Study Title: Neonatal Complications of Coronavirus Disease (COVID-19) Study

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Chief Investigator:	Professor Jennifer J Kurinczuk, NPEU, NDPH, University of Oxford
Investigators:	Dr Chris Gale, Imperial College London
	Professor Marian Knight, PI UKOSS, NPEU, NDPH, University of Oxford
	Professor Elizabeth Draper, PI PICANet, University of Leicester,
	Dr Don Sharkey, Clinical Associate Professor, University of Nottingham
	Dr Shamez, Ladhani, Public Health England
	Dr Helen Mactier, President, British Association of Perinatal Medicine
	Dr Cora Doherty Consultant Neonatologist, University Hospital of Wales, Cardiff
Sponsor:	University of Oxford University Offices Wellington Square Oxford OX1 2JD

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Chief Investigator Signature: 

Statistician Signature: Not applicable

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. KEY CONTACTS

Chief Investigator	Professor Jennifer J Kurinczuk, Director, National Perinatal Epidemiology Unit, Nuffield Department of Population Health, University of Oxford Email: jenny.kurinczuk@npeu.ox.ac.uk Phone: 077 7551 6686
Sponsor	University of Oxford University Offices Wellington Square Oxford OX1 2JD
Funder(s)	Department of Health and Social Care, through the Policy Research Programme, as a grant to the NIHR Policy Research Unit in Maternal and Neonatal Health and Care (PRU-MNHC), based at the National Perinatal Epidemiology Unit. **Contact:** Dr Alison Tingle, Senior Research Liaison Manager Science, Research & Evidence Directorate Department of Health & Social Care 7th floor, 39 Victoria St, Westminster, London SW1H 0EU alison.tingle@dhsc.gov.uk
Clinical Trials Unit	Not applicable
Statistician	Not applicable
Committees	Co-investigator group – chaired by Dr Chris Gale Parent, Patient and Public Involvement group – co-chaired by Ms Charlotte Bevan and Ms Rachel Plachcinski, co-leads of the PRU-MNHC PPPI group.

2. LAY SUMMARY

The newly emerged coronavirus SARS-CoV-2 leads to symptomatic coronavirus disease called COVID-19. The spread of COVID-19 is increasing and is recognised as an international public health crisis. COVID-19 raises three main issues in relation to the care of newborn babies:

- To date the reported incidence of COVID-19 disease in the newborn population is low, but information about this group is limited. National surveillance is therefore essential to understand the incidence, presentation, treatment and outcomes (including case fatality). This will help us to understand the mode of transmission: whether it is vertical from mother to baby during pregnancy, labour and birth; horizontal from mother to baby after birth (and the relationship between postnatal care practices); or nosocomial where transmission occurs in the healthcare setting.

- SARS-CoV-2 appears to be highly transmissible within healthcare settings. Many babies that require neonatal care have chronic respiratory illness (e.g. chronic lung disease) or are highly vulnerable (e.g. extreme preterm infants) and thus at risk of COVD-19 infection. Therefore, infants on neonatal units represent a high-risk population for severe COVID-19 and risk of death, and commonly used neonatal treatments such as non-invasive ventilation may increase transmission of SARS-CoV-2 within the neonatal unit.

- In cases where there is no vertical or horizontal transmission of SARS-CoV-2 it is nevertheless possible that COVID-19 infection in pregnancy affects outcomes for the baby indirectly. For example, through preterm birth which is a risk for pregnant women with a fever, or by the management of the mother because she is infected for example, because of delays in emergency care. Information describing such indirect impacts of COVID-19 in pregnancy has not been published to date.

Answers to these questions will provide essential information needed to guide the advice provided to pregnant women and new mothers as part of the Government's efforts to control the COVID-19 pandemic. It will also support decisions about how best to treat infected babies.

To address these uncertainties we propose a national surveillance programme using the standard British Paediatric Surveillance Unit (BPSU) approach. This study will run alongside and be cross-linked with a maternal surveillance study run through the United Kingdom Obstetric Surveillance System (UKOSS) (REC: 12/EM/0365), which is already in progress. We will later utilise linked data from the National Neonatal Research Database (NNRD) to describe neonatal treatment in detail in identified cases, and information about neonates treated in paediatric intensive care will be captured through the Paediatric Intensive Care Audit Network (PICANet). To complete the picture we will also have access to information from the on-going MBRRACE-UK national surveillance and confidential enquiries of COVID-19 related maternal and perinatal deaths. To ensure complete case ascertainment we will share information with Public Health England (PHE), the similar statutory bodies in the devolved nations and the Information Services Division in Scotland (ISD) will provide us with routine linked SMR02 (in-patient) data.

Using the standard BPSU system, we will ask paediatricians and neonatologists in the United Kingdom to report all newborn babies that need medical care who are confirmed as having COVID-19, or were born

to a mother with confirmed COVID-19. We will use the data from this study and the data collected in the UKOSS study to identify vertical transmission (mother to baby) and ensure that we identify all indirect neonatal effects of COVID-19.

3. SYNOPSIS

It may be useful to include a brief synopsis of the study for quick reference and/or to use as a standalone document. Complete information and, if required, add additional rows.

Study Title	Neonatal Complications of Coronavirus Disease (COVID-19) Study		
Internal ref. no. / short title	Neonatal complications of COVID-19		
Study registration	Not applicable		
Sponsor	University of Oxford Clinical Trials and Research Governance (CTRG) Joint Research Office, Boundary Brook House, Churchill Drive, Oxford, OX3 7GB		
Funder	Department of Health and Social Care, through the Policy Research Programme, as a grant to the NIHR Policy Research Unit in Maternal and Neonatal Health and Care, based at the NPEU.		
Study Design	National observational study		
Study Participants	Any baby: 1. That has a diagnosis of COVID-19 made on a sample taken before 29 days of age and receives inpatient care for COVID-19 (this includes postnatal ward, neonatal unit, paediatric inpatient wards, paediatric intensive care unit (PICU)) OR 2. Where the mother had confirmed COVID-19 at the time of birth or suspected COVID-19 at the time of birth that has subsequently been confirmed, and the baby was admitted for neonatal care		
Sample Size	Uncertain at this stage – too little information available to be able to estimate		
Planned Study Period	13 months surveillance with 6 months follow-up to ensure ascertainment of all outcomes.		
Planned Recruitment period	Start: As soon as all permissions are in place – 1st April 2020 End: 13 months after the start date – 31st April 2021		
	Objectives	Outcome Measures	Timepoint(s)
Primary (1)	To estimate the incidence of neonatal COVID-19 including	Incidence of confirmed SARS-CoV-2 in neonates that receive inpatient care	Collected during admission or after discharge/death

	nosocomial transmission		
Primary (2)	To estimate the incidence of vertically transmitted COVID-19	Incidence of confirmed neonatal SARS-CoV-2 from a sample taken within 12 hours of birth in neonates born to a positive mother	Collected during admission or after discharge/death
Secondary (1)	To describe the clinical presentation natural history and clinical presentation of neonatal COVID-19 and of nosocomial COVID-19	Clinical signs at presentation: respiratory rate, requirement for ventilation, temperature, other system involvement, multi-organ failure	Collected during admission or after discharge/death
Secondary (2)	To describe the clinical presentation of neonates whose mothers are COVID-19 positive	Clinical signs at presentation: respiratory rate, requirement for ventilation, temperature, other system involvement, multi-organ failure, and investigations	Collected during admission or after discharge/death
Secondary (3)	To describe the outcomes for neonates with COVID-19	Outcomes: complication as a consequence of COVID-19 e.g. chronic lung disease (y/n); discharge home (y/n); death (y/n); transfer (y/n); still admitted (y/n)	Collected during admission or after discharge/death
Secondary (4)	To describe the clinical treatments being used to manage neonatal with COVID-19	Management: respiratory support, cardiovascular support, treatment of fever and other complications; antiviral and other COVID-19 specific treatments used	Collected during admission or after discharge/death
Secondary (5)	To describe the neonatal secondary impacts of maternal management for COVID-19	Pre-term birth and reason, delayed resuscitation; Apgar scores, receipt of therapeutic hypothermia, mode of birth	Collected during admission or after discharge/death
Intervention(s)	Not applicable		
Comparator	Not applicable		

4. ABBREVIATIONS

BAPM	British Association of Perinatal Medicine
BPSU	British Paediatric Surveillance Unit
CAG	Confidentiality Advisory Group
CI	Chief Investigator
CRF	Case Report Form
CTRG	Clinical Trials & Research Governance, University of Oxford
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
MBRRACE-UK	The collaboration delivering national maternal and perinatal mortality surveillance
NNRD	National Neonatal Research Database
NDPH	Nuffield Department of Population Health
NHS	National Health Service
NPEU	National Perinatal Epidemiology Unit
PBPP	Public Benefit and Privacy Panel for Health and Social Care
PI	Principal Investigator
PICANet	Paediatric Intensive Care Audit Network
PICU	Paediatric Intensive Care Unit
PPPI	Parent, Patient, Public Involvement
PRU-MNHC	NIHR Policy Research Unit in Maternal and Neonatal Health and Care
REC	Research Ethic Committee
RES	Research Ethics Service
R&D	NHS Trust R&D Department
SOP	Standard Operating Procedure
UKOSS	UK Obstetric Surveillance System

5. BACKGROUND AND RATIONALE

Background

The novel coronavirus SARS-CoV-2 is pandemic and is increasingly being detected in the United Kingdom. The virus leads to coronavirus disease (COVID-19) in a proportion of infected patients with a higher risk of severe disease and mortality in older adults and those with co-morbidities. We expect a rapid increase in cases of COVID-19, a situation described as "the worst public health crisis for a generation" by the United Kingdom government, which has raised the national risk level to high.

To date there is only limited data describing the incidence, clinical course, treatments and outcomes of COVID-19 in newborn babies and children. A retrospective review of 1,099 cases of COVID-19 in China (14.2% of identified national cases at the end of January 2020) identified only 9 children (Guan et al., NEJM 2020). A retrospective study of 266 hospitalised children in Wuhan, China isolated the virus in only six children (range 1-7 years age), and only one child had severe disease requiring intensive care (Liu et al., NEJM 2020). Three cases of neonatal COVID-19 have been described (Lu et al., J Med Virol 2020), with the first case reported in the UK on 13th March, and as of 20th March two cases in total are known in the UK.

Transmission of neonatal COVID-19 appears to occur mainly in family clusters and a retrospective review of nine pregnant women with COVID-19 pneumonia in China found no evidence of vertical transmission (Chen et al., Lancet 2020). However, the recent UK cases raise the concern that vertical transmission is a potential issue as both mother and baby are infected in at least one of the UK cases. The virus is known to be contained within most bodily secretions and there are suggestions that faecal oral transmission occurs, raising the possibility of transmission from mother to baby at birth even if not prenatally.

Children and infants appear to be less severely affected by SARS-CoV-2 generally, but COVID-19 may lead to considerable mortality and morbidity in preterm infants or those with conditions commonly found in babies in neonatal units such as chronic lung disease. There are 184 neonatal units in the United Kingdom and approximately 90,000 infants require neonatal care annually; the 30 PICUs across the UK (including two private PICUs) treat about 3,000 neonates per year. Spread of the virus on neonatal units may be exacerbated by commonly used neonatal treatments such as CPAP and high-flow oxygen. The impact of COVID-19 in pregnancy remains uncertain but in addition to the potential for vertical transmission the disease may lead to neonatal complications such as preterm birth as a consequence of maternal fever due to COVID-19, or delay in managing maternal emergencies during labour and birth. Such neonatal impacts of maternal disease were seen in the 2009-10/H1N1 influenza pandemic (Pierce et al, BMJ 2011).

Rationale

The coronavirus SARS-CoV-2 leads to symptomatic coronavirus disease (COVID-19) spread of which is increasing and recognised as an international public health crisis. COVID-19 raises three main issues in relation to newborn babies who receive neonatal care.

- To date the reported incidence of COVID-19 disease in the newborn population is low, but information about this group is limited. National surveillance is therefore essential to understand the incidence, presentation, treatment and outcomes (including case fatality). This will help us to understand the mode of transmission: whether it is vertical from mother to baby during pregnancy, labour and birth; horizontal from mother to baby after birth (and the relationship

between postnatal care practices); or nosocomial where transmission occurs in the healthcare setting.

- SARS-CoV-2 appears to be highly transmissible within healthcare settings. Many babies that require neonatal care have chronic respiratory illness (e.g. chronic lung disease) or are highly vulnerable (e.g. extreme preterm infants) and thus at risk of COVD-19 infection. Therefore, infants on neonatal units represent a high-risk population for severe COVID-19 and risk of death, and commonly used neonatal treatments such as non-invasive ventilation may increase transmission of SARS-CoV-2 within the neonatal unit.

- In cases where there is no vertical or horizontal transmission of SARS-CoV-2 it is nevertheless possible that COVID-19 infection in pregnancy affects outcomes for the baby indirectly. For example, through preterm birth which is a risk for pregnant women with a fever, or by the management of the mother because she is infected for example, because of delays in emergency care. Information describing such indirect impacts of COVID-19 in pregnancy has not been published to date.

Answers to these questions will provide essential information needed to guide the advice provided to pregnant women and new mothers as part of the Government's efforts to control the COVID-19 pandemic and support decisions about how best to treat infected babies.

Research questions:

The research questions are:

1. What is the incidence of neonatal COVID-19?
2. What is the clinical presentation of neonatal COVID-19?
3. What clinical treatments are being used for neonatal COVID-19?
4. What is the incidence of nosocomial spread of neonatal COVID-19?
5. What are characteristics of infants with nosocomially acquired neonatal COVID-19?
6. What is the outcome of neonatal COVID-19?
7. What is incidence of vertical transmission of SARS-CoV-2 infection?
8. What are the secondary neonatal impacts (outcomes of maternal medical or obstetric management or neonatal management in the context of staff protection) of maternal COVID-19 infection in addition to vertical transmission?

Methodology:

We propose a national surveillance programme using the standard British Paediatric Surveillance Unit (BPSU) approach.

We will use the standard BPSU approach. Neonatal complications of COVID-19 will be added to the routine BPSU case notification cards that are sent to all paediatricians in the United Kingdom. The requests for notification will be sent weekly; normally they are sent monthly, but the need for information is such that more frequent surveillance will be carried out for this study. The reporters will be asked to notify any baby meeting the following case definition.

Case definition for surveillance

Any baby:

1. That has a diagnosis of COVID-19 made on a sample taken before 29 days of age and receives inpatient care for COVID-19 (this includes postnatal ward, neonatal unit, paediatric inpatient wards, PICU)

   OR

2. Where the mother had confirmed COVID-19 at the time of birth or suspected COVID-19 at the time of birth that has subsequently been confirmed, and the baby was admitted for neonatal care

Notifications will be returned to the BPSU and then forwarded to the research team. Once received by the research team a data collection forms will be sent to the doctor who notified the case to collect demographic (including identifiers) and clinical data.

This study will run alongside a maternal COVID-19 study run through the United Kingdom Obstetric Surveillance System (UKOSS), which is already in progress. We will later utilise linked data from the National Neonatal Research Database (NNRD) to describe neonatal treatment in detail in identified cases, and information about neonates treated in paediatric intensive care will be captured through the Paediatric Intensive Care Audit Network (PICANet). To complete the maternal and newborn picture we will also have access to information from the MBRRACE-UK national surveillance and confidential enquiries of COVID-19 related maternal and perinatal deaths, which is run from the NPEU. We will also share information with PHE and similar bodies in the devolved countries statutorily responsible for collecting case notifications of infectious diseases to ensure complete case ascertainment. The Information Services Division in Scotland (ISD) will also provide us with routine linked SMR02 (in-patient) data.

6. OBJECTIVES AND OUTCOME MEASURES

	Objectives	Outcome Measures	Timepoint(s)
Primary (1)	To estimate the incidence of neonatal COVID-19 including nosocomial transmission	Incidence of confirmed SARS-CoV-2 in neonates that receive inpatient care	Collected during admission or after discharge/death
Primary (2)	To estimate the incidence of vertically transmitted COVID-19	Incidence of confirmed neonatal SARS-CoV-2 from a sample taken within 12 hours of birth in neonates born to a positive mother	Collected during admission or after discharge/death

Secondary (1)	To describe the clinical presentation natural history and clinical presentation of neonatal COVID-19 and of nosocomial COVID-19	Clinical signs at presentation: respiratory rate, requirement for ventilation, temperature, other system involvement, multi-organ failure	Collected during admission or after discharge/death
Secondary (2)	To describe the clinical presentation of neonates whose mothers are COVID-19 positive	Clinical signs at presentation: respiratory rate, requirement for ventilation, temperature, other system involvement, multi-organ failure , and investigations	Collected during admission or after discharge/death
Secondary (3)	To describe the outcomes for neonates with COVID-19	Outcomes: complication as a consequence of COVID-19 e.g. chronic lung disease (y/n); discharge home (y/n); death (y/n); transfer (y/n); still admitted (y/n)	Collected during admission or after discharge/death
Secondary (4)	To describe the clinical treatments being used to manage neonatal with COVID-19	Management: respiratory support, cardiovascular support, treatment of fever and other complications; antiviral and other COVID-19 specific treatments used	Collected during admission or after discharge/death
Secondary (5)	To describe the neonatal secondary impacts of maternal management for COVID-19	Pre-term birth and reason, delayed resuscitation; Apgar scores, receipt of therapeutic hypothermia, mode of birth	Collected during admission or after discharge/death
Exploratory objectives	Not applicable		

7. STUDY DESIGN

A national observation study will be conducted using the standard BPSU British Paediatric Surveillance Unit (BPSU) methodology. The data flow is attached as Appendix A.

Eligible cases

Eligible cases for the study will be defined as follows.

Any baby or infant:

1. That has a diagnosis of COVID-19 made on a sample taken before 29 days of age and receives inpatient care for COVID-19 (this includes postnatal ward, neonatal unit, paediatric inpatient wards, PICU)

OR

2. Where the mother had confirmed COVID-19 at the time of birth or suspected COVID-19 at the time of birth that has subsequently been confirmed, and the baby was admitted for neonatal care

Data collection

The BPSU will include neonatal complications of COVID-19 on the surveillance card that is sent routinely to all paediatricians and neonatologist in the UK. The surveillance cards will be sent out on a weekly basis. The reporters will notify cases to the BPSU who will forward the notifications to the research team. The research team will then send the study-specific data collection form to the notifying doctor.

The data collected will include identifiers to: (i) cross-checking with other sources of data to ensure complete case ascertainment; (ii) de-duplication; (iii) later linkage to collect further treatment details and outcomes.

The identifier swill comprise:

Identifier	**Justification**
For the baby:	
NHS/CHI/HSCN Number	De-duplication and linkage
Date of Birth	Calculation of age at various events, de-duplication and linkage
Sex	As a clinical descriptor, de-duplication and linkage
Partial Postcode	To map the regional burden of disease
Ethnicity	As a clinical descriptor
Baby date of death	Calculation of age at death, age-specific risk of death, linkage
For the mother:	
NHS/CHI/HSCN number	Linkage

The clinical information collected will comprise: additional demographic descriptors, clinical descriptors, clinical management information and the outcome.

Where the outcome information is not known at the time of data return, the doctor will be re-contacted to collect this data later when this information is likely to be known.

The data will be collected on a data collection sheet formatted as 'fillable' pdf document (Draft attached as Appendix B). All the information required to complete the questionnaire will be available from the medical records and will not require the doctor to ask the parents for information. In line with the BPSU methodology and due to the need for complete information and urgency, parental consent will not be sought (other than in Northern Ireland – see below). Information notices will be provided in the form of posters and leaflets with additional information on the study specific website. Applications to the Confidentiality Advisory Group (CAG) for s251 support (England and Wales) and to the Public Benefit and Privacy Panel for Health and Social Care (PBPP) (Scotland) will be made in conjunction with the research ethics committee application. Given the necessity to collect date of birth of the baby in order to be able to evaluate the time from birth to a positive swab to assess the likely route of transmission, it has proved necessary to receive the full data of birth as part of the data collection. This is problematic for Northern Ireland. Previous BPSU studies have been approved to collect H&SC numbers (equivalent of NHS number in Northern Ireland) and to transfer this information out of Northern Ireland, with date of birth minimised to month and year. Such a minimisation is not possible for the purposes of this study. We sought approval from the Privacy Commissioner for Northern Ireland, under the emergency COVID-19 legislation, to allow this extended disclosure, however, this approval was not granted. It is therefore necessary for the notifying doctors in Northern Ireland to seek parental consent before they complete and submit the data collection form for eligible babies. The parent information leaflet has been modified accordingly and a consent form has been developed in collaboration with colleagues in the NIMCH office who regularly develop consent forms for these purposes. www.publichealth.hscni.net/directorate-public-health/service-development-and-screening/nimach)

Return of the notifications and completed data collection sheets will be via the NHS.net email system to ensure that the information is kept secure. The data will be extracted and entered into Excel spreadsheets in the first instance. Identifiable and clinical data will be kept in separate databases with a unique ID relating to each baby entered into both datasets. Once the study is established we will set up an Open Clinica database and enter the data already collected. We will also be able to make the Open Clinica database available for direct data entry by the clinicians. Anonymised datasets will be extracted for analysis.

If the data collection sheet is not returned within a week of the request for data, a reminder email will be sent to the notifying doctor. If the data collection sheet is still not returned after a further week we will telephone the notifying doctor.

Immediate analysis for surveillance purposes

The incidence of both neonatal COVID-19 and the incidence of babies born to mothers with COVID-19 infection that require neonatal care will be estimated cumulatively each month using an estimate of the monthly births and maternities respectively. Case fatality will also be estimated as deaths as a proportion of all confirmed cases. The proportion of COVID-19 associated neonatal admissions will be estimated using an estimate of the admissions to neonatal units. In the absence of concurrent national data, the denominators will be estimated from monthly totals of births and maternities in 2019 using data from the national MBRRACE-UK surveillance programme, and from total monthly neonatal unit admissions in 2019 using data from the National Neonatal Research Database. We will ensure that we use corresponding months from 2019 data to account for seasonal variations in both births and neonatal unit admissions.

We will also use data collected from the UKOSS study to identify cases due to vertical transmission.

Each incoming case will be reviewed by the investigator team, on a weekly basis in order to identify early signals from the surveillance of recurring patterns in presentation. For example, we may find all infections are nosocomial and would therefore examine characteristics of, for example, infections associated with particular modes of respiratory such as non-invasive ventilation. This information, together with the cumulative incidence and case fatality, will be fed through to PHE, PHS, PHW and PHNI, DHSC, NHSE, the devolved governments, and the Royal Colleges of Obstetricians and Gynaecologists and Paediatrics and Child Health and the British Association of Perinatal Medicine, and organisations responsible for ensuring that the care provided meets the needs of mothers and babies (for example CQC in England) to ensure that the information is immediately available to support policy and clinical decision-making.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

All neonates in the United Kingdom receiving care in hospital who are infected with COVID-19 and all newborn babies receiving care in a neonatal unit following birth to mothers infected with COVID-19.

8.2. Inclusion Criteria

Any baby:

1. That has a diagnosis of COVID-19 made on a sample taken before 29 days of age and receives inpatient care for COVID-19 (this includes postnatal ward, neonatal unit, paediatric inpatient wards, PICU)

OR

2. Where the mother had confirmed COVID-19 at the time of birth or suspected COVID-19 at the time of birth that has subsequently been confirmed, and the baby was admitted for neonatal care

8.3. Exclusion Criteria

There are no exclusion criteria other than babies who do not meet the inclusion criteria.

9. PROTOCOL PROCEDURES

9.1. Recruitment

Information about eligible cases in the UK will be sought via the BPSU system that involves all paediatricians across the UK who are routinely sent a BPSU surveillance card, for the purposes of this study the surveillance cards will be sent weekly. At inception, COVID-19 will be added to the BPSU surveillance card and doctors will be asked to notify the total number of eligible case they saw that

week. Once notified, the appropriate number of data collection forms will be sent to the notifying doctor to collect the study information about each eligible baby.

9.2. Screening and Eligibility Assessment

Not applicable

9.3. Informed Consent

Following the standard BSPU methodology, because of the need to identify duplicate cases, to collect the data urgently and to ensure that we have complete information about all eligible babies, consent from parents will not be sought. We will apply for s251 approval (England and Wales) and PBPP (Scotland) as the legal basis for the data collection that includes identifiable data. For the reasons given earlier, parental consent will be sought in Northern Ireland.

Following the information commissioner's advice, a layered approach to the provision of information for parents will be taken:

Posters and leaflets about the study will be emailed to all neonatal and paediatric intensive care units for printing and display in areas accessible to parents. We are unable to send physical copies in the current circumstances. The study webpage address and QR code will also be included on the posters and leaflet so that parents can access more information. Information about the study will included, alongside a privacy notice, on a study-specific page on the PRU-MNHC website. In Northern Ireland, the Northern Ireland specific parent information leaflet and consent form will be sent with each data collection form issued.

9.4. Randomisation

This study does not involve randomisation.

This study does not involve registration or enrolment

9.5. Blinding and code-breaking

Not applicable

9.6. Description of study intervention(s), comparators and study procedures (clinical)

Not applicable interventions and comparators are not involved in this study

9.6.1. Description of study procedure(s)

This is a data collection study only and thus does not involve additional clinical procedures

9.7. Baseline Assessments

Not applicable

9.8. Subsequent Visits

Not applicable

9.9. Sample Handling

Not applicable

9.10. Early Discontinuation/Withdrawal of Participants

Early discontinuation is not relevant.

Parents can chose to withdraw the information about their baby from the study. The fact that the infant was infected with COVID-19 or born to a mother with COVID-19 will be retained in the dataset to ensure that incidence rates are based on complete data. The additional identifiable and clinical and demographic data will be deleted from the dataset if parents request to opt-out their baby from the study. In Northern Ireland parents will be approached for consent and may chose not to participate in the study. They will also be able to opt-out later should they change their mind about participating.

9.11. Definition of End of Study

The start of the study is defined as the first month in which COVID-19 is included on the BPSU surveillance care. The end of the study will be defined as the 19th month following the start months (13 months for new case identification plus six months for follow-up data collection).

10. SAFETY REPORTING

Safety reporting is not applicable to this study that is a data collection only study and does not involve any interventions.

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

The statistical analysis plan will be finalised before the analysis takes place.

Health economics are not included.

The individual cases will be reviewed by the investigator team on a weekly basis to identify emerging signals about recurring patterns in presentation. For example, if there is an excess of nosocomial infection associated with particular modes of management such as non-invasive ventilation, this is important to know and the information will be fed through to decision makers as appropriate.

11.2. Description of the Statistical Methods

See the statistical analysis plan.

11.3. Sample Size Determination

There is too little information available as yet worldwide to estimate the likely number of eligible babies. Estimating this is one of the aims of the study.

11.4. Analysis populations

Both the surveillance case definition and the analytical case definition will be used in different aspects of the analysis.

11.5. Decision points

We will look at the data on a weekly basis. Advice will be provided to DHSC, PHE, NHSE, Welsh, Scottish and Northern Irish Governments. The study will continue.

11.6. Stopping rules

Not applicable

11.7. The Level of Statistical Significance

The level of statistical significance will be included in the statistical analysis plan.

11.8. Procedure for Accounting for Missing, Unused, and Spurious Data.

Data about all cases will be used even where some data items are missing.

11.9. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

This will be reported in the published paper.

11.10. Health Economics Analysis

Not applicable.

12. DATA MANAGEMENT

The plans for the data management of the study are outlined below. There is not a separate Data Management document in use for the study.

Notifications will be received by BPSU and emailed to the to the study team at the NPEU. Data collection sheets will be sent as 'fillable' pdf forms to the notifying doctor who will complete from information from the medical records of the neonate. For security the completed forms will be returned via the nhs.net email system. The forms will be downloaded on to NDPH secure servers and the data will be double entered into Excel spreadsheets held on NDPH secure servers in the first instance. Identifiable data will held in a separate database from the clinical data. A unique study ID number allocated to each baby will be entered into both databases. Once the study is up and running we will develop a study-specific Open Clinica data entry system, transfer in the data that have already been collected and then make the Open Clinica data entry externally available for direct data collection from the clinicians. Where completed

questionnaires are not returned within a week of request we will send a reminder email and follow up a week later by telephone if the form has still not been returned.

All data will be stored on password protected secure servers in the Nuffield Department of Population Health accessible by only authorised staff. The data flow diagram is given in Appendix A.

12.1. Source Data

Source data will come from the doctor completed data collection sheets.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

12.3. Data Recording and Record Keeping

The study data will be entered on to Excel spreadsheets in the first instance, because of the rapid nature of the establishment of the study. Identifiable and clinical data will be held separately. Once the study is up and running we will develop a study-specific data entry system in Open Clinica.

The participants will be identified by a unique study specific ID number in each data base.

Data will be retained for five years after completion of the study. Minimisation of identifiers will be carried out once the paper has been published; the rest of the study information will be retained for five years after publication of the paper. At five years' any remaining identifiers will be deleted and the completely anonymised data will be retained in perpetuity in line with DHSC requirements.

13. QUALITY ASSURANCE PROCEDURES

Data Collection sheets will be reviewed on arrival to ensure that there is internal coherence between the answers recorded. In the first instance, data will be double-entered into an Excel database. Once we have an electronic data entry system up and running, the notifying doctor will provide the data via single entry. Any missing values will be follow-up with the notifying doctor. In-coming cases will be reviewed on a weekly basis.

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

13.1. Risk assessment

A risk assessment and monitoring plan will be prepared soon after the study has opened (in view of the rapidity of establishing the study) and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol.

13.2. Study monitoring

Not applicable

13.3. Study Committees

Co-investigator group – to review all cases and provide on-going oversight of the study.

Parent, Patient, Public Involvement group – to provide review and PPPI oversight of the study.

14. PROTOCOL DEVIATIONS

Any deviations from the protocol will be documented on a protocol deviation form and filed with the study materials.

15. SERIOUS BREACHES

Not applicable

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

The Investigators will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3. Approvals

Following Sponsor approval the protocol, poster, leaflet, webpage text, privacy notice (Appendix D) and data collection form will be submitted to an appropriate Research Ethics Committee (REC), and HRA, the Confidentiality Advisory Group (England and Wales) and PBPP (Scotland).

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4. Other Ethical Considerations

Not applicable

16.5. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

16.6. Transparency in Research

Not applicable the research is non-interventional

16.7. Participant Confidentiality

The study will comply with the General Data Protection Regulation (GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by separating the clinical and identifiable information into two electronic database(s). Where information about date related events are needed these will be converted into days and weeks prior to transfer for analysis. All documents will be stored electronically and will only be accessible by study staff and authorised personnel. The study staff will undertake to safeguard the privacy of participants' personal data and have a contractual obligation to do so. All staff involved in this study have up to date IG and security training.

16.8. Expenses and Benefits

Not applicable

17. FINANCE AND INSURANCE

17.1. Funding

Funding for this study is from the Department of Health and Social Care, through the Policy Research Programme, as a grant to the NIHR Policy Research Unit in Maternal and Neonatal Health and Care, based at the National Perinatal Epidemiology Unit (PR-PRU-1217-21202), Nuffield Department of Population Health, University of Oxford.

17.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London).

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18. PUBLICATION POLICY

All investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the DHSC, Policy Research Programme. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

19. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Not applicable

19. ARCHIVING

Data will be retained for five years after completion of the study. Minimisation of identifiers will be carried out once the paper has been published; the rest of the study information will be retained for five years after publication of the paper. At five years' any remaining identifiers will be deleted and the de-identified data will be retained in perpetuity in line with DHSC requirements.

20. REFERENCES

Chen N, Zhou M, Dong X, Qu J, Gong F et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395(10223): 507-513.

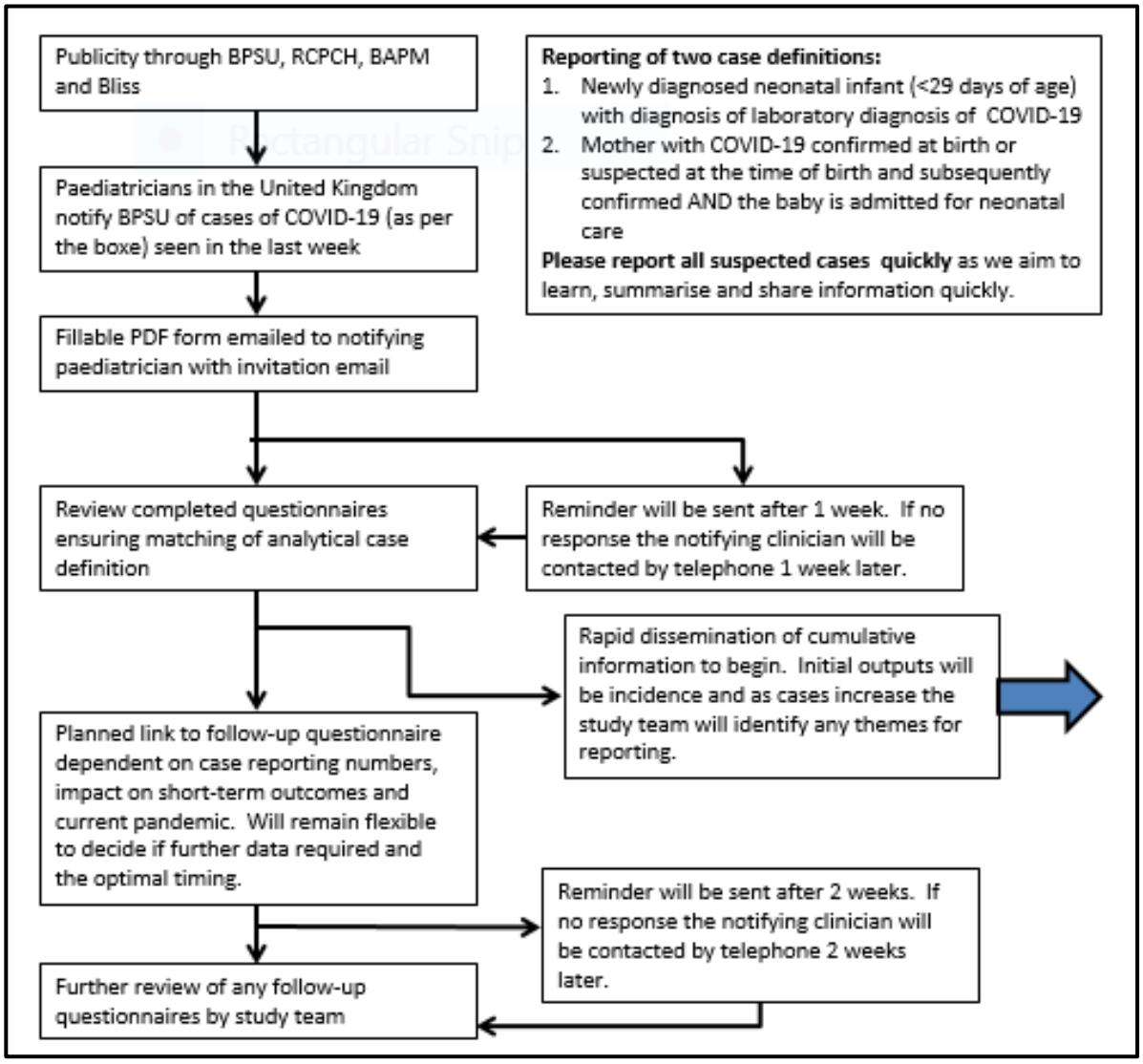
Guan WJ, Zheng-Yi N, Hu Y, Liang WH, Ou CQ et al. Clinical characteristics of coronavirus disease 2019 in China. NEJM 2020 2020 Feb 28[Online ahead of print]

Liu Q, Guan X, Wu P, Wang X, Zhou L et al. Early transmission dynamics in Wuhan, China, of novel coronavirus infected pneumonia. NEJM 2020 Jan 29[online ahead of print]

Li Y-C, Bai W-Z, Hashikawa T. The neuroinvasive potential of SARS-Co V2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol 2020; 1-4 doi 10.1002/jmv25728

Pierce M, Kurinczuk JJ, Spark P, Brocklehurst P, Knight M on behalf of UKOSS. Perinatal outcomes after maternal 2009/H1N1 infection: national cohort study. BMJ Br Med J 2011 Jun 14;342:d3214. doi: 10.1136/bmj.d3214.

21. APPENDIX A: STUDY DATA FLOW DIAGRAM



22. APPENDIX e: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	V2	11th May 2020	Jennifer J Kurinczuk	Changes relate to the need to seek parental consent in Northern Ireland. **Changes made to the following sections:** 3.Synposis – page 8 7.Study design – data collection – page 16 9.3.Informed consent – page 18 9.10.Early discontinuation – page 19

List details of all protocol amendments here whenever a new version of the protocol is produced.

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee and HRA (where required).