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BMJ Open Protocol for assessing whether cognition of preterm infants <29 weeks' gestation can be improved by an intervention with the omega-3 long-chain polyunsaturated fatty acid docosahexaenoic acid (DHA): a follow-up of a randomised controlled trial

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ABSTRACT

Introduction Docosahexaenoic acid (DHA) is an omega-3 (n-3) fatty acid that accumulates into neural tissue during the last trimester of pregnancy, as the fetal brain is undergoing a growth spurt. Infants born <29 weeks' gestation are deprived the normal in utero supply of DHA during this period of rapid brain development. Insufficient dietary DHA postnatally may contribute to the cognitive impairments common among this population. This follow-up of the N-3 fatty acids for improvement in respiratory outcomes (N3RO) randomised controlled trial aims to determine if enteral DHA supplementation in infants born <29 weeks' gestation during the first months of life improves cognitive development at 5 years of age corrected for prematurity.

Methods and analysis N3RO was a randomised controlled trial of enteral DHA supplementation (60 mg/kg/day) or a control emulsion (without DHA) in 1273 infants born <29 weeks' gestation to determine the effect on bronchopulmonary dysplasia (BPD). We showed that DHA supplementation did not reduce the risk of BPD and may have increased the risk.

In this follow-up at 5 years' corrected age, a predefined subset (n=655) of children from five Australian sites will be invited to attend a cognitive assessment with a psychologist. Children will be administered the Wechsler Preschool and Primary Scale of Intelligence (fourth edition) and a measure of inhibitory control (fruit stroop), while height, weight and head circumference will be measured. The primary outcome is full-scale IQ. To ensure 90% power, a minimum of 592 children are needed to detect a four-point difference in IQ between the groups. Research personnel and families remain blinded to group assignment.

Ethics and dissemination The Women's and Children Health Network Human Research Ethics Committee

Strengths and limitations of this study

- This will be the first adequately powered randomised controlled trial to assess cognitive development following docosahexaenoic acid (DHA) supplementation in preterm infants born <29 weeks' gestation.
- This follow-up of the N-3 fatty acids for improvement in respiratory outcomes (N3RO) trial will provide sound evidence for the effect of enteral DHA supplementation on the cognitive development of infants born <29 weeks' gestation.
- Lost to follow-up 5 years after enrolment into the trial may contribute to risk of bias.
- Partial unblinding of study group allocation permitted under the primary protocol may contribute to risk of bias.
- Although bronchopulmonary dysplasia was the primary outcome of the original N3RO trial, childhood respiratory functioning is not assessed in this follow-up

reviewed and approved the study (HREC/17/WCHN/187). Caregivers will give informed consent prior to taking part in this follow-up study. Findings of this study will be disseminated through peer-reviewed publications and conference presentations.

Trial registration number ACTRN12612000503820.

INTRODUCTION

Medical and technological advances in the care of infants born preterm have increased their survival rates. However, there is a high risk of long-term health complications and neurological deficits with preterm birth,¹⁻⁴

including higher risks of cognitive deficits^{5 6} and behavioural problems^{3 6–11} compared with term-born counterparts. The risk and severity of poor outcome increases as gestational age decreases.^{4 8 12 13}

Nutrition is thought to be one modifiable influence on neurodevelopment in preterm infants, in particular the omega-3 (n-3) long-chain polyunsaturated fatty acid (LCPUFA), docosahexaenoic acid (DHA). During the last trimester of pregnancy, the fetus is estimated to acquire ~70 mg/day of n-3 LCPUFA, largely as DHA.¹⁴ Infants born preterm are deprived of the placental transfer of DHA and hence have lower neural tissue levels of DHA compared with infants born at term.¹⁵ It has been hypothesised that providing infants born preterm with DHA may enhance normal neurodevelopment and the most recent recommendations are that the preterm infant needs approximately 60 mg/kg/day DHA (about 1% of total dietary fatty acids) to approximate the fetal accumulation rate.¹⁶

Several randomised controlled trials (RCTs) have attempted to evaluate this hypothesis, with mixed results.^{17 18} Two RCTs compared the standard dose of DHA in breastmilk and preterm infant formula (20 mg/kg/day) to the estimated in utero accretion rate (60 mg/kg/day).^{19 20} In one trial, the DHA group showed greater problem solving skills at 6 months²⁰ and improved sustained attention at 20 months,²¹ although attrition was high. In the larger trial, assessment at 18 months revealed no difference in overall mean cognitive scores but fewer infants had developmental delay in the DHA group.¹⁹ No overall differences in IQ were detected in follow-up of these trials at seven²² or 8 years of age.²³ Interestingly, both trials suggested a benefit of extra DHA in infants born at the earliest gestations (<29 weeks or <1250 g) who are most vulnerable to experiencing neurodevelopmental deficit.^{19 20} While this is promising, both trials were significantly underpowered (with only 200 children in one trial¹⁹ and under 70 in the other²⁰) to detect an effect in this subgroup.

It is clear that current neonatal feeding practices are unable to replace the placental transfer of DHA¹⁶ and despite decades of research, we still do not know whether meeting the estimated requirement of DHA during the neonatal period improves cognitive outcomes in the most vulnerable subpopulation of preterm infants.^{17 19 20 22 23}

The N-3 fatty acids for improvement in respiratory outcomes (N3RO) RCT was designed to determine the effect of an enteral DHA emulsion (providing 60 mg/kg/day) on the incidence of bronchopulmonary dysplasia (BPD).²⁴ The DHA intervention did not lower the incidence of BPD in infants born <29 weeks' gestation and may have resulted in a greater risk of BPD.²⁴ However, the N3RO trial offers an ideal opportunity to resolve whether DHA supplementation is beneficial for the cognitive development of these most vulnerable preterm infants.

The N3RO trial infants are now reaching 5 years of age. Cognition develops rapidly across early childhood²⁵ and by 5 years most cognitive domains can be reliably assessed

using standardised psychometric tests.²⁶ IQ tests are considered a robust method of estimating an individual's overall cognitive ability. Executive function is an umbrella term referring to those skills essential for undertaking goal-oriented behaviours and includes inhibitory control which has been reported to be an area of concern for children born preterm.⁶

By assessing the cognition of the N3RO infants as they turn 5 years of age, we can determine whether providing infants born <29 weeks' gestation with DHA emulsion improves cognitive development. We hypothesise that providing the estimated in utero provisions of DHA to infants born <29 weeks' gestation will result in higher cognitive scores at 5 years' corrected age compared with infants who received the control intervention.

METHODS AND ANALYSIS

This protocol details the methods for a follow-up at 5 years of age of infants enrolled in the N3RO trial. Detailed methods of the N3RO trial have been published previously²⁴ and are summarised here.

The N3RO trial

A total of 1273 infants born <29 weeks' gestation were enrolled into the N3RO trial within 3 days of their first enteral feed. Infants were recruited between June 2012 and September 2015 from 13 centres in Australia, New Zealand and Singapore.²⁴ Infants were excluded if they had a major congenital or chromosomal abnormality, were participating in another fatty acid intervention trial, were receiving intravenous lipids containing fish oil, or if a breastfeeding mother was taking greater than 250 mg/day DHA through supplements.²⁴ Infants were randomised to the intervention or control group through a secure web-based computer-generated schedule stratified for the 13 centres, sex and gestational age at birth <27 weeks' or 27 to <29 weeks' gestation. Infants from multiple births were randomised individually. A statistician not otherwise involved in the N3RO trial generated the randomisation schedule.

The N3RO trial intervention

Infants were randomised to receive a DHA emulsion that provided 60 mg of DHA per kg of body weight per day (intervention group, n=631), or a control emulsion without DHA (control group, n=642).²⁴ Infants received the study intervention from enrolment to 36 weeks' post-menstrual age or discharge home, whichever occurred first. The emulsion was administered three times per day, immediately before an enteral feed through a nasogastric or orogastric tube for the duration of the intervention period. The DHA and control emulsions were isocaloric and identical in viscosity, colour and packaging and families, clinical staff and study personnel were blinded to group allocation.²⁴

Five-year follow-up study procedure

This is a follow-up of a predefined subsample of the N3RO trial infants from five of the Australian recruiting centres.

No additional interventions will be administered. Eligible N3RO infants will be invited to attend an appointment with a psychologist when they are 5 years' corrected age to measure child abilities on selected cognitive domains; age is corrected for prematurity to avoid a known bias in cognitive test scores.²⁷ Appointments will take between 45 min to 1.5 hours, depending on the child's abilities and speed while working through the IQ test tasks, and assessments will be conducted by personnel blinded to group allocation. Assessments for this follow-up study commenced 29 August 2018 and are expected to be completed on the 31 December 2020.

Families of eligible children will be emailed a letter of invitation 2 months before their child reaches 5 years' corrected age, followed by a telephone call to answer any questions and book appointments with families that wish to participate. Where necessary, families will be offered appointments at the family's home or at a location close to their home such as a school or community centre.

Participants and sample selection

Children who participated in the N3RO trial and were recruited from the five largest recruiting centres, John Hunter Hospital (New South Wales), King Edward Memorial Hospital (Western Australia), Mercy Hospital for Women (Victoria), Royal Women's Hospital (Victoria), and the Women's and Children's Hospital (South Australia) in Australia will be invited to participate in this follow-up study. Children will not be invited if they have previously been withdrawn from the N3RO trial or have died. Of the $n=702$ children enrolled between the five centres, $n=655$ will be eligible to be approached for the 5-year follow-up once deaths ($n=4$) and withdrawals ($n=43$) are excluded.

Outcomes and measures

Primary outcome

The primary outcome is full-scale IQ, as assessed by the Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition, Australian and New Zealand (WPPSI-IV). The WPPSI-IV is a battery of subtests that provides an assessment of general cognitive ability for preschoolers and young children (2:6–7:7 years). The WPPSI-IV has strong internal consistency and test-retest stability and sound psychometric properties.²⁸ The average reliability coefficient for the full-scale IQ is 0.95.²⁸

Secondary outcomes

Wechsler Preschool and Primary Scale of Intelligence-Fourth Edition, Australian and New Zealand

Other outcomes from the WPPSI-IV will be included as secondary outcomes. These include Verbal Comprehension, Fluid Reasoning, Working Memory and the Processing Speed, General Ability and Cognitive Proficiency Primary Index Scales.

The WPPSI-IV has Australian/New Zealand norms that are age standardised with a mean of 100 and SD 15. Intellectual impairment will be defined as full-scale IQ <85 (ie,

≤ 1 SD), and moderate-to-severe intellectual impairment as full-scale IQ <70 (ie, ≤ 2 SD). Any impairment on any of the WPPSI-IV Primary Index Scales will be defined as an Index Scale score <85 (ie, ≤ 1 SD).

Fruit Stroop

The fruit stroop was administered to assess two executive functions, inhibition and mental flexibility.²⁹ The child is required to identify the correct, natural colour of a series of fruits and vegetables in four 45 s trials under a series of conditions that increase in complexity. The outcome is an interference score calculated as the difference between the number of correct responses on the final (inhibition) trial, and predicted scores on the first and third trials, where lower or negative values indicate more interference.

Growth

Anthropometrics including child height, weight and head circumference will be measured at the appointment as measures of the nutritional well-being of the children. Measurements will be converted to Z (SD) scores appropriate for corrected age and sex.³⁰

Background information and characteristics

At enrolment into the N3RO trial a range of sociodemographic data were collected through interview with the caregiver (including parental age, education and employment). As part of the N3RO trial infant medical records were used to determine a range of baseline and outcome clinical characteristics up to 40 weeks' postmenstrual age or first discharge home, whichever occurred first, including, for example, gestational age, birth weight, sex and instances of intraventricular haemorrhage.

Sample size calculation

A sample size of 296 children per group (total 592) will provide 90% power (two-tailed alpha 0.05) to detect a 4-point (0.27 SD) mean difference in the primary outcome of full-scale IQ between groups. The power calculation assumes a design effect due to the inclusion of multiple births of one, since children from a multiple birth were randomised individually in N3RO.³¹ Should enrolment be lower than planned, the study will have 80% power to detect a 4-point difference between groups provided at least 222 children per group (total 444) provide follow-up data.

Data management and analysis plan

All participants were assigned a study identification number at enrolment into the N3RO trial. Throughout the follow-up and analyses, the identification number will be used to identify data. Data will be entered into a Research Electronic Data Capture (REDCap) database, which uses a MySQL database via a secure web interface with data checks used during data entry to ensure data quality. REDCap includes a complete suite of features to support the Health Insurance Portability and Accountability Act of 1996 compliance, including a full audit trail,

user-based privileges and integration with the institutional Lightweight Directory Access Protocol server.

All analyses will be conducted according to a prespecified statistical analysis plan. Analyses will not commence until the N3RO trial Steering Committee has approved the statistical analysis plan. Intervention groups will be dummy coded to allow analyses to be performed blinded to treatment group.

Outcomes of intervention and control group children will be compared using generalised linear models, with generalised estimated equations used to account for clustering due to multiple births within the same family. Continuous and binary outcomes will be analysed using linear and log binomial models, respectively, with adjustment for variables used to stratify the randomisation: sex, centre enrolled and gestational age (<27 completed weeks' or 27 to <29 weeks' at birth). Preplanned subgroup analyses will examine the effects of DHA separately for girls or boys (all outcomes), and for infants born at <27 weeks' gestation or 27 to <29 weeks' gestation (primary outcome only). No adjustment will be made for multiple preplanned comparisons, as the single overall comparison of Full-Scale IQ between groups is of primary interest.

Missing outcome data will be addressed using multiple imputation, with imputation performed separately by treatment group using fully conditional specification.³² Imputed datasets will include all surviving children from the five included centres. Children who are missing scores on psychological assessments because they were unable to complete the assessment for cognitive or physical reasons (such as blindness or cerebral palsy) will be reviewed by a psychologist to determine whether assigning the lowest possible score is appropriate.

Ethics and dissemination

This follow-up study will be carried out in accordance with the Australian National Statement on Ethical Conduct in Research Involving Humans, which builds on the ethical codes of the Declaration of Helsinki and the principles of International Conference on Harmonisation Good Clinical Practice (as adopted in Australia). All procedures and study materials have been reviewed and approved by the Women's and Children's Health Network Human Research Ethics Committee (HREC/17/WCHN/187), as well as the research governance officers at each site.

Caregivers will be provided with a detailed information sheet about the study and will provide informed consent for their child's involvement in the study. Caregivers will be free to renegotiate consent for each procedure in the follow-up study and are able to decline any part of the follow-up. Caregivers will be free to withdraw their children from the study at any time.

The results of this follow-up study will be presented at academic conferences and published in peer-reviewed journals. Participating families will receive a lay report of the study findings. No participants will be identified in the dissemination of study results and data collected will be treated with confidence.

Access to data

Individual participant data, including data dictionaries, may be shared after deidentification on reasonable request. Proposals to access the data must be scientifically and methodologically sound and must be reviewed and approved by the N3RO trial steering committee and the Women's and Children's Human Research Ethics Committee. To gain access, data requestors will need to sign a data access agreement. Proposals should be directed to Jacqueline Gould through email (Jacqueline.gould@sahmri.com).

Patient and public involvement

Neither patients nor the public were directly involved in the development of the research question or design of this follow-up study. However, our primary outcome of IQ is based on reported concerns over long-term developmental concerns from parents of preterm infants.³³

A community board, comprising parents (including parents of a child born preterm) as well as clinicians and researchers specialising in paediatrics, will be consulted for the dissemination of the study findings to participants, including reviewing the study results and format of dissemination.

DISCUSSION

This protocol details a follow-up of an RCT of a DHA enteral emulsion (60 mg/kg/day) compared with a control emulsion (no DHA), for preterm infants born <29 weeks' gestation in the first months of life, to evaluate the effect on child cognitive ability at 5 years of age. Unlike previous DHA RCTs in preterm populations,^{17 18} our follow-up has the benefits of a population likely to be insufficient in DHA,³⁴ and a robust method of intervention.²⁴

We previously conducted a follow-up of a small subgroup of the N3RO trial infants when they were aged 18 months' corrected age. Children underwent an experimental assessment of visual attention (considered to be a basic, early emergence of higher order cognitive skills known as the executive functions).³⁵ Where available, Bayley Scales of Infant and Toddler Development-third edition Cognition, Motor and Language assessment results were collected from hospital records.³⁵ No statistically significant differences were found for attention, cognition, motor or language abilities.³⁶ However, assessments of cognition during infancy are considered poor predictors of later performance,^{37–41} and the sample was small and underpowered to detect a clinically important effect on cognition.³⁵

Our sample size calculation for the primary outcome requires a 90% follow-up rate of the N3RO trial children, 5 years after enrolment. More than 10% lost to follow-up may introduce attrition bias. After completion of the N3RO trial primary outcome analyses, families had the opportunity to request knowledge of their group allocation. Although few families requested this,

knowledge of their randomisation group prior to the 5 year follow-up assessment may introduce additional bias to the results.

For this follow-up, we have carefully selected a robust assessment of general cognitive abilities, including executive functioning (both of which domains are likely to be adversely affected by very preterm birth)^{42–44} to be administered at an age when cognitive domains can be reliably assessed,^{26 45} as well as ensuring a large, adequately powered sample. As per the recommendations of a consortium of parents and clinicians caring for high-risk preterm infants, we are assessing general cognitive ability using a Wechsler scale, which is considered the gold standard, and have included an assessment of growth.⁴⁶ Assessments of respiratory functioning are unreliable in early childhood and hence were not included in this follow-up. It is important that the long-term respiratory effects of DHA supplementation in infants born <29 weeks' gestation is addressed when the N3RO trial children reach an appropriate age.

This project has global significance, with over one million infants born <29 weeks' gestation each year, and the number rising.⁴⁷ The potential benefit of DHA on cognitive performance has never been adequately demonstrated in this population. However, because of the N3RO primary results it is extremely unlikely that such a trial will be repeated. The N3RO cohort may represent the only children in which the longer-term cognitive and behavioural effects of DHA supplementation in these infants can be assessed.

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Contributors Study concept and design: CTC, JFG, MM, AJM, PJA, RAG and TS. Drafting the protocol: JFG, CTC and TS. Comment and approval of the final draft of the protocol: JFG, CTC, MM, TS, PJA, RAG, AJM, KPB, PGD, LWD, GO, JT, JC, MS and KS. Statistical expertise: TS. Obtained funding: CTC, JFG, MM, AJM, RAG, TS and KPB. Administrative, technical or material support: JFG, CTC, MM, RAG, TS, AJM, PJA, KPB, PGD, LWD, GO, JT, JC, MS and KS.

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Competing interests Study product for the original trial was donated by Clover (Melbourne, Australia). MM and RAG report holding a patent relating to methods and compositions for promoting the neurological development for preterm infants (2009201540), owned by the South Australian Health and Medical Research Institute and licensed to Clover Corporation Limited. MM is supported by an Australian NHMRC Senior Research Fellowship ID: 1061704 and CC is supported by an NHMRC Translating Research into Practice (TRIP) Fellowship ID 1132596. TS is supported by an NHMRC Emerging Leadership Investigator Grant ID: 1173576. KPB is supported by a Women's and Children's Hospital MS McLeod Postdoctoral Fellowship. PGD is supported by an Australian NHMRC Practitioner Fellowship ID: 1157782. JC is supported by an MRFF Career Development Fellowship ID: 1141354. Honoraria have been paid to Dr JFG's institution to support conference travel by Fonterra. MM and RAG report serving on the board for Trajan Nutrition. No other authors reported any financial disclosures.

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