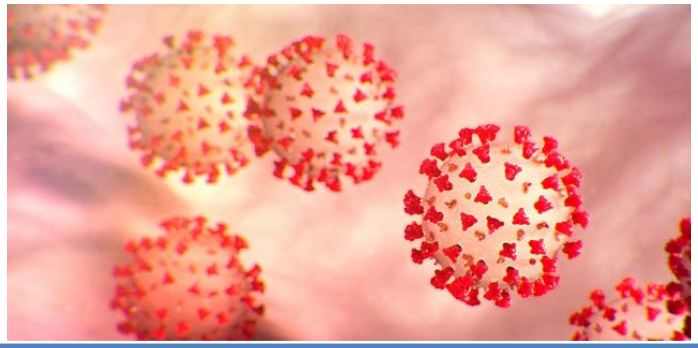

Neonatal Covid-19 Study (NCoS) protocol

Date: April 2020

Neonatal COVID-19 STUDY PROTOCOL

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Sponsor/s (in kind):
Hunter New England LHD
NSW Perinatal Services Network (SCHN)

Statement of Compliance
This document is a protocol for a research project. This study will be conducted in compliance with all stipulation of this protocol, the conditions of the ethics committee approval, the NHMRC National Statement on ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95).

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1. GLOSSARY OF ABBREVIATIONS & TERMS

Abbreviation	Description (using lay language)
COVID- 19	Coronavirus disease caused by SARS-CoV2 virus, is a new strain of coronavirus that was discovered in 2019 and has not been previously identified in humans.
COVID case	A person who tests positive to a validated specific SARS-CoV-2 nucleic acid test or has the virus identified by electron microscopy or viral culture, at a reference laboratory.
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2. The formal name of the coronavirus that causes COVID-19, as determined by the International Committee on Taxonomy of Viruses.
Neonate	An infant aged less than 28 completed days.

2. SOURCE/S OF FUNDING

No funding has been received for this research study at the time of application.

3. LAY SUMMARY AND AIMS

The aim of this project is to investigate the population health impacts of COVID -19 in mothers and their newborn infants cared for in tertiary and non-tertiary neonatal facilities. The research questions/hypothesis this study seeks to address include:

1. Incidence of COVID-19 in pregnant women and their newborn infants
2. Describe the outcomes for mothers and their newborn infants with COVID-19
3. Identify incidence of SARS-CoV-2 infection in the neonatal period and describe clinical course and outcomes for newborn infants with COVID-19
4. Collaborate with international COVID-19 registries to inform global variations and outcomes in care of newborn infants

In the midst of an unfolding global pandemic, there is a dearth of information about how COVID 19 infection affects neonates born to women with suspected or proven COVID 19. This study will contribute to an emerging and global body of information about COVID 19 in the perinatal period, enabling timely reporting and appropriate health service planning to ensure optimal outcomes for neonates, mothers and families.

4. BACKGROUND INFORMATION

The emergence of a novel coronavirus, termed SARS-CoV-2, and the potentially life-threatening respiratory disease that results, COVID-19, has rapidly spread across the globe creating a massive public health problem. Previous epidemics of many emerging viral infections have typically resulted in poor obstetric outcomes including maternal morbidity and mortality, maternal-fetal transmission of the virus, and perinatal infections and death.

Previous studies on the pneumonia outbreak caused by COVID 19 were based on information from the general population. Currently published studies aimed at evaluating the clinical characteristics of COVID-19 in pregnancy and the intrauterine vertical transmission potential of the infection, and published case reports suggest that there may be fetal compromise and pre-labour premature rupture of membranes associated with COVID 19 infection in neonates[1-8]. There is anecdotal reporting of increased incidence of premature birth in COVID-19 affected mothers; however it is unclear whether the virus was the causative factor, or if early birth was indicated because the mother was unwell.[9-11]

To date, there is lack of prospectively collected published data on clinical outcomes for COVID-19 positive neonates cared for in tertiary and non-tertiary neonatal facilities.

5. STUDY SCHEDULE

The study will be conducted according to the following timeline:

Ethics approval: 7th April 2020
CRF Ready for dissemination: 7th April.
Commencement of project officer: 1st May
Stakeholder consultation: Commence April 2020
Data collection: 1st May – 31st December 2020
Interim analysis: first week of each month (from June - December 2020)
Project completion: Depending on evolution of current situation.

6. DESIGN

This project uses a quantitative research methodology that will collect data using a prospective population based registry via a RedCap™ online database. Data collected on the study database is already routinely collected clinical data. This methodology is appropriate to answer the research question because it allows for de-identified input from multiple study sites, and ongoing quantitative analysis and reporting.

7. METHODOLOGY

Prospective clinical data will be recorded in a re-identified form on RedCap™ database for all mothers and neonates with symptoms of COVID-19 who are hospitalised in the perinatal period. Designated clinicians (local principal investigators) or their identified delegates at each facility/LHD will collect and enter the clinical data into the study database and keep a separate confidential master record of cases at each site. Time to complete data collection is anticipated to take no longer than 30 minutes per case.

Consultation with clinicians in tertiary and non-tertiary care facilities will be via the Australian and New Zealand Neonatal Network (ANZNN), Neonatal and Intensive Care Unit group (NICUS) and N34 clinical advisory groups.

8. Analysis

Descriptive analysis and reporting of comparison of outcomes of neonates in COVID suspect versus COVID confirmed infants.

9. Study participants

The inclusion criteria for participants in this study includes:

- Pregnant women and their neonates who satisfy confirmed case definition of COVID-19[12]

Exclusion criteria for this study includes:

- Pregnant and/or post-partum women and neonates who do not meet suspect or confirmed case definition of COVID-19

10. Recruitment

Designated local clinicians who already have access to the target participant group will identify mothers suspected with COVID-19 infection OR confirmed positive cases that fit the selection criteria. Participants identified as meeting recruitment criteria will be provided with written information about the study being conducted.

10. Consent, Privacy and confidentiality

A waiver of participant consent is being sought for this study in accordance with paragraph 2.3.9 and 10, chapter 2 of the National Statement.[13] Consent waiver criteria are addressed in the following table:

a) Involvement in the research carries no more than low risk (see paragraphs 2.1.6 and 2.1.7) to participants.	✓	Owing to the observational nature of this study (standard care) there is no foreseeable risk of harm or discomfort to participants.
b) The benefits from the research justify any risks of harm associated with not seeking consent.	✓	In the context of the COVID-19 pandemic the benefits of timely data collection proposed in this study far outweighs any foreseeable risk (none) of harm to participants. The study should in fact improve clinical care and outcomes for women and neonates with COVID-19
c) It is impracticable to obtain consent (for example, due to the quantity, age or accessibility of records)	✓	This would be applicable in cases where women were ventilated or receiving intensive care treatments.

d) There is no known or likely reason for thinking that participants would not have consented if they had been asked	✓	This study is capturing information already being recorded in de-identified form with the potential to improve care and outcomes for participants involved in the study.
e) there is sufficient protection of their privacy	✓	Individual identifiers will be removed from the data and replaced with codes in the password-protected (sitting on a local secure server authentication required) RedCap™ system.
f) there is an adequate plan to protect the confidentiality of data	✓	The master list for the de-identification will be stored separately to the de-identified data. Data base and master lists will be retained for 7 years after completion of the project.
g) In case the results have significance for the participants' welfare there is, where practicable, a plan for making information arising from the research available to them.	✓	Study updates and significant preliminary findings will be shared through regional news and various COVID-19 websites.
h) The possibility of commercial exploitation of derivatives of the data or tissue will not deprive the participants of any financial benefits to which they would be entitled	✓	No commercial exploitation of data, nor deprivation of financial benefits to participants.
i) The waiver is not prohibited by State, federal, or international law.	✓	No legal prohibitions anticipated.

11. ADMINISTRATIVE ASPECTS

11.1 Ethics and Regulatory Compliance

This study will be conducted according to ICH Good Clinical Practice 1995 and local regulations according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Therapeutic Goods Administration DSEB July 2000) and in compliance with applicable laws and regulations. The study will be performed in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans 2007, the NHMRC Australian Code for the Responsible Conduct of Research 2007, and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2008. To this end, no patient will be recruited to the study until all the necessary approvals have been obtained and the patient has provided written informed consent. Further, the investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a participant. In this circumstance the principal investigators and HREC will be advised immediately.

11.2 Confidentiality

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All laboratory specimens, evaluation forms, reports and other records will be identified in a manner designed to maintain participant confidentiality. All information will be stored securely using the REDCap research data capture and management system supported by the University of Sydney. Any hard copy documentation will be stored securely at study sites and will only be available to staff directly involved with the study and once entered or uploaded into REDCap such documentation will be shredded.

Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by its designee, Regulatory Authorities or the Human Research Ethics Committee. The investigators and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study.

11.3 Protocol Amendments

Approval of amendments by the Institutional HREC will be required prior to their implementation. In receive approval/advice of the revised consent form prior to implementation of the change. In addition, changes to the data collected, if required, will be incorporated in the amendment.
The investigator should not implement any changes to, or deviations from, the protocol except where necessary to eliminate immediate hazard(s) to trial participant(s).

11.4 Data Handling and Record Keeping

All trial data required for the monitoring and analysis of the study will be recorded on the (e)CRFs provided. All required data entry fields must be completed. Data corrections will be done according to the instructions provided. A random sample of entries will be cross checked with the medical record to validate accuracy of data collection.
Source documents pertaining to the trial must be maintained by investigational sites. Source documents may include a participant's medical records, hospital charts, clinic charts, the investigator's participant study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the case report forms serves as part of the investigator's record of a participant's study-related data.
This is a study involving pregnant women and research records should be retained according to NHMRC Guidelines for the retention of documentation involving pregnant women. All medical records will be retained for at least 25 years after publication of the final study report.
Guidelines on retention of other research related documents are continually under review. We plan to retain all documents for 7 years and then review according to current guidance at that time.[13]

Data can be used for future research purposes and shared with other researchers under the following conditions:

- The researchers will nominate a member of the research team at LHD and State Level to be responsible for data sharing.
- There are no individual identifiers remaining in the data and it is provided to other researchers in de-identified format.
- The researcher will ask others who wish to access the data for a copy of their ethics approval to do so before the data is shared for secondary research purposes. The researcher will

maintain a copy of other researchers' ethics approval for their records.

- The researcher will transfer the data to other researchers by sharing a link to the secure RedCap study database.
- The researcher will report to the HREC the number of times the data has been accessed for a secondary research purpose on their Annual Monitoring Report.

11.5 Study Monitoring

Data from this study will be monitored by the Principal Investigators and Project Officer or their delegates. Monitoring will include centralised review of CRFs and other study documents for data accuracy and completeness.

11.6 Publication and dissemination of results.

- Study will provide real-time data, as well as periodic reports to stakeholders in the form of weekly or monthly updates.
- Study will enable contemporaneous access in summary form of clinical data for use by clinicians and policy makers around perinatal COVID-19 best practice.
- A Clinical Study Report which summarises and interprets all the pertinent study data collected will be issued which may form the basis of a manuscript intended for publication.
- Consumer friendly summaries of the data reports will be produced and be sent in newsletter format to the families included in the registry.
- A Writing Committee to draft manuscript(s) will be appointed. Manuscript(s) will be submitted to peer-reviewed journal(s). The Writing Committee will develop a publication plan, including authorship, target journals and expected dates of publication.

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