject to quality control processes to ensure analysed data is a true reflection of the source data.

Trial data will be managed in compliance with local data management SOPs. If additional, study specific processes are required, an approved Data Management Plan will be implemented

Personally identifiable information will be shared with Public Health England regarding SARS-CoV2 PCR test results depending on the most up to date legal requirement to report on Notifiable Diseases at the time.

11.4 Archiving

- Archiving will be authorised by the Sponsor following submission of the end of trial report
- 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.
- All essential documents will be archived for a minimum of 15 years after completion of trial
- Destruction of essential documents will require authorisation from the Sponsor

12 MONITORING, AUDIT & INSPECTION

- The sponsor is responsible for ensuring appropriate monitoring of the study.
- This has been delegated to the CI and the lead research team.
- The study will be monitored remotely and via site self- assessment. If required, participating sites will permit trial-related on site monitoring, audits, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.
- During the COVID-19 outbreak, telephone visits are acceptable for collecting follow-up data and monitoring patients remotely. Relevant safety data will still be collected and the usual reporting process will be followed (see section 9.3 of study protocol).
- A Trial Monitoring Plan will be developed and agreed by the Trial Management Group (TMG), TSC and CI based on the trial risk assessment which may include on site monitoring.
- The processes reviewed can relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harm and completeness, accuracy, and timeliness of data collection
- Monitoring can be done by exploring the trial dataset or performing site visits
- Study site team members will be expected to assist the sponsor in monitoring the trial. These may include hosting site visits, providing information for remote monitoring, or putting procedures in place to monitor the trial internally

13 ETHICAL AND REGULATORY CONSIDERATIONS

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki and with Good Clinical Practice.

13.1 Research Ethics Committee (REC) review & reports

- Before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters
- Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial (note that amendments may also need to be reviewed

and accepted by the MHRA and/or NHS R&D departments before they can be implemented in practice at sites)

- All correspondence with the REC will be retained in the Trial Master File/Investigator Site File
- An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended
- It is the Chief Investigator's responsibility to produce the annual reports as required.
- The Chief Investigator will notify the REC of the end of the trial
- If the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination
- Within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC

Following Sponsor approval the protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), HRA (where required), regulatory authorities (MHRA in the UK), and host institution(s) for written approval. No amendments to this protocol will be made without consultation with, and agreement of, the Sponsor.

The Investigator is responsible for ensuring that changes to an approved trial, during the period for which regulatory and ethical committee(s) approval has already been given, are not initiated without regulatory and ethical committee(s)' review and approval except to eliminate apparent immediate hazards to the subject (i.e. as an Urgent Safety Measure).

13.2 Peer review

This study has been extensively peer reviewed as part of the application for funding (by members of VTF, NISEC, NIHR).

This study will be adopted by the NIHR CRN. In doing so the study has undergone high quality peer review which is:

a) **Independent**: At least two individual experts have reviewed the trial.

b) **Expert**: Reviewers with knowledge of the relevant discipline considered the clinical aspects of the protocol, and have the expertise to assess the methodological and statistical aspects of the trial.

c) **Proportionate**: Peer review commensurate with the size and complexity of the trial.

13.3 Public and Patient Involvement

This study has been discussed during its development with a patient and public involvement (PPI) group based at St George's, University of London which is specifically interested in studies relating to maternal and infant infections. This group is made up of pregnant women and those who have recently had a baby and their partners, and parents of young children including those who have previously participated in research studies. The study design, management of the study and participant facing documents have previously been discussed at meetings of this group and we will continue to discuss the study as it progresses.

13.4 Regulatory Compliance

The trial will not commence until Favourable REC and MHRA opinion has been obtained.

Before any site can enrol patients into the trial, the Principal Investigator must ensure written permission to proceed has been granted by that Trust Research & Development (R&D) office. The site must conduct the trial in compliance with the protocol as agreed by the Sponsor and, by the regulatory authorities as appropriate and which was given favourable opinion by the Research Ethics Committee (REC).

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.

13.5 Protocol compliance

Protocol non-compliances are departures from the approved protocol.

- prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol
- accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator and Sponsor immediately.

- deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.
- Major protocol deviations should be reported to the Chief Investigator and Sponsor immediately.

13.6 Notification of Serious Breaches to GCP and/or the protocol

A "serious breach" is a breach of GCP or the trial protocol which is likely to effect to a significant degree

(a) the safety or physical or mental integrity of the participants of the trial; or
(b) the scientific value of the trial

- the sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase
- the sponsor of a clinical trial will notify the licensing authority (REC authority, regulatory authority, and the relevant NHS host organisation) in writing of any serious breach of

(a) the conditions and principles of GCP in connection with that trial; or
(b) the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

The Sponsor should be notified within 24 hours of becoming aware of a serious breach.

13.7 Data protection and patient confidentiality

All investigators and trial site staff must comply with the requirements of the Data Protection Act 2018 and GDPR, with regards to the collection, storage, processing, and disclosure of personal information, and will uphold the Act's core principles.

Complete the St George's Research Data Protection Impact Assessment (DPIA) (Appendix 7).

13.8 Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

The Chief Investigator, Principal Investigators and all members of the trial management group will be asked to declare any competing interests. This disclosure will reflect:

- ownership interests that may be related to products, services, or interventions considered for use in the trial or that may be significantly affected by the trial

- commercial ties requiring disclosure include, but are not restricted to, any pharmaceutical, behaviour modification, and/or technology company

- any non-commercial potential conflicts e.g. professional collaborations that may impact on academic promotion.

A record of this disclosure of competing interests will be kept locally in the ISFs and in the TMF.

13.9 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.

13.10 Amendments

Under the Medicines for Human Use (Clinical Trials) Regulations 2004, the sponsor may make a non-substantial amendment at any time during a trial. If the sponsor wishes to make a substantial amendment to the CTA or the documents that supported the original application for the CTA, the sponsor must submit a valid notice of amendment to the licencing authority (MHRA) for consideration. If the sponsor wishes to make a substantial amendment to the REC application or the supporting documents, the sponsor must submit a valid notice of amendment to the REC for consideration. The MHRA and/or the REC will provide

a response regarding the amendment within 35 days of receipt of the notice. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial for the purposes of submission to the MHRA and/or REC.

Amendments also need to be notified to the national coordinating function of the UK country where the lead NHS R&D office is based and communicated to the participating organisations (R&D office and local research team) departments of participating sites to assess whether the amendment affects the NHS permission for that site. Note that some amendments that may be considered to be non-substantial for the purposes of REC still need to be notified to NHS R&D.

- Amendments can be made whilst the study is ongoing.
- The decision about the need for an amendment would be made by the Chief Investigator, informed by discussions with the trial management group and the JRES.
- The decision about whether the amendment is substantial or non-substantial will be made by the Chief Investigator in discussion with the JRES.
- The amendment will be prepared by a member of the central study team and the JRES and will be submitted to the REC through the IRAS system.
- Substantive changes will be communicated to all sites by a member of the central study team or a representative of the JRES.
- Details of the amendment history will be stored in ISFs at sites and in the TMF.

13.11 Post trial care

Women will receive study vaccines (COVID-19 and dTaP/IPV) in their pregnancy and will be reviewed at planned timepoints during the duration of the study participation for that participant. There is no other post trial care to be arranged.

13.12 Access to the final trial dataset

All members of the trial management group will have access to the full dataset on request. This will include the principal investigators at all sites.

14 DISSEMINATION POLICY

14.1 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.

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

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16. APPENDICES

16.1 Appendix 1-Risk

Risks associated with trial interventions

☒ A ≡ Comparable to the risk of standard medical care

☐ B ≡ Somewhat higher than the risk of standard medical care

☐ C ≡ Markedly higher than the risk of standard medical care

Justification: Briefly justify the risk category selected and your conclusions below (where the table is completed in detail the detail need not be repeated, however a summary should be given):

This study involves vaccinating pregnant women with COVID-19 vaccines within a time period in the UK. There is a small risk of adverse reaction to any vaccine, but this risk is low and is no higher in this study than in routine practice. All staff administering vaccines in this study will be appropriately trained in vaccine administration and in managing any side effects from this and all vaccines will be given in an environment where emergency equipment is available.

What are the key risks related to therapeutic interventions you plan to monitor in this trial?		How will these risks be minimised?		
IMP/Intervention	Body system/Hazard	Activity	Frequency	Comments
Vaccination	Adverse reaction	Post vaccination observation period to assess for adverse reactions	Post vaccination	Trained clinical research team members will be responsible for the assessments
As above	As above	Completion of eDiaries by participants post vaccination for 28 days	Daily eDiary entrees	Trained clinical research team members will be responsible for the assessments
As above	As above	Review of AE, SAE, and unscheduled medically attended AE during follow-up visits	Regular follow-up visits (up to 12 visits) during the participant's study involvement	Trained clinical research team members will be responsible for the assessments

Outline any other processes that have been put in place to mitigate risks to participant safety (e.g. DMC, independent data review, etc.)

A Data Safety Monitoring Board (DSMB) will be convened. The DSMB will evaluate frequency of events, safety and efficacy data as specified in the DSMB charter. The DSMB will make recommendations concerning the conduct, continuation or modification of the study for safety reasons to the Trial Steering Committee.

The DSMB will review SAEs or AESIs deemed possibly, probably or definitively related to study interventions. The DSMB will be notified within 24 hours of the Investigators' being aware of their occurrence. The DSMB can recommend placing the study on hold if deemed necessary following a study intervention-related SAE. A Trial Steering Committee will be formed to oversee the study and advise the Study Management Committee on key issues of study conduct, including, but not limited to, study pauses due to safety concerns on the advice of the DSMB.
Outline any processes (e.g. IMP labelling +/- accountability +/- trial specific temperature monitoring) that have been simplified based on the risk adapted approach. Clinical Study Plans and SOPs detailing the above safety measures will be made available to all sites.

16.2 Appendix 2 - Trial management / responsibilities

16.2.1 Patient registration/randomisation procedure

Participants will be registered as taking part when their eligibility is confirmed on the REDCap system and when they are randomised. This information will be available to the central team and no further procedure is required.

16.2.2 Data management

Data will be entered directly by members of the local research team into the eCRF using the REDCap programme. The data will be checked by members of the central team and data queries sent to local teams. The central team will aim to check data (CRF checking, data queries / clarifications) within a month of it being entered and send queries out within this period. The central team will ask for sites to respond to data queries within a month of receiving the request.

16.2.3 Trial documentation and archiving

The Trial Master File (TMF), trial database and Sponsor documents will be archived centrally. Each local PI will archive the trial essential documents generated at the site for the agreed archiving period in accordance with the signed Clinical Trial Site agreement. All trial related documents will be archived for a minimum of fifteen years.

Please note, we are not able to archive source data or the ISF for participating sites

16.3 Appendix 4 – Schedule of Events / Procedure

Cohort 1 and 2 Visit Schedule - Pregnant women enrolled between 13 0/7 - 27 6/7 gestational weeks

	PRENATAL						DELIVERY	POSTNATAL				
	Screening + V1	V2	V3	V4[b]	V5[b]	V6[c]	V7	V8[e]	V9[f]	V10	V11	V12
Study timeline	D0	D14	D28-42	D56-84	D84-112	D112 - 140	Delivery	Delivery up to 7 days (*where possible*)	Delivery +14 days (*where possible*)	Delivery +28-42 days **OR** 70-84 days	Delivery +182 days (+/- 14 days)	Delivery +364 days (+/- 14 days)
Study window	D0	Day 10-21 post V1 (phone)	Day 28-42 post V1	Day 56-84 post V1	Day 28-42 post V3	Day 56-84 post second COVID vaccine	N/A	0 - 7 days post delivery	Day 12-16 post delivery (phone)	Day 28-42 **OR** 70-84 post delivery	Day 168-196 post delivery (phone)	Day 349-379 post delivery
Informed consent	X											
Screening bloods - maternal (HIV, Hep B, Syphilis) from routine prenatal visits	X (routine)											
Ultrasound dating and anomaly scan from routine prenatal visit	X (routine)											
Medical History	X											
Physical examination - maternal	X		(X)	(X)	(X)	(X)	(X)			(X)		
Vital signs, height and weight	X		X	X								
Vaccination	X		X[a]	X[a]								
COVID-19 immunogenicity bloods - maternal	X		X	X	X	X	X			X		X
eDiary review		X	X	X	X	X						
SAE/AESI/Medically attended AE check		X	X	X	X	X		X	X	X	X	X
Concomitant medication check	X	X	X	X	X	X		X	X	X	X	X
Physical examination - infant							X					X
COVID-19 immunogenicity bloods - infant										X[d]		
Neurodevelopmental assessment (Ages & Stages questionnaire) - infant												X
Cord blood sample (selected sites)							X					
Colostrum / Breast milk sample (selected sites)								X	X			

[a] For cohort 1, this will be a COVID-19 vaccine or pertussis-containing vaccine depending on randomisation to long or short course. A pertussis-containing vaccine may also be offered in cohort 2, 3, 4.
[b] Participants will either have blood sampling for Neutralising Antibody, ELISpot, Intracellular Cytokine Staining assays at V4 or V5 depending on whether they are on the short course or long course.
[c] This visit will take place if the window starts before their due date.
[d] Infant is randomised at V9 to blood sampling at 4-6 weeks or 10-12 weeks after birth except cohort 3 (cohort 3 will have infant and maternal blood samples taken at 28-42 days post-delivery).
[e] V8 only for breast milk sub-study sites or Cohort 3
[f] V9 is a telephone call review except for breast milk sub-study sites (*in brackets*) - as required

Cohort 3 Visit Schedule - Pregnant women enrolled between 28 0/7 - 34 0/7 gestational weeks

	PRENATAL						DELIVERY	POSTNATAL				
	Screening + V1	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8[b]**	**V9[c]**	**V10**	**V11**	**V12**
Study timeline	D0	D14	D28-42	No visit in this cohort	No visit in this cohort	No visit in this cohort	Delivery	Delivery up to 7 days (*where possible*)	Delivery +14 days (*where possible*)	Delivery +28-42 days	Delivery +182 days (+/- 14 days)	Delivery +364 days (+/- 14 days)
Study window	D0	Day 10-21 post V1 (phone)	Day 28-42 post V1				N/A	0 - 7 days post delivery	Day 12-16 post delivery (phone)	Day 28-42 post delivery	Day 168-196 post delivery (phone)	Day 349-379 post delivery
Informed consent	X											
Screening bloods - maternal (HIV, Hep B, Syphilis) from routine prenatal visits	X (routine)											
Ultrasound dating and anomaly scan from routine prenatal visit	X (routine)											
Medical History	X											
Physical examination - maternal	X		(X)				(X)	(X)		(X)		
Vital signs, height and weight	X							X				
Vaccination	X							X				
COVID-19 immunogenicity bloods - maternal	X		X				X			X		X
eDiary review		X	X						X	X		
SAE/AESI/Medically attended AE check		X	X					X	X	X	X	X
Concomitant medication check	X	X	X					X	X	X	X	X
Physical examination - infant							X					X
COVID-19 immunogenicity bloods - infant										X[a]		
Neurodevelopmental assessment (Ages & Stages questionnaire) - infant												X
Cord blood sample (selected sites)							X					
Colostrum / Breast milk sample (selected sites)								X	X			

[a] Cohort 3 will have infant and maternal blood samples taken at 28-42 days post-delivery
[b] V8 only for breast milk sub-study sites or Cohort 3
[c] V9 is a telephone call review except for breast milk sub-study sites
(*in brackets*) - as required

Cohort 4 Visit Schedule - Pregnant women enrolled between 13 0/7 - 27 6/7 gestational weeks and received a COVID-19 vaccine before pregnancy or during first trimester (0 0/7 – 12 6/7 gestational weeks)

	PRENATAL						DELIVERY	POSTNATAL				
	Screening[a]	**V1**	**V2**	**V3**	**V4 + V5**	**V6[b]**	**V7**	**V8[c]**	**V9[d]**	**V10**	**V11**	**V12**
Study timeline	Screening	D0	D14	D28-42	No visit in this cohort	D112 - 140	Delivery	Delivery to 7 days (*where possible*)	Delivery +14 days (*where possible*)	Delivery +28-42 days **OR** 70-84 days	D182 (+/- 14 days)	D364 (+/- 14 days)
Study window		<26 weeks gestation **OR** >26 weeks gestation	Day 10-21 post V1 (phone)	Day 28-42 post V1		Day 112 - 140 post V1	N/A	0 - 7 days post delivery (phone)	Day 12-16 post delivery (phone)	Day 28-42 **OR** 70-84 post delivery	Day 168-196 post delivery (phone)	Day 349-379 post delivery
Informed consent	X											
Screening bloods - maternal (HIV, Hep B, Syphilis) from routine prenatal visits	X (routine)											
Ultrasound dating and anomaly scan from routine prenatal visit	X (routine)											
Medical History	X											
Physical examination - maternal	X	(X)		(X)		(X)	(X)			(X)		
Vital signs, height and weight	X	X										
Vaccination		X										
COVID-19 immunogenicity bloods - maternal		X		X		X	X			X		X
eDiary review			X	X		X						
SAE/AESI/Medically attended AE check		X	X	X		X		X	X	X	X	X
Concomitant medication check	X	X	X	X		X		X	X	X	X	X
Physical examination - infant							X					X
COVID-19 immunogenicity bloods - infant										X[e]		
Neurodevelopmental assessment (Ages & Stages questionnaire) - infant												X
Cord blood sample (selected sites)							X					
Colostrum / Breast milk sample (selected sites)								X	X			

[a] Screening and V1 can be done at the same time if randomisation to vaccination schedule allows.
[b] V6 will take place if the window starts before their due date.
[c] V8 only for breast milk sub-study sites or Cohort 3
[d] V9 is a telephone call review except for breast milk sub-study sites
[e] Infant is randomised at V9 to blood sampling at 4-6 weeks or 10-12 weeks after birth except cohort 3 (cohort 3 will have infant and maternal blood samples taken at 28-42 days post-delivery).
(*in brackets*) - as required

Cohort 1 and 2 Laboratory Sampling Schedule - Pregnant women enrolled between 13 0/7 - 27 6/7 gestational weeks

	PRENATAL						DELIVERY	POSTNATAL				
	Screening + V1	V2	V3	V4[b]	V5[b]	V6[c]	V7	V8	V9	V10[d]	V11	V12
Study timeline	D0	D14	D28-42	D56-84	D84-112	D112 - 140	Delivery	Delivery up to 7 days	Delivery +14 days	Delivery + 28-42 days **OR** 70-84 days	D182 (+/- 14 days)	D364 (+/- 14 days)
Study window	D0	Day 10-21 post V1	Day 28-42 post V1	Day 56-84 post V1	Day 28-42 post V3	Day 56-84 post second COVID vaccine	N/A	0 – 7 days post delivery	Day 12-16 post delivery	Day 28-42 **OR** 70-84 post delivery	Day 168-196 post delivery	Day 349-379 post delivery
Vaccination	X		X[a]	X[a]								
COVID-19 immunogenicity bloods - maternal	X **Nexelis** Anti-spike IgG **PHE** Anti-nucleocapsid IgG ADCD **IMMUNOTEC** ELISpot & ICS (7 sites)		X **Nexelis** Anti-spike IgG	X **Nexelis** Anti-spike IgG **PHE** Neutralising Abs ADCD **IMMUNOTEC** ELISpot & ICS (7 sites)	X **Nexelis** Anti-spike IgG **PHE** Neutralising Abs ADCD **IMMUNOTEC** ELISpot & ICS (7 sites)	X **Nexelis** Anti-spike IgG	X **Nexelis** Anti-spike IgG **PHE** Anti-nucleocapsid IgG Neutralising Abs ADCD **SGUL Lab** ELISpot & ICS (2 site)			X **Nexelis** Anti-spike IgG		X **Nexelis** Anti-spike IgG **PHE** Anti-nucleocapsid IgG ADCD **IMMUNOTEC** ELISpot & ICS (7 sites)
Cord blood sample (at selected sites)							X **Nexelis** Anti-spike IgG **PHE** Anti-nucleocapsid IgG **SGUL Lab** ELISpot & ICS					
Colostrum / Breast milk sample (at selected sites)								X **SGUL Lab** Anti-spike IgG ELISpot + ICS (2 sites)	X **SGUL Lab** Anti-spike IgG ELISpot + ICS (2 sites)			
COVID-19 immunogenicity bloods - infant										X **Nexelis** Anti-spike IgG **PHE** Anti-nucleocapsid IgG		
Sample volumes (+ blood bottles)	**Maternal:** Up to 50mls (20mls red, 30mls green/ LiHep)		**Maternal:** Up to 20mls (20mls red)	**Maternal:** Up to 50mls (20mls red, 30mls green/ LiHep)	**Maternal:** Up to 50mls (20mls red, 30mls green/ LiHep)	**Maternal:** Up to 20mls (20mls red)	**Maternal:** Up to 50mls (20mls red, 30mls green/ LiHep) **Cord blood:** up to 30mls	**Colostrum:** 1-2mls	**Breast milk:** 2-5mls	**Maternal:** Up to 20mls (20mls red) **Infant:** up to 5mls		**Maternal:** Up to 50mls (20mls red, 30mls green/ LiHep)

[a]This will either be a COVID vaccine or pertussis-containing vaccine for cohort 1 depending on randomisation to long or short course. A pertussis-containing vaccine may also be offered in cohort 2, 3, 4.
[b]Participants will either have Neutralising Abs, ELISpot, Intracellular Cytokine Staining assays at V4 or V5 depending on whether they are in the short course or long course.
[c]This visit will take place if the window starts before their due date.
[d]Infant is randomised at V9 to blood sampling at 4-6 weeks or 10-12 weeks after birth except cohort 3. Cohort 3 will have infant and maternal blood samples taken at 28-42 days post-delivery.

Cohort 3 Laboratory Sampling Schedule - Pregnant women enrolled between 28 0/7 - 34 6/7 gestational weeks

	PRENATAL						DELIVERY	POSTNATAL				
	Screening + V1	V2	V3	V4	V5	V6	V7	V8	V9	V10**	V11	V12
Study timeline	D0	D14	D28	No visit in this cohort	No visit in this cohort	No visit in this cohort	Delivery	Delivery up to 7 days	Delivery +14 day	Delivery + 28-42 days	D182 (+/- 14 days)	D364 (+/- 14 days)
Study window	D0	Day 10-21 post V1	Day 28 post V1				N/A	0 – 7 days post delivery	Day 12-16 post delivery	Day 28-42 post delivery	Day 168-196 post delivery	Day 349-379 post delivery
Vaccination	X							X				
COVID-19 immunogenicity bloods - maternal	X Nexelis Anti-spike IgG PHE Anti-nucleocapsid IgG ADCD IMMUNOTEC ELISpot & ICS (7 sites)		X Nexelis Anti-spike IgG PHE Anti-nucleocapsid IgG Neutralising Abs ADCD IMMUNOTEC ELISpot & ICS (7 sites)				X Nexelis Anti-spike IgG PHE Anti-nucleocapsid IgG Neutralising Abs ADCD SGUL Lab ELISpot & ICS (2 sites)			X Nexelis Anti-spike IgG		X Nexelis Anti-spike IgG PHE Anti-nucleocapsid IgG ADCD IMMUNOTEC ELISpot & ICS (7 sites)
Cord blood sample (at selected sites)							X Nexelis Anti-spike IgG PHE Anti-nucleocapsid IgG SGUL Lab ELISpot & ICS					
Colostrum / Breast milk sample (at selected sites)								X SGUL Lab Anti-spike IgG ELISpot + ICS	X SGUL Lab Anti-spike IgG ELISpot + ICS			
COVID-19 immunogenicity bloods - infant										X Nexelis Anti-spike IgG PHE Anti-nucleocapsid IgG		
Sample volumes (+ blood bottles)	Maternal: Up to 50mls (20mls red, 30mls green/ LiHep)		Maternal: Up to 20mls (20mls red)				Maternal: Up to 50mls (20mls red, 30mls green/ LiHep) Cord blood: up to 30mls	Colostrum: 1-2mls	Breast milk: 2-5mls	Maternal: Up to 20mls (20mls red) Infant: up to 5mls		Maternal: Up to 50mls (20mls red, 30mls green/ LiHep)

**Infant plus maternal blood samples to be taken at 28-42 days post-delivery

Cohort 4 Prenatal Laboratory Sampling Schedule - Pregnant women enrolled between 13 0/7 - 27 6/7 gestational weeks and received a COVID-19 vaccine before pregnancy or during first trimester (0 0/7 – 12 6/7 gestational weeks)

	PRENATAL							DELIVERY	POSTNATAL				
	Screening	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10**	V11	V12
Study timeline	Screening	D0	Day 14	D28-42	No visit in this cohort	No visit in this cohort	D112 - 140	Delivery	Delivery up to 7 days	Delivery +14 days	Delivery + 28-42 days OR 70-84 days	D182 (+/- 14 days)	D364 (+/- 14 days)
Study window		<26 weeks gestation OR >26 weeks gestation	Day 10-21 post V1	Day 28-42 post V1			Day 112 - 140 post V1	N/A	0 – 7 days post delivery	Day 12-16 post delivery	Day 28-42 OR 70-84 post delivery	Day 168-196 post delivery	Day 349-379 post delivery
Vaccination		X											
COVID-19 immunogenicity bloods - maternal		X Nexelis Anti-spike IgG PHE Anti-nucleocapsid IgG ADCD IMMUNOTEC ELISpot & ICS (7 sites)		X Nexelis Anti-spike IgG PHE Neutralising Abs ADCD IMMUNOTEC ELISpot & ICS (7 sites)			X Nexelis Anti-spike IgG	X Nexelis Anti-spike IgG PHE Anti-nucleocapsid IgG Neutralising Abs ADCD SGUL Lab ELISpot & ICS (2 sites)			X Nexelis Anti-spike IgG		X Nexelis Anti-spike IgG PHE Anti-nucleocapsid IgG ADCD IMMUNOTEC ELISpot & ICS (7 sites)
Cord blood sample (at selected sites)								X Nexelis Anti-spike IgG PHE Anti-nucleocapsid IgG SGUL Lab ELISpot & ICS					
Colostrum / Breast milk sample (at selected sites)									X SGUL Lab Anti-spike IgG ELISpot + ICS	X SGUL Lab Anti-spike IgG ELISpot + ICS			
COVID-19 immunogenicity bloods - infant											X Nexelis Anti-spike IgG PHE Anti-nucleocapsid IgG		
Sample volumes		**Maternal:** Up to 50mls (20mls red, 30mls green/ LiHep)		**Maternal:** Up to 20mls (20mls red)				**Maternal:** Up to 50mls (20mls red, 30mls green/ LiHep) **Cord blood:** up to 30mls	**Colostrum:** 1-2mls	**Breast milk:** 2-5mls	**Maternal:** Up to 20mls (20mls red) **Infant:** up to 5mls		**Maternal:** Up to 50mls (20mls red, 30mls green/ LiHep)

** Infant is randomised at V9 to blood sampling at 4-6 weeks or 10-12 weeks after birth.

16.4 Appendix 5 – Safety Reporting Flow Chart

A Development Safety Update Report (DSUR) will be prepared annually, reporting on this study and 'Comparing COVID-19 Vaccines in Pregnancy' Preg-CoV) **(**Ethics Ref: XXXX**,** IRAS Project ID: XXXX, within 60 days of the anniversary of the MHRA approval for the 'first' Preg-CoV study. The DSUR will be submitted by the CI to the Competent Authority, Ethics Committee, HRA (where required), Host NHS Trust and Sponsor.

Reporting procedures for Serious Adverse Events

In order to comply with current regulations on SAE reporting to regulatory authorities, the event will be documented accurately, and notification deadlines respected. SAEs will be reported to members of the study team immediately the Investigators become aware of their occurrence, as described in the clinical study plan. Copies of all reports will be forwarded for review to the Chief Investigator (as the Sponsor's representative) within 24 hours of the Investigator being aware of the suspected SAE. The DSMB will be notified of SAEs that are deemed possibly, probably or definitely related to study interventions; the chair of DSMB will be notified immediately (within 24 hours) of the sponsor being aware of their occurrence. SAE/AESIs will not normally be reported immediately to the ethical committee(s) unless there is a clinically important increase in occurrence rate, an unexpected outcome, or a new event that is likely to affect safety of trial participants, at the discretion of the Chief Investigator and/or DSMB. In addition to the expedited reporting above, the Investigator shall include all SAE/AESIs in the annual Development Safety Update Report (DSUR) report provided for Preg-CoV.

Safety to Investigator Reporting Process

Reference Materials Distributed to Sites by Clinical Team

Safety reports uploaded- automatic email notification sent to sites

Distribution report provided to clinical teams periodically for site monitoring

16.5 Appendix 6

Amendment History				
Amendment No.	**Protocol version no.**	**Date issued**	**Author(s) of changes**	**Details of changes made**

16.6 Appendix 7

Complete the form below. It will require review and sign-off by the Institute Director (SGUL) or the Care Group Lead (SGHFT).

Research Data Protection Impact Assessment (DPIA)

Data Protection Impact Assessments (DPIAs) are a tool which can help organisations identify the most effective way to comply with their data protection obligations under the Data Protection Act 2018 (DPA 18) and meet individuals' expectations of privacy.

A DPIA helps identify data privacy risks when planning new, or revising existing, projects and to identify actions to mitigate these risks. In the rare cases where risks cannot be mitigated at all it may be necessary to consult with the Information Commissioner's Office (ICO). Under data protection legislation it is a legal requirement to complete a DPIA in the following circumstances:

- • where data processing is likely to result in a high risk of harm to individuals, e.g. new, invasive technology is proposed
- • when large volumes of personal data are processed, e.g. use of behavioural profiles based on website usage
- • when processing special category personal data on a large scale, e.g. healthcare data, genetic tests to assess and predict the disease/health risks

• where publicly accessible areas are monitored, e.g. CCTV or when filming public areas

Therefore a DPIA will be carried out for both internal and partnership projects which require the collection/processing of personal data in any format for the purpose of research.

The DPIA should be carried out towards the start of the project, in order to identify any associated information risks and mitigate in the early stages, before you start processing.

Study Title/Acronym:	A Phase II, randomised, single-blind, platform trial to assess safety, reactogenicity and immunogenicity of COVID-19 vaccines in pregnant women in the United Kingdom. Preg-CoV
JRES Reference Number:	2021.0144
Chief Investigator Name:	Professor Paul Heath
Chief Investigator Email Address:	pheath@sgul.ac.uk

PROJECT DETAILS
Project / process description: **- include / attach processing operations (include a flow diagram or another way of explaining data flows), the purpose and, where applicable, what St George's lawful basis is for the processing of the information.**
The Preg-CoV trial aims to find out which COVID-19 vaccine is the most effective in pregnancy and the optimal interval between doses to protect both mother and baby. Ongoing global studies have so far found that pregnant women are more likely to develop severe COVID-19 disease compared to non-pregnant women of the same age. Pregnant women who develop COVID-19 symptoms are two to three times more likely to have their baby early. Pregnant women with COVID-19 also have a higher mortality rate than pregnant women without COVID-19. For these reasons, the current UK national guidance on immunisation is that COVID-19 vaccination should be offered to pregnant women at the same time as the rest of the population. However, further pregnancy-specific research is needed on COVID-19 vaccines. The trial will compare vaccines that are currently being used for the UK vaccination programme, as well as new vaccines as they are approved. Low-risk pregnant women aged 18 - 45 years and between 13-34 weeks gestation can be considered for enrolment into the study. Once they have given their consent, participants who have not yet received any COVID-19 vaccines will be randomised to receive two doses in a short-time interval (4-6 weeks) or a long-time interval (8-12 weeks). For some participants this means they will receive their second dose after delivery. Participants will be blinded to the vaccine they receive. The majority of participants will also be blinded to the interval between doses by incorporating the pertussis (whooping cough) vaccine into the trial schedule. Alternatively, for those who have already received their first dose of a COVID-19 vaccine prior to pregnancy, participants will receive a second dose of the same COVID-19 vaccine they have previously received. Participants will be followed up until one year after delivery. Blood samples will be taken from participants throughout the study. A cord blood sample will be taken after delivery. This is taken from the umbilical cord after the baby has been born and the cord has been cut; this is not a sample taken from the baby. A baby blood sample will then be taken at either 4-6 weeks or 10-12 weeks of age. Participants will be asked to complete a symptom diary and any significant medical events will be investigated. For a sub-group of participants breast milk samples will also be collected. The plans for this trial have been discussed with our research discussion group which is made up of pregnant women, those who have recently had a baby, and their partners and we have received input from this group about the design of the trial. Results of the trial will be disseminated in peer-reviewed scientific journals, internal reports, conference presentations and online publications.

Data flow:
Participating sites

- Recruitment and enrolment of participants.
- Storage of participant contact details, held securely with limited access to only research study members
- Study samples couriered to lead/sponor site and laboratories pseudonymised, labelled with Participant Idenitification Number.

Lead / sponsor site

- Recruitment and enrolment of participants.
- Storage of participant contact details, held securely with limited access to only research study members
- Study site samples labelled with Participant Idenitification Number
- Study samples from participating sites couriered to lead/sponsor site and laboratories pseudonymised, labelled with Participant Idenitification Number.

What personal data do you intend to use, and why? (List all categories)

Each site will hold contact details of their participants to enable correspondence with the participant for visit bookings and safety reviews. Study samples and eDiaries are pseudonymised using Participant Identification Numbers.

Will the personal data be identifiable, pseudonymised or anonymised (if a mix tick accordingly)

Identifiable	X	At participating sites, kept secure with strict controlled access
*Pseudonymised	X	Used data accessible to lead site and sponsor identified by Participant Idenification Number only
Anonymised		

**Confirm that the key to this data is kept securely away from the used data with strict controlled access*

List all organisations / agencies which will have access to the personal data collection used for this project / process

Study Sites TBA

Length of the study – include an assessment of the necessity and proportionality of the processing in relation to the purpose. Also include who, internally & externally, has been consulted in the preparation of this DPIA.

Length of study is 2 years. Identifiable information such as contact details will be stored for a minimum of 15 years from the end of the study. This includes storage of consent forms. Storage of these data will be reviewed every 15 years and files will be confidentially destroyed if storage is no longer required. Considerations at the time of this review will include the value of retaining this information for participant safety (e.g. to inform participants of unexpected safety signals emerging from post-licensing surveillance), as a resource for the participants (e.g. if they wish to check which vaccines they have received in the study) and any regulatory requirements. Financial information will be stored for 7 years. De-identified research data maybe be stored indefinitely. If volunteers consent to be contacted for future research, a record of this consent will be recorded, retained, and stored securely and separately from the research data. If volunteers consent to have their samples stored and used in future research, information about their consent form will be retained and stored securely as per Biobanking procedures and SOP.

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits, and inspections- in line with participant consent.

If external organisations / agencies are involved, is there a contract or information sharing agreement in place with suitable clauses for data protection and data incident reporting,? If not why not?

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorised third party, without prior written approval of the sponsor.

Personally identifiable information will be shared with Public Health England regarding SARS-CoV2 PCR test results depending on the most up to date legal requirement to report on Notifiable Diseases at the time.

RISK

Can you achieve your objectives using anonymised data? – see ICO Code of Practice on Anonymisation

Yes			
No	X	Why not?	Multiple samples will be taken from the participant over the study period of 2 years. Psuedonymised data (Participant Idenitification Number) is required to link these samples to the same participant.

What are the benefits to the individual of their personal data being used for this purpose?

This process will ensure complete and accurate data be generated to meet the study objectives and inform the general public of the findings.

What are the organisational benefits of the individual's personal data being used for this purpose?

This process will ensure complete and accurate data be generated to meet the study objectives and inform the general public of the findings.

What are potential negative impacts to the individual of their personal data being used for this purpose in the event of a Data Breach occurring?

Data breach would occur at the participating site level as only pseudonymised data I transferred to the lead site and sponsor.

How will you avoid causing unwarranted or substantial damage/distress to the individual when using their personal data for this purpose?

Ensuring that data remain secure with strict access at the participating sites.

Is the data already held by St George's?			
Yes			
No	X	Only data of the site's particpants will be held there	
Is it held by one of the partner organisations / agencies involved in this process/project?			
Yes	X		
No		Which agency will be collecting the data	Participating study sites TBA
Have you told the individuals whose personal data you want to use for this purpose, how and why you intend to use their data?			
Yes	X	Participants will consent to this	
No			
If not, are you intending to tell them?			
Yes			
No		Why not?	
Do you already have the individual's consent to use their data for this purpose?			
Yes			
No	X	Why not?	Study is currently in set up
If not, are you going to ask for their permission?			
Yes	X	Once the study is approved	
No		Why not?	
Have individuals been given the opportunity to refuse us permission to use their data for this purpose?			
Yes	X	Participants will have to agree to this to take part in the study	
No			

How will you make sure that the personal data you are using is kept accurate and up to date?

Regular monitoring procedures will take place throughout the study.

What steps or controls are you taking to minimise risks to privacy?
Please tick those which apply and provide details of how each is ensured

• √ Risks to individual privacy are minimal • √ Personal data is pseudonymised • Encryption of data at rest, i.e. when stored	

• √ Encryption used in transfers • √ Information compliance training for staff will be completed - data protection, information security, FOI • √ Adherence to privacy by design principles • Special category personal data is not used • √ Participant opt out at any stage of the research • √ Personal data kept in the UK • √ Research is not used to make decisions directly affecting individuals • Short retention limits • √ Restricted access controls • Other (please specify)	The Investigators will maintain appropriate medical and research records for this trial, in compliance with GCP and regulatory and institutional requirements for the protection of confidentiality of volunteers. The Chief Investigator, co-Investigators and clinical research nurses will have access to records. The Investigators will permit authorised representatives of the Sponsor(s) and Host institution, as well as ethical and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress.

How long will you need to hold the personal data for after the study has completed?

15 years

How will you make sure that you are holding data for the appropriate length of time and no longer?

In compliance with GCP and regulatory and institutional requirements.

How will the data be held /stored?

The investigators will maintain appropriate medical and research records for this trial, in compliance with GCP and regulatory and insititutional requirements for the protection of confidentiality of volunteers.

Will you be using any electronic and/or paper Case Report Forms (CRFs) to collect data? If so what are these and how will they be held securely and managed at the end of the project?

Both paper and electronic CRFs will be used to collect data. Electronic data (study data) will be entered and stored in REDCap.
All protocol-required information will be collected in CRFs designed by the Investigator. All source documents will be filed in the participant file. Source documents are original documents, data, and records from which the participant CRF data are obtained. For this study, these will include, but are not limited to, volunteer consent form, blood results, GP response letters, laboratory records, diaries, medical records and correspondence.

Will personal data be transferred/shared between the organisations involved in this project? If so how?

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits, and inspections- in line with participant consent.

Will you be transferring personal data to a country or territory outside of the UK? *If yes, name countries and receiving parties*.

Yes – within EEA	X	Potential for anonymised/pseudonymised research data to be shared nationally/internationally for public health purposes, as stipulated in the funding agreement
Yes – outside of EEA	X	Potential for anonymised/pseudonymised research data to be shared nationally/internationally for public health purposes, as stipulated in the funding agreement
No		

How will you ensure that third parties will comply with data protection obligations?

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data will be released to any unauthorised third party, without prior written approval of the sponsor.
Any data shared with third parties will be anonymised/pseudonymised. Identifiable data will not be shared with any third parties to ensure participant anonymity.

What measures are in place to ensure only appropriate and authorised access to and use of, personal data?

The investigators will maintain appropriate medical and research records for this trial, in compliance with GCP and regulatory and insititutional requirements for the protection of confidentiality of volunteers. Data will remain secure with only strict access at the participating sites.

How will technical and organisational security be monitored/audited?

Information security policies will be in place including password protection, information governance training and GDPR training.

Study team members will follow organisational policies and procedures to comply with the Data Protection Act 2018.

Access will be strictly controlled and limited to appropriate study team members.

The sponsor is responsible for ensuring appropriate monitoring of the study.

This has been delegated to the CI and the lead research team.

The study will be monitored remotely and via site self- assessment. If required, participating sites will permit trial-related on site monitoring, audits, and regulatory inspection(s), providing direct access to source data/documents. Trial participants are informed of this during the informed consent discussion. Participants will consent to provide access to their medical notes.

During the COVID-19 outbreak, telephone visits are acceptable for collecting follow-up data and monitoring patients remotely. Relevant safety data will still be collected and the usual reporting process will be followed (see section 9.3 of study protocol).

A Trial Monitoring Plan will be developed and agreed by the Trial Management Group (TMG), TSC and CI based on the trial risk assessment which may include on site monitoring.

The processes reviewed can relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harm and completeness, accuracy, and timeliness of data collection

Monitoring can be done by exploring the trial dataset or performing site visits Study site team members will be expected to assist the sponsor in monitoring the trial. These may include hosting site visits, providing information for remote monitoring, or putting procedures in place to monitor the trial internally

Declaration

I confirm that the information recorded on this form is, to the best of my knowledge, an accurate and complete assessment of the potential privacy impacts of this study.

Name: Professor Paul Heath

Signature: 

Date: 23/07/2021

Institute Director (SGUL) or Care Group Lead (SGHFT)

Name: Julian Ma

Signature: 

Date: 23/07/2021

JRES Reviewer

Name: Sarah Burton

Signature: 

Date: 23/07/2021