N-3 fatty acids for improvement of Respiratory Outcomes – The N3RO trial

Scientific title: *Docosahexaenoic acid (DHA) for the reduction of bronchopulmonary dysplasia in preterm infants born at less than 29 weeks gestational age: a randomised controlled trial.*

You are invited to take part in a study to help us find out if giving preterm babies extra DHA improves important respiratory (lung) outcomes associated with preterm birth. This is a multi-centre study coordinated by the Women's and Children's Health Research Institute, Adelaide.

What is docosahexaenoic acid (DHA) and why might it be important for preterm babies? DHA is a type of fat (sometimes called "omega 3 or n-3") that is found in breast milk, fish and fish oil. Because babies can't make much DHA they rely on the amount they get from their mother during pregnancy. Although preterm babies get a small amount of DHA from breast milk or formula, this is much less than they would have received from their mothers had they not been born early.

What studies have been done? Some years ago we tested the effect of increasing the supply of DHA to preterm babies. This was achieved by asking the mothers to take capsules that increased the natural level of DHA in their breast milk. When this high DHA breast milk was given to their babies we saw a modest benefit in the mental development of girls, but not boys, and it also suggested that fewer babies had lung disease.

However, the importance of both these effects was hard to judge. As a result at the WCH it was thought advisable to provide fish oil capsules to mothers who were providing breast milk for preterm girls. This practice was not adopted in any other centre in Australia or overseas because many people thought that it was possible that the benefits seen in the children who received high DHA breast milk arose by chance and testing child development at the age we did (18 months) is not always a good measure of longer term learning.

What is the new study? In order to resolve this important issue we have received support from the Australian Government to carry out a new study. The study will be larger and importantly, we have developed a new emulsion that allows us to get the DHA to the baby much sooner; we hope this will mean that we will see greater benefits to the health of preterm babies. Because a DHA or control solution will be given directly to the baby it doesn't matter how much milk they are getting.

What lung conditions can preterm infants get? Because preterm infants are born before many of their organs are mature, about half develop a lung condition called 'bronchopulmonary dysplasia', or BPD. This means that they still need breathing support or extra oxygen when they reach 36 weeks 'corrected' age (which is 4 weeks before they were due to be born). It is now thought that inflammation is one of the factors that lead to BPD. DHA is a known anti-inflammatory so it is possible that if the infant gets an adequate supply of DHA, it could help protect the lungs.

What does the study involve? If you choose to participate, your baby will be randomly assigned (like tossing a coin to decide) to receive one of two solutions – either one that contains extra DHA (around 3 times more than breast milk or formula) or one that does not contain any DHA. All babies will still receive some DHA through breast milk or infant formula as at present. Neither you, nor the clinicians nor the research team will be able to choose the group, nor will anyone in the care team know the group.

The study solution will be given to babies through their feeding tube three times a day, just before a normal feed. We aim to commence the solution as soon as possible after the first milk feed. The study solution will be given until your baby reaches 36 weeks corrected age.

During the study we will ask for 1-2 drops of blood to measure the amount of DHA in your baby's blood. This will be done once at the start of the study and once at the end of the study. Whenever possible the blood samples will be collected at the same time as your baby is having other tests. The blood samples are taken carefully by experienced collectors. If your baby has a line in place the blood will be taken from this, otherwise the sample will be taken by a 'heel prick' and your baby will receive pain relief beforehand.

We will look to see if your baby has BPD when they reach 36 weeks corrected age or discharge home, whichever occurs first. If you are breastfeeding you will be asked to provide a small sample (1 - 2 drops) of breast milk when your baby is around 36 weeks corrected age.

One of the research staff working on the study will review your medical records to document any pregnancy complications and details of your child's birth. Your baby's medical records will also be reviewed for feeding and health information.

Optional additional samples

The following samples are optional, if you decide not to have these samples taken you can still participate in the study. For those who choose to have these samples taken they will be used to measure immune markers (substances like antibodies) that provide information about how the immune system is developing and will help us to understand how DHA may help BPD.

The samples include:

- An extra 0.5 mls of blood (this is the same as around 1/10th of a teaspoon or 10 drops of blood), at the start of the study, on day 14 of life and at the end of the study. This will be collected at the same time as your baby is having other routine blood tests
- A cheek swab, once at the start of the study and once at the end of the study. The inside of the cheek is gently rubbed with a swab similar to a 'cotton bud'
- A stool sample at the start of the study and one sample every week until the end of the study. This will be collected from the nappy during a normal nappy change
- If your baby has a breathing tube one small amount of fluid (1-2 drops) from the tube. This will be taken during normal clinical care procedures or at the time your baby's doctors say the tube is no longer needed and is removed.

Future follow-up studies. DHA has the potential to improve longer-term outcomes. We would like to see the babies who participate in this study at two years of age and again in the early school years. If you would like to be informed about any such further studies we would contact you to see if you were interested in receiving any information.

However, we recognise that people often change their telephone number and address, and therefore cannot be contacted by researchers. To help keep in contact with you we are asking you to provide us with the names and contact details of persons who would be able to let us know your new contact details; these people are usually relatives or friends and are called 'alternate contacts'. If we needed to use one of the alternate contacts we would call them, explain who we are and that you were involved in a study and have given us their contact details so that they can put us in touch with you.

Study progress. When this study is completed we will send you a summary of the study findings. During the study we will also send you newsletters once or twice a year updating you on the progress of the study and keeping you informed of plans for future studies.

Risks and benefits of the study. There is no known increased risk to the health of your baby of giving extra DHA. In our previous trial of 657 preterm babies that were born at <33 weeks gestation, breast milk or formula with extra DHA was safely given to these infants. Blood tests will cause some temporary pain and may cause a short term bruise.

Your rights. It is entirely your decision to participate or not in this study. If you do decide to participate and are breast feeding we would ask that you don't take any fish oil capsules.

You are free to withdraw from the study at any time without explanation of why you have chosen to do so and without prejudice to you and your baby's current or future treatment. All information gathered will be treated with confidence and no information that could identify you or your baby will be released to any person not associated directly with the study, except in the case of a legal requirement to pass on personal information to authorised third parties.

This requirement is standard and applies to information collected both in research and non-research situations. Such requests to access information are rare; however we have an obligation to inform you of this possibility. The results of this trial may eventually be published in medical journals or presented at professional meetings, but you or your baby will not be identified in any way.

The blood and breast milk samples will be discarded at the end of this study unless you have consented to store them for future use. It is possible that new knowledge may become available to indicate that other nutrients or factors are important for breathing outcomes or child development relating to DHA supplementation. Stored samples would only be used by N3RO Investigators with the permission of the Human Research Ethics committee. Any stored samples will be identified by a study number only and will be discarded at the end of the proposed two year follow-up study. Stored samples will not be used for genetic testing. If you are providing breast milk for a preterm girl and choose not to participate we can advise you about how to increase the amount of DHA in your breast milk if you would like to do this.

Any questions? If you would like further information about the study please contact Dr Carmel Collins (8204 5755), Dr Andrew McPhee (8161 7631) or Dr Michael Stark (8161 7631).

This study has been reviewed by the Human Research Ethics Committee of the Women's and Children's Health Network (WCHN). Should you wish to discuss the study with someone not directly involved, in particular in relation to matters concerning policies, or your rights as a participant, or should you wish to make a confidential complaint, you may contact the executive secretaries of the committee, Ms Brenda Penny, WCH, 8161 6521.