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Longitudinal cohort study investigating neurodevelopmental and socioemotional outcomes in school-entry aged children after open heart surgery in Australia and New Zealand: the NITRIC follow-up study protocol

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ABSTRACT

Introduction Despite growing awareness of neurodevelopmental impairments in children with congenital heart disease (CHD), there is a lack of large, longitudinal, population-based cohorts. Little is known about the contemporary neurodevelopmental profile and the emergence of specific impairments in children with CHD entering school. The performance of standardised screening tools to predict neurodevelopmental outcomes at school age in this high-risk population remains poorly understood. The NITric oxide during cardiopulmonary bypass to improve Recovery in Infants with Congenital heart defects (NITRIC) trial randomised 1371 children <2 years of age, investigating the effect of gaseous nitric oxide applied into the cardiopulmonary bypass oxygenator during heart surgery. The NITRIC follow-up study will follow this cohort annually until 5 years of age to assess outcomes related to cognition and socioemotional behaviour at school entry, identify risk factors for adverse outcomes and evaluate the performance of screening tools.

Methods and analysis Approximately 1150 children from the NITRIC trial across five sites in Australia and New Zealand will be eligible. Follow-up assessments will occur in two stages: (1) annual online screening of global neurodevelopment, socioemotional and executive functioning, health-related quality of life and parenting stress at ages 2–5 years; and (2) face-to-face assessment at age 5 years assessing intellectual ability, attention, memory and processing speed; fine motor skills; language and communication; and socioemotional outcomes. Cognitive and socioemotional outcomes and trajectories of neurodevelopment will be described and demographic, clinical, genetic and environmental predictors of these outcomes will be explored.

Ethics and dissemination Ethical approval has been obtained from the Children's Health Queensland (HREC/20/QCHQ/70626) and New Zealand Health and Disability

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The use of a longitudinal cohort design based on a large high-quality pragmatic trial with broad inclusion criteria to map neurodevelopmental outcomes will help to improve prediction and early identification of children at risk for poor outcomes following cardiopulmonary bypass surgery for congenital heart disease (CHD).
⇒ The NITric oxide during cardiopulmonary bypass to improve Recovery in Infants with Congenital heart defects (NITRIC) Follow-up Study data will be combined with prospective well characterised data sets on clinical, socioeconomic and biological variables, including multiomics obtained pre and post cardiopulmonary bypass (CPB).
⇒ CHD families, clinicians and other stakeholders have co-designed the NITRIC Follow-up Study methods, ensuring the project is meaningful to CHD families and has the potential to optimise neurodevelopment in children following open heart surgery.
⇒ Limitations of this study are the sensitivity to loss to follow-up of participants and potential variations in follow-up timings.

(21/NTA/83) Research Ethics Committees. The findings will inform the development of clinical decision tools and improve preventative and intervention strategies in children with CHD. Dissemination of the outcomes of the study is expected via publications in peer-reviewed journals, presentation at conferences, via social media, podcast presentations and medical education resources, and through CHD family partners.

Trial registration number The trial was prospectively registered with the Australian New Zealand Clinical Trials Registry as 'Gene Expression to Predict Long-Term Neurodevelopmental Outcome in Infants from the NITric oxide during cardiopulmonary bypass to improve Recovery in Infants with Congenital heart defects (NITRIC) Study – A Multicentre Prospective Trial'. Trial registration: ACTRN12621000904875.

INTRODUCTION

One out of every 200 children is born with congenital heart disease (CHD) requiring surgery during childhood. Over the past two decades considerable improvements have been achieved in relation to survival following paediatric cardiac surgery, resulting in decreasing mortality rates for most lesions.[1–3] Correspondingly, the number of children surviving with CHD has been rapidly increasing with a rising proportion of complex CHD. The burden and cost of physical and neurological morbidities in CHD survivors are forecast to represent a major challenge for healthcare systems in the coming decades.[4]

Neurodevelopmental disabilities remain among the most common, and the most serious, sequelae in children undergoing surgery for CHD.[5] These can manifest as cognitive impairment, speech and language difficulties, visuospatial and visuomotor challenges, attention deficits, motor delays, socioemotional problems, secondary learning disabilities and reduced quality of life (QoL).[6 7] Early postoperative assessment after infant surgery often reveals abnormalities in muscle tone, poor suck and swallow and feeding difficulties.[8 9] However, developmental milestones show wide variation, with distinction between children with delayed development who will 'catch-up' to their peers and those who will experience persistent impairments remaining a major challenge.[10 11] The full extent of neurodevelopmental sequelae may only manifest once children reach school age.[11 12] If not detected and managed early, these sequelae may translate into secondary academic problems and reduced QoL, with longlasting consequences for the patient, family, future offspring and society. Furthermore, these represent a major contributor to excessive longer-term health costs, which are usually unaccounted for in health economic models.[13] To optimise outcomes for all children with CHD, early identification and appropriate supportive and/or rehabilitative management of children at risk for neurodevelopmental difficulties are essential. Historically, neurodevelopmental studies in other at-risk populations, such as preterm infants, have focused on the detection of moderate-to-severe impairment (eg, cerebral palsy, blindness, deafness).[14] An evolving landscape now acknowledges the importance of more subtle outcomes, including milder degrees of impairment which will have a significant influence on everyday functioning and QoL.[15] In particular, two recent systematic reviews have demonstrated consistent evidence for executive function impairment in school-aged children with CHD, underscoring the lifelong impact of CHD and the need for follow-up.[16 17] Despite the median age at follow-up in these papers being closer to high school age, the American Heart Association guidelines recommend starting screening for executive function at 6 years of age.[18] Moreover, problems may present prior to formal schooling, therefore earlier screening may be beneficial. Executive functions begin to emerge during infancy and are core skills critical for the life-course, including success in school and in life.[19]

Over the last decade, research has identified a range of neurodevelopmental impairments in children with CHD and, at the same time, highlighted some distinct CHD outcome patterns. While the prevalence of severe cognitive impairment in children with CHD has declined, deficits in multiple cognitive and psychosocial domains are increasingly observed.[20–22] Several studies have shown that even children whose IQ falls within the normal range may exhibit pervasive but subtle neuropsychological weaknesses, which are often underestimated or go undetected.[23–26] Emerging data show that, while severity of CHD is associated with outcome, patients with both univentricular and biventricular surgeries demonstrate variable neurodevelopmental outcomes.[21 27] These impairments in children with CHD are important indicators of school readiness, with increasing awareness of the need to obtain an adequate developmental assessment before school entry so that education, family and child supports can be put into place to optimise outcomes.[28] In addition to events surrounding cardiac surgery, research increasingly demonstrates that prenatal, patient-specific and environmental factors, including socioeconomic status, play a large role in determining the outcomes of children with CHD[22 29] and may contribute to identifying those at risk for poor neurodevelopmental outcomes.

In order to design and evaluate strategies which can mitigate the impact of CHD on neurocognitive outcomes, a better understanding of the risk factors and contemporary trajectories in these patients is urgently needed. At present, it remains unclear which tools, at which specific time points, have the best performance to predict child outcomes at school entry.[30] The Cardiac Neurodevelopmental Outcome Collaborative, an international multidisciplinary group committed to optimising neurodevelopmental outcomes for children with CHD, has recently recommended for future research to prioritise longitudinal trajectories of CHD, designed to identify socioemotional phenotypes and evaluate the effects of early risk factors on later outcomes including clinical, genetic, socioeconomic, sex and ethnic factors.[31] Such a nuanced characterisation of CHD will require adequately powered, large, contemporary, longitudinal cohorts representative of the CHD population with a high granularity of clinical and follow-up data.

Between 2017 and 2021, the NITric oxide during cardiopulmonary bypass to improve Recovery in Infants with Congenital heart defects (NITRIC) trial recruited 1371 infants less than 2 years of age undergoing cardiopulmonary bypass (CPB) surgery and represents the largest randomised controlled trial (RCT) in the field of CHD to date. This RCT evaluated if the addition of nitric oxide into the CPB oxygenator would result in more ventilator-free days compared with standard CPB. The protocol,[32] analysis plan[33] and 28-day outcomes[34] of this study have been reported previously. The NITRIC trial represents a unique population-based and well characterised large contemporary cohort of CHD children undergoing CPB. The NITRIC Follow-up Study has been designed to follow-up the NITRIC trial cohort to address significant gaps in knowledge of neurodevelopmental outcomes associated with CHD as children approach school age, and to explore associations of outcome with the host response to CPB assessed by transcriptomics and other biochemical markers. Below we describe the protocol to follow-up the NITRIC trial cohort from 2 to 5 years of age.

Aims

The primary objective of the NITRIC Follow-up Study is to improve the prediction and early identification of children at risk for poor developmental outcomes following CPB surgery for CHD, using a comprehensive protocol of age-appropriate standardised assessments. The study has four aims:

1. Map the neurodevelopmental, executive function and socioemotional trajectories following CPB surgery for CHD from 2 to 5 years of age.
2. Explore CHD neurodevelopmental and socioemotional phenotypes at 5 years.
3. Determine whether neurodevelopmental screening from 2 to 5 years of age predicts outcomes for children with CHD once they reach school age.
4. Identify sociodemographic, parent, child, disease, biochemical and treatment factors that differentiate neurodevelopmental and socioemotional outcomes following CPB surgery.

METHODS AND ANALYSIS

Study design

This is a prospective multicentre, international, longitudinal follow-up study of the NITRIC trial cohort. The results of this study will be reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist[35] or respective reporting guidelines for specific nested studies.

Participants

Children who underwent CPB surgery for CHD prior to 2 years of age and participated in the NITRIC trial.[34] Children were recruited prior to surgery from six tertiary paediatric hospitals in Australia, New Zealand and the Netherlands between 2017 and 2021. In the NITRIC Follow-up Study, we anticipate that 1150 surviving children from Australian and New Zealand sites will be eligible to participate. Children from the Netherlands may be included in future iterations of this protocol.

Recruitment procedure

Parents of eligible children will be invited to participate in annual online assessments from 2 (2 years 0 months) to 5 years (5 years 11 months) of age. Due to the variation in age at recruitment (0–2 years) and the 4-year conduct of the original NITRIC trial, some children may participate in as few as one, and others in as many as four, annual assessments. Following annual assessment at age 5, families will be asked to have their child participate in a face-to-face comprehensive neurodevelopmental assessment, and parents will complete a battery of questionnaires. Acknowledging a small number of children may have already turned 5 years of age at study commencement, to ensure inclusiveness we will allow the 5-year online and face-to-face assessments to occur in children up to 6 years 11 months.

Prior to the initial contact, site research coordinators will review patient records to ensure the child is not deceased, and then provide eligible families with information about the NITRIC Follow-up Study and a link to an informational video (https://www.nitricfollowup.com/). Coordinators will contact parents who indicate willingness to participate to further explain the study. Consent for completion of each annual questionnaire will be implied on return of the questionnaire. Parents will be contacted to verbally reconfirm their willingness to participate at each annual time point. Parents will be asked to provide written consent for the face-to-face neurodevelopmental assessment.

Measures

Demographic and clinical information

At their first annual online screening, parents will complete a study-specific demographic survey which includes sex, age, ethnicity, highest education, living arrangements, relationship status, number of children in their care and languages spoken. Each subsequent annual questionnaire will ask parents to document any changes in demographic status. Socio-economic status will be determined using the Socio-Economic Indexes for Areas – Index of Relative Socio-economic Disadvantage deciles and The New Zealand Index of Deprivation derived from the postcode recorded at paediatric intensive care unit (PICU) admission.[36 37] Postcode will also be used to determine regionality, using the Australian Bureau of Statistics' 5 classes of remoteness (Accessibility and Remoteness Index of Australia) and the Statistics New Zealand Urban Rural 2018 Classification.[38 39] Clinical information pertaining to the child's surgery and PICU admission has been recorded prospectively as part of the NITRIC study and includes diagnosis, CPB and surgical characteristics, severity, and treatments in PICU, and PICU and hospital length of stay.

Follow-up assessments

The annual screening questionnaire and the face-to-face follow-up were designed in consultation with the multidisciplinary study team, considering the measure's reliability and validity, relevance to the CHD literature[40] and subsequent discussion with CHD family representatives.

Annual online screening

Parents will be contacted annually until the child's fifth birthday to complete the online screening questionnaire (telephone, tablet, laptop, computer) using a secure link to their electronic questionnaire and contact details of their recruiting site. The questionnaire will be individualised based on each child's chronological age and development as per the respective tool. One questionnaire will be completed per child by a primary caregiver. The questionnaire takes approximately 45–60 min to complete and can be completed over several periods by returning to the saved questionnaire. In the case of parent comorbidity or circumstances limiting completion of the annual online screen, questionnaires will be administered via telephone interview by the research coordinator. Unless parents notify of their withdrawal from the study, attempts will be made to contact parents each year, even if the previous year's assessment was lost to follow-up. Online supplemental table S1 details the questionnaires included in annual screening assessments to be completed by parents. These measures assess child neurodevelopment, socioemotional status, QoL, parent emotional well-being and parenting stress. We will also collect health service usage data, and any other major illnesses or surgery in the previous 12 months, via a study-specific survey.

Face-to-face neuropsychological assessment

Following the child's fifth birthday, a face-to-face child assessment will also be conducted. Parents will be asked to provide written consent to participate in this component of the study and an assessment appointment will be scheduled. Assessments will be conducted in outpatient clinics at recruiting sites or alternative sites to suit families. The face-to-face assessment will take 2–3 hours and will be divided into several sessions, with breaks according to the individual child's needs based on best neuropsychological practice. Order of assessment will be set, with the intellectual ability (Wechsler Preschool and Primary Scale of Intelligence) tool administered first. Missing data (due to child or parent disability or lack of cooperation) will be recorded and categorised. Online supplemental table S2 details the face-to-face test battery which focuses on direct assessment of children's overall intellectual ability (IQ) and targets cognitive domains vulnerable to early childhood brain insult including attention, language, memory, motor skills and executive function. Parents will also rate their child's adaptive ability, socioemotional function, fatigue and parent–child attachment.

Sample size

The sample size is determined by the existing cohort. Of the 1371 recruited participants for the NITRIC trial, 7 did not ultimately undergo CPB surgery, 82 were recruited in the Netherlands and 44 children are known to be deceased by day 28 post-surgery. Based on available literature on long-term mortality in infants with CHD,[41] we estimate that 1150 children will be eligible for inclusion in the NITRIC Follow-up Study. Based on our previous experience and published reports of other follow-up cohorts,[42 43] we aim for an overall follow-up rate of 70% (n=805) at the 5-year face-to-face assessment.

Data analysis

Cohort description

Characteristics of the cohort will be presented descriptively, including comparison between responders and non-responders to assess potential bias.

Outcomes

The outcomes for each of the assessments (online supplemental table S1 and S2) will be presented at each time point with the point estimate and measure of variation. In addition to continuous outcome measures, secondary analyses will use cut-offs to categorise outcomes. Comparison of outcomes against appropriate normative values will be undertaken.

Developmental trajectories

Growth mixture models will be developed to investigate different post-surgery developmental profiles using data from the annual screening (Ages and Stages Questionnaire Total Score, Strengths and Difficulties Questionnaire Total Difficulties Score, and Behaviour Rating Inventory for Executive Function for Pre-schoolers Global Executive Composite Score) at 2, 3, 4 and 5 years of age. Child, parent, surgical, PICU treatment and sociodemographic factors known at the time of surgery, and collected during the NITRIC RCT, will be added to the model as covariates. Previous experience has demonstrated that variables from the NITRIC RCT have minimal missing data, however when missing data is evident, multiple imputation methods will be used for covariate data. The data will be explored graphically to determine the functional form, and a series of models will be developed and compared using the χ^2 difference tests (nested models) or another criterion (such as the Bayesian information criterion for non-nested models) to identify the number of trajectories.

Derivation of neurodevelopmental and socioemotional phenotypes

To derive neurodevelopmental and socioemotional phenotypes at 5 years of age, the cohort will first be split into derivation and validation subsets (65:35 using a temporal split). We will ensure the subsets are balanced for the original intervention in the NITRIC trial to avoid bias by intervention, as well as the original NITRIC trial stratification variables (age group and cardiac pathophysiology). Outcomes from the assessments undertaken at

5 years of age (listed in online supplemental table S2) will be used to derive neurodevelopmental and socioemotional phenotypes. These will include the language, attention, executive functioning, and memory and social behaviour and functioning domains. As such, the cohort will be restricted to children who have completed at least one assessment at the 5 years face-to-face visit. Where children have not completed the full assessment, multiple imputation will be used to impute missing outcome data. Descriptive analysis will first be performed to assess missingness, correlation and distribution and to identify highly correlated outcomes. If two outcomes are highly correlated (r>0.8), only one will be retained in the clustering analysis to avoid redundancy. Due to the potential for missing outcome data, multiple imputed data sets will be generated, and k-means clustering undertaken on each to assess stability. Standard indices will be used to identify the optimal number of phenotypes (eg, Silhouette Index, Gap Index, Dunn Index), and one set of phenotypes from the multiple imputed data sets used for the remaining analyses. Graphical methods will be used to describe and visualise the composition of the phenotypes. Latent class analysis will then be used to assess the reproducibility of the phenotypes within the entire data set.

Structural equation modelling

Structural equation modelling will be used to examine the associations between the neurodevelopmental screening outcomes from 2 to 5 years of age and neurodevelopmental outcomes for children with CHD once they reach school age. Specifically, longitudinal panel models will be developed to assess the continuity of the neurodevelopmental outcomes from 2 to 5 years, as well as their association with the neurodevelopmental outcomes assessed at age 5. Missing data patterns will be explored and full information maximum likelihood estimation methods will be used to produce unbiased parameter estimates in the presence of missing data.

Prediction models

Mixed-effects models will be developed to investigate which individual, parent, surgical, PICU treatment and sociodemographic factors known at the time of surgery are associated with both neurodevelopmental and socioemotional outcomes, and derived phenotypes. The models will account for risk factors for cognitive delays (identified through existing literature and clinical judgement), the original NITRIC trial intervention and stratification variables (as fixed effects) and study site (random effect).

In addition to the exploration of the impact of clinical and sociodemographic factors on neurodevelopmental outcome, prediction models will be developed incorporating biomarkers of host response to CPB. Transcriptomics data will be generated on the full cohort with matched pre-surgery and post-surgery samples and metabolomics data and proteomics data will be generated on subset of the cohort. We will use forward selection algorithms to identify variables from each data set to discover novel biomarkers to predict patient outcomes after CPB. We will also combine these data sets to derive a combination biomarker (including gene expression, metabolites and proteins) to predict short-term and long-term patient outcomes.

Feasibility and engagement

To maximise follow-up rates, we have developed detailed standardised training on a follow-up delivery package for the study informed by published reports[44–47] including the collection of detailed contact information, using systematic methods for patient contact, visit/appointment scheduling and cohort retention monitoring (templates for telephone scripts and written material); log of each contact attempt made to participants; providing reminders about visits/appointments; providing benefits to children and families that are directly related to the nature of the study (eg, reports which can be shared with educators or healthcare professionals); providing reimbursement for direct research-related expenses such as travel and accommodation to facilitate participation; providing tokens of appreciation (developed in consultation with family group); and procedures for escalating efforts to reach participants,[48] including varying contact modes and reminders.

Assessment feedback for participants

All parents will receive written results of their child's development from both the annual and face-to-face assessments in a formal report. The annual report results will be articulated in terms of performance ranges (ie, within/below the range as same-aged peers) for each assessment and emailed to parents at the completion of the online assessment. The report includes a summary of the areas of development assessed and a guide for interpreting the results. The face-to-face report will include an explanation of the areas assessed and will report on each domain area, which will be summarised as below average, average or above average for cognitive profiles and average or elevated for socioemotional profiles. If the assessment results raise areas of concern not previously identified/diagnosed, parents are encouraged to contact their primary healthcare providers to discuss the findings and options for referral to appropriate services for further clinical neuropsychological testing as indicated. Reports have been developed in consultation with the CHD family group.

Patient and public involvement

The development of the research questions and outcome measures are based on the findings of our previous research into long-term outcomes in critically ill cohorts.[32 49 50] The importance of long-term outcomes has been investigated by members of the research team through national and international research.[51 52] Prior to study commencement, there has been direct involvement of CHD families with lived experience in the development

of study materials, including the formal annual reports and further interviews and focus groups exploring engagement in research, which will be published separately. CHD families have assessed the burden of the follow-up questionnaires, the suitability of domains measured and the acceptability of the annual report. Families will also advise on the dissemination strategy, particularly in relation to participating families and community groups.

Limitations

This study has potential limitations. First, cohort studies are sensitive to loss to follow-up of the participants. To address this, we have formulated a comprehensive follow-up quality control plan prior to study commencement and will explore patterns of lost to follow-up through sensitivity analyses. Provision of reports may also encourage parents to seek additional early support and intervention for their child, thus potentially changing the trajectory of outcomes (although positively); hence the collection of healthcare usage data is an important inclusion in this study. Follow-up timing may range among participants; therefore we will include age at completion of assessments in statistical modelling.

Contribution

This study also offers several strengths. First, the cohort is based on a large high-quality pragmatic trial with broad inclusion criteria offering approximation for population-based coverage, which is representative of the contemporary CHD population. Second, follow-up data will be combined with the prospective well characterised data sets on clinical, socioeconomic and biological variables, including multiomics obtained pre-CPB and post-CPB. Furthermore, this cohort allows for exploring which sociodemographic variables predict neurodevelopment in a large binational cohort. This will enable us to control for their potential confounding effects on the association between risk factors and neurodevelopmental outcomes. By integrating neurodevelopmental, socioemotional, functional and QoL measures, we will undertake the largest population-based follow-up cohort of infants undergoing CPB for CHD and collect extensive patient-centred and family-centred outcomes between 2 and 5 years of age. Through the combination with biochemical data obtained pre-CPB and post-CPB, the programme will seek to unravel links between early host response to CPB and late outcomes. As a result, this study will assist us in identifying the most informative time points and predictors to detect problems and the functions that are most at risk of impairment for these children.

Data management

A purpose-built REDCap (Research Electronic Data Capture) database has been developed (hosted by The University of Queensland) to store participant information, administer annual assessments in survey form and record outcomes of the face-to-face neuropsychological assessment. In-built dashboards have been developed to enable centralised, and site monitoring of recruitment and survey completion rates. Following principles of the International Council of Harmonisation, Good Clinical Practice guidelines, a risk-based assessment has been undertaken to guide the development of the study monitoring plan.

Study oversight

A Steering Group has been established with clinical, long-term follow-up, data, consumer and research coordination representatives, and has oversight of the progress of the study, supported by a Research and Operations Manager. Whole programme meetings will be convened during the study to update all programme members on the progress of the study.

ETHICAL CONSIDERATIONS

The study protocol has been approved by the Children's Health Queensland Human Research Ethics Committee (HREC/20/QCHQ/70626; original submission approved on 21 December 2020) and New Zealand Health and Disability Ethics Committee (21/NTA/83; original submission approved on 6 September 2021). Recruitment commenced on 10 May 2022.

DISSEMINATION OF RESULTS

Participants will be given the option to receive a summary of results at the completion of the study, in addition to the ongoing feedback provided from the outcomes of the annual screening questionnaires and face-to-face assessments. Additionally, publication in high impact peer-reviewed journals will be sought and presentation at national and international conferences is anticipated. Novel and modern information dissemination strategies will also be used including social media, podcast presentations and Free Open Access Medical education resources to generate discussion and disseminate the outcomes of the study.

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Contributors DL, VA, WB, KSG and LJS conceived the study, developed the protocol, co-wrote the first draft of the manuscript and approved the final draft. All other authors (LC, NTS, KC, ADM, SB, CFP, KM, NAP, PJA, NB, BR, HB, KM, JCF, CS, SR, JB, SE, MF, BWA, PV, DY, DA, MC, CB, TLG, AI, IN, JA) assisted with development of the interventions and methods, outcomes and materials, reviewed the manuscript and approved the final version.

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Competing interests None declared.

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