

## Welcome to our April ON TRACK Network Newsletter

**Kia ora.** With the current COVID-19 pandemic in this month's edition of the ON TRACK newsletter we provide: a summary of the evolving evidence on the virus's impact on pregnancy; links to COVID-19 guidance for pregnant women and their healthcare providers; information on how the clinical trials community is responding; and updates on current New Zealand maternal and perinatal clinical trials.



### COVID-19 and pregnancy

As coronavirus 2019-nCoV is new, little is known about its effect on pregnancy. COVID-19 infection typically presents with fever and cough, and may progress to pneumonia. The physiological changes of pregnancy predispose women to pneumonia with subsequent effects on maternal and fetal morbidity and mortality, hence women and healthcare providers are understandably anxious. However, limited evidence and expert opinion around the world currently suggests COVID-19 is unlikely to affect the fetus or be associated with worse outcomes for pregnant women compared to the general population.

Current data on **maternal and perinatal outcomes** suggest:

- **Pregnant women are not more susceptible to acquiring COVID-19 than non-pregnant women**
- **Vertical transmission is possible, although the proportion of pregnancies affected and the significance to the infant has yet to be determined**
- **Most pregnant women will have mild to moderate cold/flu-like symptoms**
- **There is no current data on pregnancies that are ongoing after the mother has recovered from COVID-19, and no data on first or second trimester cases or on effects on fetal growth**
- **Obstetric decision making around delivery and neonatal care should be guided by clinical indications.**

**Neonatal outcomes** 33 infants born to mothers with COVID-19 infection in Wuhan, China showed mild clinical symptoms only and had favourable outcomes. Three infants had symptomatic COVID-19 with the most seriously ill neonate likely to be symptomatic from prematurity, asphyxia, and sepsis, rather than the infection itself (DOI:[10.1001/jamapediatrics.2020.0878](https://doi.org/10.1001/jamapediatrics.2020.0878)).

The first **systematic review** exploring maternal and perinatal outcomes of COVID-19 infection has been published (DOI: <https://doi.org/10.1016/j.ajogmf.2020.100107>). 79 pregnant women with a confirmed coronavirus related illness, including Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) or COVID-19 (19 studies). 41 pregnancies were affected by COVID-19, 12 by MERS and 26 by SARS. The authors concluded that mothers with coronavirus related illness are at increased risk of miscarriage, preterm birth, preeclampsia, and caesarean delivery, and their babies are at higher risk of perinatal death and admission to the NICU, compared to the general population. The authors found no published cases providing clinical evidence of vertical transmission. It should be noted this review had several limitations and the data itself is limited. **It focussed largely on sick women (>90 % of all women included had pneumonia).** More reassuringly this week the AJOG has published a case series of 43 women with COVID-19 at two New York hospitals over a period of two weeks in March (available online [here](#)). One third were asymptomatic at diagnosis and although most of these (71%) went on to develop symptoms only 14% of the whole series exhibited severe or critical disease; **86% possessed mild disease only.** Of those that were delivered during the time period 55% (n=10) had uncomplicated vaginal births.

With new evidence emerging daily, **we encourage healthcare providers to keep up to date with the latest evidence coming to light as the COVID-19 pandemic continues.**

**Keep up to date with the latest findings and evidence by visiting the following:**

- **NZ Ministry of Health** <https://www.health.govt.nz/our-work/diseases-and-conditions/covid-19-novel-coronavirus>
- **RANZCOG** <https://ranzocg.edu.au/statements-guidelines/covid-19-statement>
- **Cochrane** <https://cgf.cochrane.org/news/covid-19-coronavirus-disease-fertility-and-pregnancy>
- **JAMA Network** <https://jamanetwork.com/journals/jama/pages/coronavirus-alert>
- **British Association of Perinatal Medicine** <https://www.bapm.org/pages/182-perinatal-covid-19-resources>
- **RCOG** <https://www.rcog.org.uk/en/guidelines-research-services/guidelines/coronavirus-pregnancy/>
- **European Society of Human Reproduction and Embryology** <https://www.eshre.eu/en>
- **Action on Pre-eclampsia (APEC)** [apec.org.uk](http://apec.org.uk)





## What happens to clinical trials research during a global pandemic?

Clinical trials often require additional activities such as clinic visits by participants. Those who agree to participate have done so with an understanding of what their involvement will entail, and they are informed of all protocol procedures, clinic visits and all other expectations of them. Clinical trial investigators are responsible for following Good Clinical Practice (GCP) and to ensure trial data remain accurate and robust. So, when a pandemic such as COVID-19 occurs requiring physical distancing, self-isolation and significant changes to usual clinical care, clinical trial practice has to change too, but trial participants must be kept safe and fully informed, and where possible investigators must comply with approved trial protocols. Fortunately, guidance is provided from various global agencies to help all those involved in clinical trials during these unprecedented times.

**New Zealand Health & Disability Ethics Committees** (HDECs) are ministerial committees, whose function is to ensure all research involving human participants meets established ethical standards. In response to the pandemic a '**COVID-19 Emergency Response Ethical Review Operating Procedure**' has been published to expedite robust ethics review of research applications that have a COVID-19 element. This reflects the importance of new research and amendments to active research concerning COVID-19 being approved and rolled out across New Zealand as soon as possible. Full guidance: <https://ethics.health.govt.nz/home>

**Australian Government Department of Health COVID-19 Guidance for Clinical Trials** Australian territory Departments of Health, the Therapeutic Goods Administration (TGA - responsible for approving drug trials in Australia), National Health and Medical Research Council (NHMRC) and the Clinical Trials Project Reference Group (CTPRG) provide advice to everyone concerned with delivering clinical trials regarding the COVID-19 pandemic (<https://www1.health.gov.au/internet/main/publishing.nsf/Content/Clinical-Trials>). Principles of the guidance are:

- **Protecting the safety and well-being** of patients, research participants and their families, and health care professionals, researchers and other staff involved in patient care and research.
- **Public health systems remaining able to respond to the needs of the community** both those impacted by COVID-19 and those with non-COVID-19 related health needs.
- Maintaining the **conduct of research related to COVID-19 as a significant priority** while considering the initiation and continuation of other ongoing and proposed research that may also be critical for the well-being of patients, participants, communities and the research sector.
- Ongoing **compliance with or adherence to regulations, guidelines, codes, policies** and other standards, while allowing for interpretation of research responsibilities in the context of COVID-19, informed by flexibility, consultation and good sense.

The **U.S Food and Drug Administration (FDA)** who regulate clinical trials originating from the US have also published guidance to assist those overseeing clinical trials during the pandemic. The FDA acknowledge challenges may arise from quarantines, site closures, travel limitations, interruptions to the supply chain for investigational drugs, and other considerations if site personnel or trial participants become infected with COVID-19. The guidance states:

**“the need to put new processes in place or to modify existing processes will vary by the protocol and local situation. For example, this assessment could include consideration of whether it is appropriate to delay some assessments for ongoing trials, or, if the study cannot be properly conducted under the existing protocol, whether to stop ongoing recruitment, or even withdraw trial participants.”**

Full guidance: <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders>

The **Medicines and Healthcare products Regulatory Agency (MHRA)** regulate clinical trials originating from the UK. They have stated they will be as flexible and pragmatic as possible with regard to regulatory requirements for clinical trials during this time. They recognise the fact that clinical trial resource may be absent or redeployed from research activities and trial management towards front-line care. Once again, as with other agencies the MHRA highlight the first priority should be the safety of trial participants. Full guidance: <https://www.gov.uk/guidance/managing-clinical-trials-during-coronavirus-covid-19>

So, despite the challenges posed by the COVID-19 pandemic to clinical trials research, it appears all clinical trial regulatory agencies from various regions are on the same page in their commitment to supporting the safety of trial participants first and foremost, while accepting a pragmatic approach to clinical trial management and continued regulatory oversight.





**Guidance on COVID-19 in pregnancy** RANZCOG is carefully monitoring the evolving COVID-19 pandemic. They are accessing expertise in Australia, New Zealand and around the world to enable them to publish up to date guidance for both pregnant women and healthcare professionals.

RANZCOG's advice and information **for pregnant women and their whānau** is provided as an online Q & A statement. As of 29<sup>th</sup> March it states "the safest place to birth your baby is in a hospital, where you have access to highly trained staff and emergency facilities, if they are required. It is important to emphasise that a woman's experience of labour and vaginal birth, or caesarean section, should not be significantly impacted and women should be encouraged, and supported, to approach this extraordinary time of their lives without fear or apprehension. **Medical intervention, other than that specifically related to infection control, should not differ significantly from usual practice.** Active mobilisation, use of water immersion in labour, nitrous oxide and epidural analgesia are not affected. "

The statement goes on to say "some babies born to women with symptoms of COVID-19 in China have been born prematurely. It is unclear whether coronavirus was the causative factor, or the doctors made the decision for the baby to be born early because the woman was unwell. **Newborn babies and infants do not appear to be at increased risk of complications from the infection.** " Full details: <https://ranzcof.edu.au/statements-guidelines/covid-19-statement>

Of note also is Te Rōpu Whakakaupapa Urutā/National Māori Pandemic Group has been established to bring together leading Māori medical health experts to provide health advice for whānau, iwi and health providers. RANZCOG's He Hono Wāhine is currently working to add information for hapū māmā (<https://ranzcof.edu.au/news/supporting-maori-wahine-and-whanau-during-covid-19>) .



Royal College of  
Obstetricians &  
Gynaecologists

Guidance for healthcare professionals on COVID-19 infection in pregnancy has also been published by the RCOG, Royal College of Midwives, Royal College of Paediatrics and Child Health, Public Health England and Health Protection Scotland. Although this is UK guidance it will be regularly updated with latest global data and publications making it a helpful resource for everyone. The guidance contains:

- Advice for health professionals to share with pregnant women
- Advice for all midwifery and obstetric services caring for pregnant women
- Advice for services caring for women with suspected or confirmed COVID-19
- Advice for services caring for women following recovery from confirmed COVID-19

Full details: <https://www.rcog.org.uk/en/guidelines-research-services/guidelines/coronavirus-pregnancy/>

**COVID-19 Registries** recording relevant medical information of pregnant women who have been affected by COVID-19 are being established globally including here in New Zealand. With limited information on the impact of COVID-19 in pregnancy, establishing these registries will enable rapid and secure collection of data that will provide much needed information for women and whānau and to inform optimal care of mothers and babies affected by COVID-19.

An ethics application is currently under review for the **New Zealand COVID-19 in Pregnancy Registry**. This is planned to include all women in New Zealand who are pregnant and up to six weeks after birth who have been diagnosed with COVID-19. The Registry aims to include women at all gestations of pregnancy cared for in the community and in hospital. Routinely collected information regarding the mother's health, current pregnancy and birth, and newborn health and COVID-19 status will be included.

It is expected that the Registry will be live within weeks. We will keep you updated on its progress and how to use the Registry for case notification.

## COVID-19 Clinical Trials Outcomes

COVID-19 clinical trials are rapidly being set up and conducted to inform best practice for management of people with suspected or confirmed COVID-19. It is important COVID-19 trials have input from patients, public and health professionals, and other stakeholders to identify, prioritise and agree the most important outcomes for COVID-19 clinical trials. The COVID-19 Core Outcomes Project is bringing people together to help ensure evidence generated from all COVID-19 clinical trials consistently addresses the impacts of disease and treatment in the most meaningful way with outcomes that are most important to patients. Find out more: [covid-19-cos.org](https://covid-19-cos.org)



**Save the date** **NZ College of Midwives 16<sup>th</sup> Biennial Conference** Christchurch 15<sup>th</sup>-17<sup>th</sup> Oct 2020 <https://www.midwife.org.nz/midwives/conference-2020/>



New Zealand Trials		New Zealand recruits
<b>C*STEROID Feasibility</b>	C*STEROID Feasibility: Corticosteroids before planned CS from 35 <sup>+0</sup> to 39 <sup>+6</sup> weeks	88
<b>DIAMOND</b>	Different Approaches to MOderate & late preterm Nutrition	318
<b>FIIX Trial</b>	The Fertility, IVF and Intrauterine Insemination trial in couples with uneXplained infertility	58
<b>LATTE Dosage</b>	The most effective and best tolerated dose of caffeine to reduce intermittent hypoxaemia	90
<b>Little Eye Drop</b>	Microdrop Administration of Phenylephrine and Cyclopentolate Eye Drops in Neonates	30
<b>OBLIGE</b>	Comparing two methods of starting an induction of labour in pregnant women (balloon at home versus hormone gel in hospital) to assess chance of vaginal birth	765
<b>PAEAN</b>	Preventing Adverse Outcomes of Neonatal Hypoxic Ischaemic Encephalopathy with Erythropoietin	58
<b>PIPPA</b>	Paracetamol and Ibuprofen in Primary Prevention of Asthma	1487
<b>PLUSS</b>	Preventing Chronic Lung Disease in Extremely Preterm Infants Using Surfactant + Steroid	39
<b>PROTECT</b>	IV pentoxifylline as adjunct therapy to improve long-term disability in preterm infants	24
<b>Recruitment completed - follow up to primary outcome ongoing</b>		
<b>ECOBABe</b>	The ECOBABe study (Early Colonisation with Bacteria After Birth)	
<b>GEMS</b>	Gestational Diabetes Mellitus Trial of Diagnostic Detection Threshold	
<b>MAGENTA</b>	Magnesium Sulphate at 30 to 34 weeks' gestational age: Neuroprotection Trial	
<b>PROVIDE</b>	Higher IV protein intake for extremely low birthweight babies in the first week after birth on survival free from neurodevelopmental disability at 2 years' corrected age	
<b>Childhood outcome studies</b>		
<b>hPOD@2YR Follow-up Study</b>	Hypoglycaemia Prevention in newborns with Oral Dextrose	
<b>STRIDER NZAus Childhood Outcome Study</b>	Sildenafil TheRapy In Dismal prognosis Early onset fetal growth Restriction (2-3 years)	
<b>TARGET Follow up Study</b>	Optimal glycaemic targets for women with gestational diabetes: the randomised trial	

## How are clinical trials across the ON TRACK Network being impacted by the COVID-19 pandemic?

Recruitment to the **C\*STEROID Feasibility study** is now closed. Although recruitment ceased early due to COVID-19 we are pleased to report all study objectives were achieved within nine months (original plan of 12 months). Results will be published in the coming months and be used to strengthen the main C\*STEROID trial anticipated to open later this year.

**DIAMOND, FIIX, LATTE Dosage, Little Eye Drop, OBLIGE** and **PIPPA** trials have all suspended recruitment until further notice.

**PIPPA Tamariki** website reports that even though there is no substantive evidence to support the suggestion that ibuprofen may worsen coronavirus infection in children, they have elected to recommend that all children in the ibuprofen arm of the study should temporarily take paracetamol if required for fever and pain (<https://pippatamariki.ac.nz/posts-page/>).

**PAEAN** trial coordinators are advising sites to follow local site/health district policy, but if permitted, to continue recruiting and collecting all six monthly follow up.

**PROTECT** trial recruitment is continuing where possible, although some units have made the decision to suspend recruitment.

**PLUSS** trial have communicated their status via Twitter as pictured. The trial is still recruiting at Middlemore and Auckland hospitals.

All trial investigators are keeping trial participants up to date with the latest COVID-19 implications via direct communications, through their websites and social media.

