ON TRACK NETWORK
BETTER HEALTH FOR MOTHERS AND BABIES
Te Awhi Rito

ON TRACK

Welcome to our September ON TRACK Network newsletter

Kia ora. Welcome to the September edition of ON TRACK news. This month we invite clinical trial concepts for our next trial development workshop and hear from concept lead investigators who participated in the last workshop, we look at the ETTNO trial in Update Your Practice, and we take a look at the latest evidence concerning COVID-19 and pregnancy.

ON TRACK Network Educational Site Visits

Despite any uncertainty with recent and further potential changes in New Zealand's COVID-19 alert levels, we are continuing to host our ON TRACK Network educational site visits. We receive lots of interest in these enjoyable sessions and are pleased to be continuing to offer them. Educational site visits provide the latest in evidence-based best practice in maternal and neonatal care on topics selected by sites as well as providing information on clinical trials research and getting involved with the ON TRACK Network.

We have visited 8 sites across New Zealand to date, and sessions are currently being planned for **Counties Manukau** and **Palmerston North**. If you want your site to participate next year speak with your Site Network Leader or email us directly (ontracknetwork@auckland.ac.nz). We have so many interesting topics available for discussion by your multidisciplinary teams that could really help to enhance your local clinical practice e.g.:

⇒ **Induction of labour - Developing national guidelines and filling the evidence gaps**
⇒ **Nutritional management of the moderate-late preterm baby**
⇒ **Glucose levels in babies: too high, too low and does it matter?**
⇒ **Antenatal and intrapartum interventions to improve outcomes after pre-term birth – what can midwives and obstetricians do?** ……..and that is just to mention a few!

Trial Development Workshop 2020 Concept update

Jane (third from left), Michelle (centre) & Professor Adrienne Gordon (centre right) who facilitated the group that selected Michelle's concept to help develop during workshop

During our 2020 Trial Development Workshop, Dr Michelle Wise, obstetrician at Auckland City Hospital and senior lecturer, University of Auckland, and Dr Jane Alsweiler, neonatal paediatrician at Starship Hospital and senior lecturer, University of Auckland, considered their concept titled '**Peer review of Induction of Labour (IOL) booking requests to improve adherence to a national guideline: a stepped wedge randomised trial**.' The aim of the trial is to determine whether an implementation strategy (including peer review of IOL requests) for district health boards is effective to ensure IOL practice in New Zealand is evidence-based. Here is what Drs Wise and Alsweiler had to say about their workshop experience.

"The two-day workshop was very helpful to refine the trial intervention and the primary outcome. We received considered feedback from consumers, Māori researchers, statisticians, midwives, obstetricians, and neonatologists. Our group was facilitated by Professor Adrienne Gordon, a very experienced researcher from Australia who challenged us and provided useful input."

"We learned about the ON TRACK Network's *Forum for Women & Whanau* which we can use as a resource when further developing the protocol. The workshop was hands-on, such that by the end, we had a working document that later became the basis for a grant application to the Health Research Council of New Zealand. We even brainstormed an acronym for the study: SAILING (Supporting Appropriate Inductions of Labour: Implementing a National Guideline)."

"**This was our second experience at an ON TRACK Network Trial Development Workshop, and we would highly recommend it as a safe and supportive network to share research ideas, find collaborators, and ensure that the research project you set out to do is feasible and of high quality.**"

ON TRACK Network Trial Development Workshop 2021: Call for concepts

Do you have an idea for a clinical trial? Why not submit it for development at the ON TRACK Network Trial Development Workshop 2021? The workshop provides you with the opportunity to develop your trial concept from an idea through to a structured plan, which may lead to a large collaborative multicentre clinical trial in New Zealand. The highly interactive and collaborative workshop aims to further develop clinical trials within the ON TRACK Network.

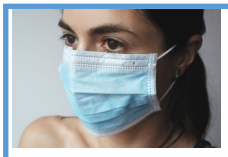
The workshop will be guided by highly experienced facilitators and interested investigators will contribute from all over New Zealand to provide information, advice, and guidance. There will be senior ON TRACK Network members and trialists, experts in health economics and trial statistics, Māori health representatives, and consumers available to share their knowledge and expertise.

Who will be participating in 2021?

Concept investigators and collaborators. Those who submit a concept will bring along their team to discuss and energise their concepts with expert input from colleagues experienced in clinical trials design and conduct.
Emerging researchers and those wishing to observe and gain skills in the process of clinical trial development.
Māori health and research representatives imparting their experience and knowledge for supporting Māori responsiveness in our research.
Consumers interested in clinical trial research in maternal and perinatal health.
Clinicians and researchers in maternal and perinatal health interested in new collaborations

If you have an idea for a clinical trial here is what to next:

- You can request a trial concept pro-forma now by emailing us (ontracknetwork@auckland.ac.nz). You will receive further instructions and support for your submission.
- The workshop is currently planned to take place in Auckland on **25th and 26th February 2021**. You will want to save the date and advise your team to save the date too.



What is the latest evidence concerning the impact of COVID-19 on pregnancy? SARS-CoV-2 infection in pregnancy: A systematic review and meta-analysis of clinical features and pregnancy outcomes

With New Zealand recently placed again into COVID-19 Alert Levels 2 and 3 it is timely to look at the latest evidence concerning the impact of COVID-19 on pregnancy. A previous systematic review that reported an aggregate summary of all coronavirus-related illnesses (including SARS and MERS) concluded that the risk of miscarriage, preeclampsia, preterm birth, and perinatal death is higher for infected mothers and their babies. However, the review included few data for outcomes related to COVID-19 specifically and emphasised the need for regular updates. We recommend you also watch for emerging literature suggesting the rates of very early preterm birth have fallen in some populations - the possible effects of lockdown and changed behaviours (hear more here).

A systematic review and meta-analysis published in the Lancet in July includes reports of pregnant women with confirmed COVID-19 from 6th April to 8th June 2020. 86 studies were included, 17 studies (2567 pregnancies) in the quantitative synthesis; other small case series and case reports were used to extract rarely reported events and outcomes. Most women (73.9%) were in the third trimester; 52.4% had delivered, half by caesarean section (48.3%). The proportion of Black, Asian or minority ethnic group members (50.8%); obesity (38.2%), and chronic co-morbidities (32.5%) were high.

- Most reported clinical symptoms were fever (63.3%), cough (71.4%) and dyspnoea (34.4%)
- Preterm birth before 37 weeks' gestation was common (21.8%), usually medically indicated (18.4%)
- Maternal intensive care unit admission was required in 7.0%, with intubation in 3.4%
- Maternal mortality was uncommon (~1%) and was higher in cohorts with higher rates of antiviral drug use (beta=0.03, p<0.001), likely due to residual confounding
- Maternal intensive care admission was higher in cohorts with higher rates of co-morbidities (beta=0.007, p<0.05) and maternal age over 35 years (beta=0.007, p<0.01)
- Maternal mortality Neonatal nasopharyngeal swab RT-PCR was positive in 1.4%

This analysis includes the largest number of pregnancies with COVID-19 reported to date and has raised concerns about higher risks of iatrogenic preterm birth and caesarean delivery. The evidence suggests **preterm birth is due to sick mothers needing to be delivered rather than preterm labour.** The review also provides reassuring evidence that **women and babies are not at increased risk of serious illness resulting from SARS-CoV-2.**

Update Your Practice: Effects of Liberal versus Restrictive Transfusion Thresholds on Survival and Neurocognitive Outcomes in Extremely Low-Birth-Weight Infants: The ETTNO Randomised Clinical Trial

JAMA. 2020;324(6):560-570. doi:10.1001/jama.2020.10690

Background: Use of red blood cell transfusions (RBCT) in the treatment of preterm infants is complex. RBCT are often given to extremely low birth weight infants (ELBW) in the first weeks of life to keep haemoglobin (HB) levels above a certain threshold. RBCT are also given due to acute blood loss (e.g. fetal-maternal haemorrhage or placental abruption) or due to clinical symptoms regardless of the Hb level. In treating anaemia, anaemia does not occur universally at the same Hb for all infants, but when there is an imbalance between oxygen delivery and consumption, which will vary among individuals. Symptoms of anaemia are non-specific and can be due to alternative causes such as sepsis, lung conditions, or gastro-oesophageal reflux. No universal Hb threshold for RBCT has been defined, meaning that some infants are exposed to progressive anaemia, which may result in gut hypoxia and injury.

There are generic risks of RBCT (e.g. transfusion-related reactions), and in the neonatal population there is increasing concern regarding significant morbidity and mortality in preterm infants associated with intra-ventricular haemorrhage (IVH), retinopathy of prematurity (ROP), broncho-pulmonary dysplasia (BPD) and necrotizing enterocolitis (NEC). Although RBCT is lifesaving in an acutely bleeding preterm infant, the optimal timing, and indicators for "top-up" RBCT are unknown. It is unclear whether a liberal or restrictive transfusion policy is best, particularly with regards to NEC, ROP, and IVH, as well as long-term neurodevelopmental outcomes. ETTNO is the first large trial looking into this to be published. There is another large trial, TOP trial, currently in progress. Transfusion thresholds of haematocrit levels used in both trials are provided below (source).

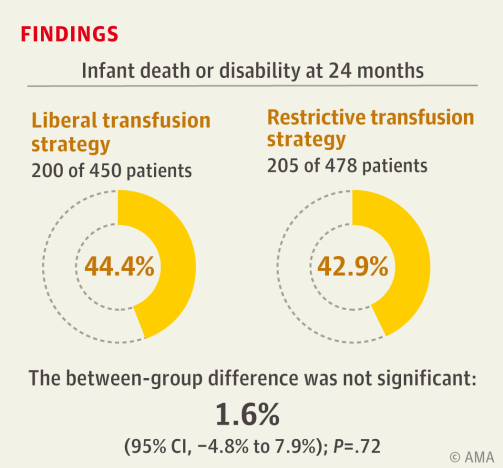
Age	Liberal, %		Restrictive, %	
	critical	non-critical	critical	non-critical
ETTNO Trial [52]				
3–7 days	<41	<35	<34	<28
8–21 days	<37	<31	<30	<24
≥21 days	<34	<28	<27	<21
TOP Trial [45]				
1 week	38	35	32	29
2 weeks	37	32	29	25
≥3 weeks	32	29	25	21

ETTNO, Effects of Transfusion Thresholds on Neurocognitive Outcome; TOP, Transfusion of Prematures.

Methods: The ETTNO trial was deigned to investigate if liberal versus restrictive transfusion strategies in extremely low-birth-weight infants (ELBW) improve survival and neurodevelopmental outcomes at 24 months of corrected age. This multicentre, randomised-controlled trial took place across 36 European level III/IV NICUs between July 2011 and November 2014. 1013 infants with a birth weight <1000 g were randomised to liberal (n = 492) or restrictive (n = 521) RBCT thresholds based on infants' postnatal age and current health state. The **primary outcome was death or disability, defined as any of cognitive deficit, cerebral palsy, or severe visual or hearing impairment, measured at 24 months of corrected age.**

Results: Among 1013 infants randomised (median gestational age at birth, 26.3 [interquartile range {IQR}, 24.9-27.6] weeks; 509 [50.2%] females), 928 (91.6%) completed the trial. Among infants in the liberal versus restrictive transfusion threshold groups, respectively, incidence of any transfusion was 400/492 (81.3%) versus 315/521 (60.5%); median volume transfused was 40 mL (IQR, 16-73 mL) vs 19 mL (IQR, 0-46 mL); and weekly mean hematocrit was 3 percentage points higher with liberal thresholds.

Interpretation: The authors concluded that among infants with birth weights of less than 1000 g, a strategy of liberal RBCT compared with restrictive transfusions did not reduce the likelihood of death or disability at 24 months of corrected age.



What do these results mean for New Zealand practice and future research? ETTNO Trial limitations included loss of follow up of 85 infants (8%), and death/BDP substantially lower than population data indicating sicker infants were not enrolled, which may have impacted outcomes. The trial did not stratify infants according to gestational and chronological age and yet it is likely that neonatal haemodynamics are variable in these groups. There were transfusions given outside of protocol guidelines with a net result that the haematocrit difference between groups was only 3%. This was lower than that of the PINT study (5%) which did suggest improved neurodevelopmental outcome in the liberal group. However, the ETTNO trial was large and did study the most vulnerable preterm group and allowed low haematocrit values to be reached in the restrictive group. Although no evidence of benefit was found, there was no harm either and there was a median decrease of one transfusion per infant. The results of this trial support the need for future research to better inform standardised use of RBCT in the treatment of preterm infants. The large USA TOP study is in progress and results awaited. In the meantime, it appears we can be reasonably confident that the trend toward more restrictive transfusion criteria does not appear to be harmful.

New Zealand Trials		New Zealand recruits
DIAMOND	DIfferent Approaches to MOderate & late preterm Nutrition	357
FIIX Trial	The Fertility, IVF and Intrauterine Insemination trial in couples with uneXplained infertility	134
LATTE Dosage	The most effective and best tolerated dose of caffeine to reduce intermittent hypoxaemia	114
Little Eye Drop	Microdrop Administration of Phenylephrine and Cyclopentolate Eye Drops in Neonates	64
NeoGluco	Neonatal Glucose Care Optimisation Study (I)	17
OBLIGE	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	842
PAEAN	Preventing Adverse Outcomes of Neonatal Hypoxic Ischaemic Encephalopathy with Erythropoietin	63
PIPPA	Paracetamol and Ibuprofen in Primary Prevention of Asthma	1719
PLUSS	Preventing Chronic Lung Disease in Extremely Preterm Infants Using Surfactant + Steroid	68
PROTECT	IV pentoxifylline as adjunct therapy to improve long-term disability in preterm infants	32
Recruitment completed - follow up to primary outcome ongoing		
C*STEROID Feasibility	C*STEROID Feasibility: Corticosteroids before planned CS form 35^{+0} to 39^{+6} weeks	
ECOBABe	The ECOBABe study (Early Colonisation with Bacteria After Birth)	
GEMS	Gestational Diabetes Mellitus Trial of Diagnostic Detection Threshold	
MAGENTA	Magnesium Sulphate at 30 to 34 weeks' gestational age: Neuroprotection Trial	
PROVIDE	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	
Childhood outcome studies		
hPOD@2YR Follow-up Study	Hypoglycaemia Prevention in newborns with Oral Dextrose	
STRIDER NZAus Childhood Outcome Study	Sildenafil TheRapy In Dismal prognosis Early onset fetal growth Restriction (2-3 years)	
TARGET Follow up Study	Optimal glycaemic targets for women with gestational diabetes: the randomised trial	

Save the date

ACTA Summit 2020 4 - 6 Nov 2020 (Virtual)

PSANZ IMPACT Network (Virtual) Meeting & Symposium 6 Nov 2020

Nga Maia National Hui/AGM 2020 - Waikato - 30 Nov - 2 Dec 2020

Society for Maternal Fetal Medicine 41st Annual Pregnancy Meeting 2021 - Las Vegas - 25-30 Jan 2021

PSANZ Annual Congress (2020 postponement) Sydney - 10-13 Feb 2021 (format to be confirmed)

RANZCOG 2021 ASM Hobart 14-17 Feb 2021

ON TRACK Network Trial Development Workshop - Auckland - 25 - 26 Feb 2021

RANZCOG 2020 NZ Annual Scientific Meeting (2020 postponement) Wellington - 16 - 18 Jun 2021

New Zealand College of Midwives 16th Biennial National Conference - Christchurch - 2-4 Sept 2021

PSNZ 72nd Annual Scientific Meeting 2021 - Rotorua - 2-5 Nov 2021