BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-075429
Article Type:	Protocol
Date Submitted by the Author:	08-May-2023
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Keywords:	Congenital heart disease < CARDIOLOGY, Paediatric intensive & critical care < ANAESTHETICS, Developmental neurology & neurodisability < PAEDIATRICS, Paediatric cardiology < CARDIOLOGY, Paediatric cardiac surgery < PAEDIATRIC SURGERY

Title Page:

A Longitudinal Cohort Study Investigating Long-Term Neurodevelopmental and Socio-emotional Outcomes in Children after Open Heart Surgery: The NITRIC Follow-up Study Protocol

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Competing Interests Statement:

None declared.

Key words: child; congenital heart disease; cognition; behavior; neurodevelopment; trajectories; phenotype; preschool; school readiness; screening; latent effects

Funding: This work is supported by grants from the Medical Research Future Fund (ARGCHDG000036), Australia; the Children's Hospital Foundation, Australia; the Starship Foundation, New Zealand; and the Green Lane Research and Educational Fund, New Zealand. VA is supported by a National Health and Medical Research Council (Australia) Investigator Grant. The funding sources were not involved in study design, analyses, nor interpretation of the results.

Word Count: 3571

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 standardized 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 randomized 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 behavior at school entry, identify risk factors for adverse long-term outcomes, and evaluate the performance of screening tools.

Methods and analysis: Children from the NITRIC trial across 5 sites in Australia and New Zealand are eligible. Follow-up assessments will occur in two stages: i) annual online screening of global neurodevelopment, socioemotional and executive functioning, health-related quality of life and parenting stress at ages 2-5 years; and ii) 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: All relevant ethical approvals have been obtained. 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 consumer partners.

Registration details: 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

ARTICLE SUMMARY

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.

- The NITRIC Follow-Up Study data will be combined with prospective well characterized datasets on clinical, socioeconomic, and biological variables, including multi-omics obtained pre and post CPB.

- Consumers, clinicians and other stakeholders have co-designed the NITRIC Follow-Up study methods, ensuring the project is meaningful to consumers 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.

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 pediatric 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 long-term 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 amongst 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, visuo-spatial and visuo-motor challenges, attention deficits, motor delays, socioemotional problems, secondary learning disabilities and reduced quality of life (QoL) (6, 7). Early post-operative 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 quality of life, with long-lasting consequences for the patient, family, future offspring, and society. Furthermore, these represent a major contributor to excessive long-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 (e.g., 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 quality of life (15). The EPICure cohort studies of extremely preterm infants provide an example of the role of epidemiological studies in advancing understanding of the life-course consequences of extreme prematurity (16).

Over the last decade, research has identified a range of neurodevelopmental impairments in children with CHD and, at the same time, highlighted that some CHD long-term outcome patterns are distinct from preterm populations. Whilst the prevalence of severe cognitive impairment in children with CHD has declined, deficits in multiple cognitive and psychosocial domains are increasingly observed (17-19). Several studies have shown that even children whose intelligence quotient falls within the normal range may exhibit pervasive but subtle neuropsychological weaknesses, which are often underestimated or go undetected (20-23). Emerging data show that, while severity of CHD is associated with outcome, patients with both univentricular and biventricular surgeries demonstrate variable neurodevelopmental outcomes (18, 24). 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 long-term outcome of children with CHD (19, 25) 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 age (26). The Cardiac Neurodevelopmental Outcome Collaborative (CNOC), an international

multidisciplinary group committed to optimizing neurodevelopmental outcomes for children with CHD, has recently recommended for future research to prioritize 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 (27). 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 CPB surgery and represents the largest randomized 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 to standard CPB. The protocol (28), analysis plan (29) and 28-day outcomes (30) of this study have been reported previously. The NITRIC trial represents a unique population-based and well characterized 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, 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 standardized 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 multicenter, 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 (31) 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 (30). Children were recruited prior to surgery from six tertiary pediatric hospitals in Australia, New Zealand and the Netherlands between 2017 and 2021. In the NITRIC Follow-Up Study, all surviving children from Australian and New Zealand sites will be approached 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 to 2 years) and the four-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 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 timepoint. 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 (SEIFA IRSD) deciles and The New Zealand Index of Deprivation (NZDep) derived from the postcode recorded at PICU admission (32, 33). Postcode will also be used to determine regionality, using the Australian Bureau of Statistics' 5 classes of remoteness (Accessibility and Remoteness Index of Australia [ARIA]) and the Statistics New Zealand Urban Rural 2018 Classification (34, 35). 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.

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 individualized 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 minutes 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.

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 & Primary Scale of Intelligence) tool administered first. Missing data (due to child or parent disability or lack of cooperation) will be recorded and categorized.

Follow-up Assessments

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

Annual questionnaires: Table 1 details the questionnaires included in annual screening assessments to be completed by parents. These measures assess child neurodevelopment, socioemotional status, quality of life, parent emotional well-being and parenting stress. We will also collect health service utilisation data, and any other major illnesses or surgery in the previous 12 months, via a study-specific survey.

Face-to-face neurodevelopmental assessment at five years of age: Table 2 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.

Table 1. Parent-completed online screening assessments conducted at 2- to 5-years of age

Construct	Instrument[#]	Number of Items	Scoring and Interpretation	Comments
Child-focused Measures				
Neurodevelopment	Ages and Stages Questionnaire, 3rd Edition (ASQ-3) (36)	30	Each item scored: Yes, Sometimes, or Not yet. Above, close to, and below cut-off scores provided based on aged norms for each domain. Domain scores added to create total score. Higher scores indicate better neurodevelopment. *Main outcome definition: Total ASQ-3 Score (continuous)*	5-10 mins to complete. 21 age-appropriate questionnaires 1-66 months. Domains: communication, gross motor, fine motor, problem-solving and personal-social.
Socioemotional Behavior	Strengths and Difficulties	25	Each item scored on a 3-point Likert scale: Not true, somewhat true,	5-10 mins to complete.

Construct	Instrument[#]	Number of Items	Scoring and Interpretation	Comments
	Questionnaire (SDQ) (37)		certainly true. Scale scores derived for Emotional problems, Conduct problems, Hyperactivity, Peer problems, Prosocial, and Total Difficulties, compared to aged norms. Higher scores indicate better socioemotional behavior. *Main outcome definition: Total Difficulties Score (continuous)*	Two age-appropriate questionnaires 2-17 years. Domains: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, prosocial behaviors.
Health Related Quality of Life (HRQoL)	Pediatric Quality of Life Inventory (PedsQL) (38, 39)	23-38[a]	Each item scored on a 5-point Likert scale: 0 = Never a problem to 4 = Almost always a problem. Psychosocial Health Summary Score, Physical Health Summary	5 mins to complete. Five age-appropriate questionnaires 1 month – 18 years.

Construct	Instrument[#]	Number of Items	Scoring and Interpretation	Comments
			Score, and Total Score, compared to aged norms. Higher scores indicate better HRQoL. *Main outcome definition: Total PedsQL Score (continuous)*	Domains: physical, emotional, social, and school functioning.
Executive Functioning	Behavior Rating Inventory for Executive Function for Pre-schoolers (BRIEF-P) (40)	63	Each item scored. Inhibitory Self-Control Index, Flexibility Index, Emergent Metacognition and Global Executive Composite score, compared to aged norms. The recommended cut-off for clinical significance is ≥ 65. Lower scores indicate better executive functioning.	10-15 mins to complete. One questionnaire 2 - 5 years 11 months. Domains: inhibit, shift, emotional control, working memory, plan/organize.

Construct	Instrument[#]	Number of Items	Scoring and Interpretation	Comments
			Main outcome definition: Global Executive Composite Score (continuous)	
Fatigue	The Pediatric Quality of Life Inventory (PedsQL) Multidimensional Fatigue Scale (41)	6	Each item scored on 5-point Likert scale: 0 = Never a problem to 4 = Almost always a problem. Total score compared to aged norms. Higher scores indicate lower problems. *Main outcome definition: Total General Fatigue Score (continuous)*	General Fatigue subscale only 2 minutes to complete. Four age-appropriate questionnaires 2 – 18 years. Domains: General fatigue, Sleep/rest fatigue, and Cognitive fatigue.
Parent-focused Measures				
Emotional Wellbeing	The Kessler-6 (K6) (42)	6	Items are scored on a 5-point Likert scale (1= 'none of the time' to 5 =	1 minute to complete

Construct	Instrument[#]	Number of Items	Scoring and Interpretation	Comments
			'all of the time'). Total score ranged from 0-24, with higher scores representing higher levels of psychological distress such as anxiety and depression. *Main outcome definition: Total K6 Score (continuous)*	
Parenting Stress	The Parenting Stress Index-4 Short Form (PSI-4-SF)(43)	36	Items are scored on a 4-point Likert scale: 1 = Strongly agree to 5 = strongly disagree. A percentile score on Total stress ≥ 91% indicates clinically significant levels of stress. Higher scores indicate more parenting stress.	10 minutes to complete. Domains: Parental distress, Parent-child dysfunctional interaction, and Difficult child

Construct	Instrument[#]	Number of Items	Scoring and Interpretation	Comments
			Main outcome definition: Total PIS-4-SF Percentile Score (continuous)	
Healthcare Utilisation	Developed by research team.	12	*Main outcome definition*: *Total parent-reported utilisation of in- and out-patient visits and costs (continuous)*	2 minutes to complete. Domains: Visits to healthcare professionals and facilities, and finances relating to appointments and care

[#]All measures used in accordance with associated user manuals; [^]Order of administration of questionnaires standardized; [§] All child-focused measures validated for use as parent-reported; [a] Depending on age.

Table 2. Face-to-face neurodevelopmental assessment at 5-years of age

Construct	Instrument[#]	Number of Items	Scoring and Interpretation	Comments
Face-to-Face Measures				
Cognition	Wechsler Preschool & Primary Scale of Intelligence – 4th Edition Australia and New Zealand Standardised Edition (WPPSI-IV A&NZ) (44)	15 subtests	Three levels of interpretation: Full Scale, Primary Index scales, and Ancillary Index scales. The Full Scale and all indexes have a mean score of 100 and SD of 15. Higher scores indicate higher cognition. *Main outcome definition:* *Full Scale IQ (continuous)*	Block design, Information, Matrix reasoning, Bug search, Picture memory, Similarities, Cancellation and Zoo location subtests only. Administration time: 45-60 mins

Construct	Instrument#	Number of Items	Scoring and Interpretation	Comments
Motor function	Movement Assessment Battery for Children, 2nd Edition (MABC-2) (45)	8 tasks	8 Task standard scores and a Total test score. Manual dexterity component score: sum of standard scores of MD1, MD2 and MD3. Higher scores indicate better motor function. *Main outcome definition: Manual Dexterity Component Score (continuous)*	Posting coins, Threading beads and Drawing trail 1 subtests only. Administration time: 10 mins
Executive Function	Day/Night Task (46)	16 cards	Total correct, Total Self Corrections, Total Time, Efficiency Score (Total	Administration time: 5 mins

Construct	Instrument[#]	Number of Items	Scoring and Interpretation	Comments
			Correct/Total Time to Complete). Higher scores indicate better executive function. *Main outcome definition:* *Efficiency Score (continuous)*	
Attention - Visual	Test of Everyday Attention for Children, 2nd Edition (TEA-Ch2) (47)	5 trials	Scaled scores have a mean of 10 and SD of 3 (Range 1-19). Percentile ranked score. Higher scores indicate better attention. *Main outcome definition:* *Attention Score (continuous)*	Balloon Hunt and Balloons 5 subtests only. Administration time: 7 mins

Construct	Instrument[#]	Number of Items	Scoring and Interpretation	Comments
Language	Clinical Evaluation of Language Fundamentals – Australian and New Zealand 5th Edition Screening Test (CELF-5 A&NZ Screening Test) (48)	13	Total Score: sum of the student's score points. Total score compared to a research-based criterion score appropriate for the student's age. Age 5:0-8:11 have one criterion score. Higher scores indicate better language. *Main outcome definition: Total Score (continuous)*	Word structure, Word Classes, Following directions and Recalling sentences subtests only. Administration time: 10-15 mins
Attention	Conners Kiddie Continuous Performance Test, 2nd Edition (K-CPT 2) (49)	Up to 200 trials	Higher scores indicate poorer attention. *Main outcome definition: Composite Attention Score*	4 domains of attention: Impulsivity, Inattentiveness, Sustained attention, and Vigilance.

Construct	Instrument#	Number of Items	Scoring and Interpretation	Comments
				Administration time: 7 mins
Memory	Wide Range Assessment of Memory and Learning, 3rd Edition (WRAML3) (50)	4 stories 85 questions	Scaled score, M=10, SD=3. Subtest scaled scores derived from the total raw scores on a given subtest- and describe the overall performance on that subtest. Story Memory – story memory total raw score. Story Recognition – story memory recognition total raw score. Higher scores indicate better memory.	Story Memory subtest only. Administration time: 20 mins

Construct	Instrument[#]	Number of Items	Scoring and Interpretation	Comments
			Main outcome definition: Verbal Memory Score (continuous)	
Memory	Working Memory Test Battery for Children (WMTB-C) (51)	9	Trials Correct Score: Total number of correct trials achieved before testing is discontinued. Higher scores indicate better memory. *Main outcome definition: Total Trials Correct (continuous)*	Digit Recall subtest only. Administration time: 5 mins
Parent-completed Online Measures				

Construct	Instrument[#]	Number of Items	Scoring and Interpretation	Comments
Social behavior/Autism	Social Responsiveness Scale, 2nd Edition (SRS-2) (52)	65	Each item scored on a 4-point Likert scale: 1 = Not true to 4 = Almost always true. Scores: Total, Treatment subscales, DSM-5 compatible subscales. Higher scores indicate clinically significant deficiencies in social behavior *Main outcome definition: Total Score (continuous)*	Administration time: 15-20 mins
ADHD	ADHD Rating Scale, 5th Edition (ADHD-RS-5) (53)	18	Each item scored on a 4-point Likert scale.	Administration time: 5 mins

Construct	Instrument#	Number of Items	Scoring and Interpretation	Comments
			Scores: Total, Inattention and Hyperactivity-Impulsivity. Total raw score: Sum of inattention and hyperactivity subscale raw scores. Converted to total percentile score. Higher scores indicate more impairment in attention. *Main outcome definition: Total Percentile Score (continuous)*	
Social functioning	Adaptive Behavior Assessment System, 3rd Edition (ABAS-3) (54)	46	Each item is scored on a 4-point Likert scale: 0 = Is not	Leisure and Social subscales only Administration time: 10 mins

Construct	Instrument#	Number of Items	Scoring and Interpretation	Comments
			able to do this behavior to 3 = Always (or almost always) Standard Score for Social Adaptive domain compared to norms. Mean of 100 and SD of 15. Lower scores indicate lower adaptive behaviors. General Adaptive Composite Score: Composed on all measured skill areas, providing an overall estimate of adaptive behavior. Higher scores indicate better social functioning.	One age-appropriate questionnaire 5-21 years.

Construct	Instrument[#]	Number of Items	Scoring and Interpretation	Comments
			Main outcome definition: General Adaptive Composite Score (continuous)	
Fatigue	Pediatric Quality of Life Inventory (PedsQL) Multidimensional Fatigue Scale – Full scale (41)	18	Each item scored on .5-point Likert scale: 0 = Never a problem to 4 = Almost always a problem. Total score: Sum of general, sleep/rest and cognitive fatigue. Higher scores indicate lower problems. *Main outcome definition: Total Fatigue Score (continuous)*	Administration time: 5 mins Four age-appropriate questionnaires 2 – 18 years. Domains: General fatigue, Sleep/rest fatigue, and Cognitive fatigue.

Construct	Instrument[#]	Number of Items	Scoring and Interpretation	Comments
Parent-Child Attachment	Attachment Relationship Inventory-Caregiver Perspective (ARI-CP 2-5) (55)	48	Each item scored on a 6-point Likert scale: 1 = Not at all applicable to 5 = Fully applicable. Four subscales (secure, avoidant, ambivalent, disorganized). Scale scores represent the sum scores of all items of the scale. Higher scores indicate better attachment. *Main outcome definition: Global Attachment Score (continuous)*	Administration time: 5 mins

[#]All measures used in accordance with associated user manuals; [^]Order of administration of questionnaires standardized; [a] Depending on age.

Sample Size

The sample size is determined by the existing cohort. Of the 1371 recruited participants for the NITRIC trial, seven 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 (56), 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 (57, 58), 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 (Tables 1 and 2) will be presented at each timepoint with the point estimate and measure of variation. In addition to continuous outcome measures, secondary analyses will use cut-offs to categorize outcomes. Comparison of outcomes against appropriate normative values will be undertaken.

Developmental Trajectories

Latent, group-based trajectory models will be developed to investigate different post-surgery developmental profiles using data from the annual screening (Ages and Stages Questionnaire [ASQ] Total Score, Strengths and Difficulties Questionnaire [SDQ] Total Difficulties Score, and Behavior Rating Inventory for Executive Function for Pre-schoolers [BRIEF-P] Global Executive Composite Score) at 2, 3, 4, and 5 years of age. The data will be explored graphically

to determine the most functional form, and a series of models will be developed and compared using the chi-squared difference tests (nested models) or another criterion (such as Akaike information criterion for non-nested models).

Derivation of Socioemotional Phenotypes

The cohort will be split into derivation and validation subsets, ensuring that 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). Candidate variables to be included in the phenotype derivation process will be drawn from the language, attention, executive functioning, memory and social behavior and functioning domains. A data-driven approach will be used, and as such, all available variables will be included. Descriptive analysis will firstly be performed to assess missingness, correlation and distribution. The appropriate clustering method will be chosen following review of the data structure. Following determination of the optimal number of socioemotional phenotypes, graphical methods will be used to describe and visualize the relationship between candidate variables and phenotypes. Latent class analysis will then be used to assess the reproducibility of the phenotypes within the entire dataset. Sensitivity analyses will be undertaken by excluding highly correlated variables.

Prediction Models

Multivariable models will be developed to investigate which individual, parent, surgical, PICU treatment and sociodemographic factors known at the time of surgery are associated with outcomes in the neurodevelopmental and socioemotional domains for both the annual questionnaires, and the face-to-face assessment at five years of age, as well as assess the ability of the annual questionnaires to predict the outcomes documented at the face-to-face assessment. The model will account for risk factors for cognitive delays (identified through

existing literature and clinical judgement), the original NITRIC trial intervention, the NITRIC trial stratification variables, and study site. Repeated questionnaires for a single child will also be taken into consideration; the model will allow for instances where the child does not have a full set of questionnaires (either due to age of enrolment into the NITRIC Follow-up Study or non-completion of some surveys), through both the choice of statistical model and exploration and inclusion of risk factors to quantify reason and type of missed follow-up. Additionally, sensitivity analyses will be undertaken exploring different approaches to account for loss-to-follow up. In addition to the exploration of the impact of clinical and sociodemographic factors on neurodevelopmental outcome, the prediction models will be developed assessing several layers of biomarkers on host response to CPB (transcriptomics, metabolomics, proteomics) obtained pre- and post-surgery where available.

Feasibility and Engagement

To maximize follow-up rates, we have developed detailed standardized training on a follow-up delivery package for the study informed by published reports (59-62) 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 (e.g. 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 consumer group); and procedures for escalating efforts to reach participants.

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 (i.e. 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 summarized 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 consumer group.

Consumer 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 (28, 63, 64). The importance of long-term outcomes has been investigated by members of the research team through national and international research (65, 66). There has been direct involvement of CHD families with lived experience in the development of study materials and further interviews and focus groups exploring engagement in research, which will be published separately.

Data Management

A purpose-built REDCap™ 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 centralized, and site monitoring of recruitment and survey completion rates. Following principles of the International Council of Harmonisation, Good Clinical Practice (ICH-GCP) 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 program meetings will be convened during the study to update all program 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 21st December 2020) and New Zealand Health and Disability Ethics Committee (21/NTA/83; original submission approved 6th September 2021). Recruitment commenced on May 10th, 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 (FOAM) resources to generate discussion and disseminate the outcomes of the study.

Discussion

This study aims to map neurodevelopmental outcomes and will analyze the effects of CHD on neurodevelopmental trajectories through longitudinal comparisons, socioemotional phenotypes and risk prediction models. Further, we aim to identify screening assessments that predict later neurodevelopmental and socioemotional outcomes. We will use reliable and valid clinical assessment tools and include prospectively collected predictors and potential confounders across socioeconomic, clinical and biochemical datasets.

This study has potential limitations. Firstly, 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 (albeit positively); hence the collection of healthcare utilization data is an important inclusion in this study. Follow-up timing may range amongst participants, therefore we will include age at completion of assessments in statistical modelling.

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 characterized datasets on clinical, socioeconomic, and biological variables, including multi-omics obtained pre- and post-CPB. Furthermore, this cohort allows for exploring social determinant interactions with 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 quality of life measures,

we will undertake the largest population-based follow-up cohort of infants undergoing CPB for CHD and collect extensive patient- and family-centered outcomes between 2 and 5 years of age. Through the combination with biochemical data obtained pre- and post-CPB, the program will seek to unravel links between early host response to CPB and late outcomes. As a result, this study will assist us in identify the most informative time points and predictors to detect problems and the functions that are most at risk of impairment for these children.

In summary, the NITRIC Follow-Up Study will characterize the neurodevelopmental profiles at school entry in a large prospective cohort of children born with CHD. It is expected to yield novel data on risk factors and timely identification of neurodevelopmental sequelae after CHD surgery, which can enable future prevention and intervention strategies.

Author Statement:

DAL, VA, WB, KG and LJS conceived the study, wrote the grant, developed the protocol and funding applications, co-wrote the first draft of the manuscript, and approved the final draft. All other authors assisted with development of the interventions and methods, outcomes, and materials, reviewed the manuscript, and approved the final draft.

Acknowledgements:

We would like to thank the families who have generously participated in the development of the methods and consumer materials, and who will participate in the study.

Patient and public involvement:

Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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Standard Protocol Items for Observational Studies (SPIROS)

Table 1: Checklist of preliminary items

Section and topic	Description / sub-categories	Addressed on page number
i) General Information		
Title	Descriptive title identifying study design	Page 1
Protocol version	Version or amendment number and date and summary of changes	NA
Protocol summary	Brief summary of protocol research	Pages 6-8
Sponsor and partner institute name	Name of sponsor and participating institutes (if applicable)	Page 12
Investigators name	Name of principal and co investigators.	Pages 1-4
Affiliation of investigators	Affiliated institutions of investigators	Pages 1-4
Principal researcher contact detail	Name, email address, affiliation of Principal researcher for correspondence.	Corresponding author page 4
Table of content	Table of content	NA
Page number	Page number on each page of protocol	Pages 1-49
List of Abbreviations	A detailed List of all abbreviations used in protocol with full form.	NA
ii) Introduction		
Background of study	Scientific background of study	Pages 9-11
Review of prior research	Summary of all previous relevant research	Pages 9-11

Rationale of study	Justification for conducting the study	Page 11
Aim	Broader aims and specific objectives of the study	Pages 11-12
Objective of study	Primary and secondry objectives of study	Page 11
Prespecified hypothesis	Prespecified null or alternative hypothesis	NA
iii) Methods		
Study design	Description of type/design of study	Page 12
Study setting	Description of setting, locations, relevant dates, including periods of recruitment/survey, exposure, follow-up, and data collection. Schedule of study procedure – Figure or table	Pages 12-13 Tables 1-2
Sample size	Estimated number, calculation and assumptions Power calculation	Page 34 NA
Sampling procedure	Description of sampling strategy to ensure representativeness and control of potential bias	Page 13
Participants	**Cohort study**—eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. For matched studies, give matching criteria and number of exposed and unexposed **Case-control study**—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls For matched studies, give matching criteria and the number of controls per case	Pages 12-15 Tables 1-2 NA

	Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	• All outcomes • Exposures- definition of exposure of interest, • Predictors • Potential confounders • Effect modifiers	Page 15 Tables 1-2
Data Sources/ Measurement	• For each variable of interest, give sources of data and details of methods of assessment (measurement). • Describe comparability of assessment methods if there is more than one group • Data collection points table • Blinding procedure	Page 15 Tables 1-2 NA NA NA
Bias	Describe any efforts to address potential sources of bias More specifically- • Information bias • Selection Bias • Control for confounding	Pages 34-36, 39
Statistical analysis plan	• Method of primary / secondary outcomes and additional analysis • Handling of missing data • Post-hoc analysis	Pages 34-36 Pages 34-36 NA

Handling of withdrawals and lost to follow up	Describe the procedures to be followed when a participant ceases participation in the study prematurely or is lost to follow up	Pages 14-15
Replacements	Provide information on whether or not participants who discontinue the study will be replaced via additional recruitment to maintain the required sample size.	NA
Outcome	Define and describe all primary and secondary outcome or lost to follow up	Pages -36 Tables 1-2
Database management	• Detail plan of database management including: • Data collection (electronic or paper based), • Source data • Data entry • Data editing • Coding • Data storage • Record retention • Data confidentiality	 Pages 37-38 Pages 37-38 Pages 37-38 Pages 37-38 Pages 37-38 Pages 37-38 Pages 37-38 Pages 37-38
Validation of instrument	Reliability / validity of instrument or plan to establish validation	Page 15 Tables 1-2
Follow up	Plan of follow up and addressing lost to follow up	Page 15; Tables 1-2
Quality control	• Method of quality control • Monitoring (internal and external) • Training of surveyors	Pages 37-38 Pages 37-38 Pages 14-15
Quality assurance	Plan of quality assurance	Pages 37-38

Expected outcome /results	A brief description of expected outcome or results	Pages 39-40
iv) Ethical consideration		
Ethical approval	Whether it has been obtained and name of ethical committees. If approval not sought , Reason	Page 38
Agreement and consent	Method of taking consent. Reason if consent not sought	Pages 14-15, 38
Risk / Harm to participants	Any potential risk or harm to study participants	NA
Adverse event and Severe adverse event reporting	Outline how Adverse Event and Severe adverse event information will be collected.	NA
v) Reporting and dissemination		
Protocol amendments	Methods of communicating to investigators/IRBs and documenting	Pages 37-38
Dissemination	How results will be disseminated to participants, practitioners, public	Page 38
Publication Plan	Who has right to publish; restrictions; authorship guidelines Open Access	NA
Reporting of early stopping	Dissemination of results if trial is stopped early (for any reason)	NA
vi) Others		
Limitations	Limitations of proposed study, including risk of bias	Page 39
Strength of study	Highlight strengths of proposed study	Page 39-40
References	List of references cited in protocol	Pages 42-49

Data collection forms	Summary table of all forms used for data collection at each point of study	Page 37
Informed consent forms	Sample of informed consent form, translated into local language	NA
Funding	Source of funding and the role of the funders for the present study	Page 5
Acknowledgement for protocol development	Acknowledgement of persons involved in protocol preparation	Page 41
Data sharing policy	To describe how data will be made available in public domain.	NA
Contributions of authors to protocol	Listed authors should have participated sufficiently in prepartion of protocol with details of their contribution.	Page 41
Trial registry	For observational studies also registered as trial	Page 7
Annexures	Data collection form /instruments Informed consent form Standard operating procedures (SOPs) Detailed Statistical analysis plan (SAP)	NA NA Tables 1-2 NA

BMJ Open

A Longitudinal Cohort Study Investigating Neurodevelopmental and Socio-emotional Outcomes in School-Entry aged Children after Open Heart Surgery in Australia and New Zealand: The NITRIC Follow-up Study Protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-075429.R1
Article Type:	Protocol
Date Submitted by the Author:	07-Aug-2023

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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Cardiovascular medicine, Intensive care
Keywords:	Congenital heart disease < CARDIOLOGY, Paediatric intensive & critical care < ANAESTHETICS, Developmental neurology & neurodisability < PAEDIATRICS, Paediatric cardiology < CARDIOLOGY, Paediatric cardiac surgery < PAEDIATRIC SURGERY

Title Page:

A Longitudinal Cohort Study Investigating Neurodevelopmental and Socio-emotional 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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Competing Interests Statement:

None declared.

Key words: child; congenital heart disease; cognition; behavior; neurodevelopment; trajectories; phenotype; preschool; school readiness; screening; latent effects

Funding: This work is supported by grants from the Medical Research Future Fund (ARGCHDG000036), Australia; the Children's Hospital Foundation, Australia; the Starship Foundation (SF4226), New Zealand; and the Green Lane Research and Educational Fund (21/22/4158), New Zealand. VA is supported by a National Health and Medical Research Council (Australia) Investigator Grant. The funding sources were not involved in study design, analyses, nor interpretation of the results.

Word Count: 3571

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 standardized 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 randomized 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 behavior 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 5 sites in Australia and New Zealand will be eligible. Follow-up assessments will occur in two stages: i) annual online screening of global neurodevelopment, socioemotional and executive functioning, health-related quality of life and parenting stress at ages 2-5 years; and ii) 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 (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.

Registration details: 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

ARTICLE SUMMARY

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.

- The NITRIC Follow-Up Study data will be combined with prospective well characterized datasets on clinical, socioeconomic, and biological variables, including multi-omics obtained pre and post CPB.

- CHD families, clinicians and other stakeholders have co-designed the NITRIC Follow-Up sSudy 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.

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 pediatric 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 amongst 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, visuo-spatial and visuo-motor challenges, attention deficits, motor delays, socioemotional problems, secondary learning disabilities and reduced quality of life (QoL) (6, 7). Early post-operative 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 quality of life, with long-lasting 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 (e.g., 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 quality of life (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.

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. Whilst the prevalence of severe cognitive impairment in children with CHD has declined, deficits in multiple cognitive and psychosocial domains are increasingly observed (19-21). Several studies have shown that even children whose intelligence quotient falls within the normal range may exhibit pervasive but subtle neuropsychological weaknesses, which are often underestimated or go undetected (22-25). Emerging data show that, while severity of CHD is associated with outcome, patients with both univentricular and biventricular surgeries demonstrate variable neurodevelopmental outcomes (20, 26). 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. 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 (21, 27) 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 (28). The Cardiac Neurodevelopmental Outcome Collaborative (CNOC), an international multidisciplinary group committed to optimizing neurodevelopmental outcomes for children with CHD, has recently recommended for future research to prioritize 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 (29). 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 CPB surgery and represents the largest randomized 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 to standard CPB. The protocol (30), analysis plan (31) and 28-day outcomes (32) of this study have been reported previously. The NITRIC trial represents a unique population-based and well characterized 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 standardized 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 multicenter, 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 (33) 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 (32). Children were recruited prior to surgery from six tertiary pediatric 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 to 2 years) and the four-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 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 timepoint. 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 (SEIFA IRSD) deciles and The New Zealand Index of Deprivation (NZDep) derived from the postcode recorded at PICU admission (34, 35). Postcode will also be used to determine regionality, using the Australian Bureau of Statistics' 5 classes of remoteness (Accessibility and Remoteness Index of Australia [ARIA]) and the Statistics New Zealand Urban Rural 2018 Classification (36, 37). 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 measure's reliability and validity, relevance to the CHD literature (38) 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 individualized 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 minutes 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. Supplemental Table S1 details the questionnaires included in annual screening assessments to be completed by parents. These measures assess child neurodevelopment, socioemotional status, quality of life, parent emotional well-being and parenting stress. We will also collect health service utilisation 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 & Primary Scale of Intelligence) tool administered first. Missing data (due to child or parent disability or lack of cooperation) will be recorded and categorized. 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, seven 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 (39), 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 (40, 41), 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 (Supplemental Tables S1 and S2) will be presented at each timepoint with the point estimate and measure of variation. In addition to continuous outcome measures, secondary analyses will use cut-offs to categorize 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 [ASQ] Total Score, Strengths and Difficulties Questionnaire [SDQ] Total Difficulties Score, and Behavior Rating Inventory for Executive Function for Pre-schoolers [BRIEF-P] 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 chi-squared 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 firstly 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 Supplemental Table S2) will be used to derive neurodevelopmental and socioemotional phenotypes. These will include the language, attention, executive functioning, and memory, and social behavior 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 firstly 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 datasets 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 (e.g., Silhouette index, Gap index, Dunn index), and one set of phenotypes from the multiple imputed datasets used for the remaining analyses. Graphical methods will be used to describe and visualize the composition of the phenotypes. Latent class analysis will then be used to assess the reproducibility of the phenotypes within the entire dataset.

Structural Equation Modelling

Structural equation modelling (SEM) 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 aged five. 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- and post-surgery samples and metabolomics data and proteomics data will be generated on subset of 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 datasets to derive a combination biomarker (including gene expression, metabolites and proteins) to predict short-term and long-term patient outcomes.

Feasibility and Engagement

To maximize follow-up rates, we have developed detailed standardized training on a follow-up delivery package for the study informed by published reports (42-45) 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 (e.g. 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 (46), 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 (i.e. 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 summarized 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 (30, 47, 48). The importance of long-term outcomes has been investigated by members of the research team through national and international research (49, 50). 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. Firstly, 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 (albeit positively); hence the collection of healthcare utilization data is an important inclusion in this study. Follow-up timing may range amongst 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 characterized datasets on clinical, socioeconomic, and biological variables, including multi-omics obtained pre- 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 quality of life measures, we will undertake the largest population-based follow-up cohort of infants undergoing CPB for CHD and collect extensive patient- and family-centered outcomes between 2 and 5 years of age. Through the combination with biochemical data obtained pre- and post-CPB, the program will seek to unravel links between early host response to CPB and late outcomes. As a result, this study will assist us in identify 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™ 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 centralized, and site monitoring of recruitment and survey completion rates. Following principles of the International Council of Harmonisation, Good Clinical Practice (ICH-GCP) 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 program meetings will be convened during the study to update all program 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 21st December 2020) and New Zealand Health and Disability Ethics Committee (21/NTA/83; original submission approved 6th September 2021). Recruitment commenced on May 10th, 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 (FOAM) resources to generate discussion and disseminate the outcomes of the study.

Author Statement:

DAL, VA, WB, KG and LJS conceived the study, developed the protocol, co-wrote the first draft of the manuscript, and approved the final draft. All other authors (LHC, NTS, KRC, ADM, SB, CFP, KM, NP, PJA, NB, BR, HB, KM, JCF, CS, SR, JB, SE, MSF, BWA, PV, DY, DA, MMHC, CPB, TLG, AI, IAN, JA) assisted with development of the interventions and methods, outcomes, and materials, reviewed the manuscript, and approved the final version.

Acknowledgements:

We would like to thank the families who have generously participated in the development of the methods and family materials, and who will participate in the study.

Patient and public involvement:

Patients and/or the public were involved in the design, conduct, reporting, and dissemination plans of this research. Refer to the Methods section for further details.

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Supplemental materials for:
A Longitudinal Cohort Study Investigating Neurodevelopmental and Socio-emotional 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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Table of Contents:

Table S1. Parent-completed online screening assessments conducted at 2- to 5-years of age

Construct	Instrument[#^]	Number of Items	Scoring and Interpretation	Comments
Child-focused Measures[§]				
Neurodevelopment	Ages and Stages Questionnaire, 3rd Edition (ASQ-3) (1)	30	Each item scored: Yes, Sometimes, or Not yet. Above, close to, and below cut-off scores provided based on aged norms for each domain. Domain scores added to create total score. Higher scores indicate better neurodevelopment. *Main outcome definition: Total ASQ-3 Score (continuous)*	5-10 mins to complete. 21 age-appropriate questionnaires for 1-66 months. Domains: communication, gross motor, fine motor, problem-solving and personal-social.
Socioemotional Behavior	Strengths and Difficulties Questionnaire (SDQ) (2)	25	Each item scored on a 3-point Likert scale: Not true, somewhat true, certainly true. Scale scores derived for Emotional problems, Conduct problems, Hyperactivity, Peer problems, Prosocial, and Total Difficulties, compared to aged norms. Higher scores indicate better socioemotional behavior. *Main outcome definition: Total Difficulties Score (continuous)*	5-10 mins to complete. Two age-appropriate questionnaires for 2-17 years. Domains: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, prosocial behaviors.
Health Related Quality of Life (HRQoL)	Pediatric Quality of Life Inventory (PedsQL) (3, 4)	23-38[a]	Each item scored on a 5-point Likert scale: 0 = Never a problem to 4 = Almost always a problem. Psychosocial Health Summary Score, Physical Health Summary Score, and Total Score, compared to aged norms. Higher scores indicate better HRQoL. *Main outcome definition: Total PedsQL Score (continuous)*	5 mins to complete. Five age-appropriate questionnaires for 1 month – 18 years. Domains: physical, emotional, social, and school functioning.

Construct	Instrument[#^]	Number of Items	Scoring and Interpretation	Comments
Executive Functioning	Behavior Rating Inventory for Executive Function for Pre-schoolers (BRIEF-P) (5)	63	Each item scored. Inhibitory Self-Control Index, Flexibility Index, Emergent Metacognition and Global Executive Composite score, compared to aged norms. The recommended cut-off for clinical significance is ≥ 65. Lower scores indicate better executive functioning. *Main outcome definition: Global Executive Composite Score (continuous)*	10-15 mins to complete. One questionnaire 2 - 5 years 11 months. Domains: inhibit, shift, emotional control, working memory, plan/organize.
Fatigue	The Pediatric Quality of Life Inventory (PedsQL) Multidimensional Fatigue Scale (6)	6	Each item scored on 5-point Likert scale: 0 = Never a problem to 4 = Almost always a problem. Total score compared to aged norms. Higher scores indicate lower problems. *Main outcome definition: Total General Fatigue Score (continuous)*	General Fatigue subscale only 2 minutes to complete. Four age-appropriate questionnaires for 2 – 18 years. Domains: General fatigue, Sleep/rest fatigue, and Cognitive fatigue.
Healthcare Utilisation	Developed by research team.	12	*Main outcome definition: Total parent-reported utilisation of in- and out-patient visits and costs (continuous)*	2 minutes to complete. Domains: Visits to healthcare professionals and facilities, and finances relating to appointments and care
Parent-focused Measures				
Emotional Wellbeing	The Kessler-6 (K6) (7)	6	Items are scored on a 5-point Likert scale (1= 'none of the time' to 5 = 'all of the time'). Total score ranged from 0-24, with higher scores representing higher levels of psychological distress such as anxiety and depression. *Main outcome definition: Total K6 Score (continuous)*	1 minute to complete

Construct	Instrument[#^]	Number of Items	Scoring and Interpretation	Comments
Parenting Stress	The Parenting Stress Index-4 Short Form (PSI-4-SF)(8)	36	Items are scored on a 4-point Likert scale: 1 = Strongly agree to 5 = strongly disagree. A percentile score on Total stress ≥ 91% indicates clinically significant levels of stress. Higher scores indicate more parenting stress. *Main outcome definition: Total PIS-4-SF Percentile Score (continuous)*	10 minutes to complete. Domains: Parental distress, Parent-child dysfunctional interaction, and Difficult child

[#]All measures used in accordance with associated user manuals; [^]Order of administration of questionnaires standardized; [§] All child-focused measures validated for use as parent-reported; [a] Depending on age.

Table S2. Face-to-face neurodevelopmental assessment at 5-years of age

Construct	Instrument[#^]	Number of Items	Scoring and Interpretation	Comments
Face-to-Face Measures				
Cognition	Wechsler Preschool & Primary Scale of Intelligence – 4th Edition Australia and New Zealand Standardised Edition (WPPSI-IV A&NZ) (9)	15 subtests	Three levels of interpretation: Full Scale, Primary Index scales, and Ancillary Index scales. The Full Scale and all indexes have a mean score of 100 and SD of 15. Higher scores indicate higher cognition. *Main outcome definition: Full Scale IQ (continuous)*	Block design, Information, Matrix reasoning, Bug search, Picture memory, Similarities, Cancellation and Zoo location subtests only. Administration time: 45-60 mins
Motor function	Movement Assessment Battery for Children, 2nd Edition (MABC-2) (10)	8 tasks	8 Task standard scores and a Total test score. Manual dexterity component score: sum of standard scores of MD1, MD2 and MD3. Higher scores indicate better motor function. *Main outcome definition: Manual Dexterity Component Score (continuous)*	Posting coins, Threading beads and Drawing trail 1 subtests only. Administration time: 10 mins
Executive Function	Day/Night Task (11)	16 cards	Total correct, Total Self Corrections, Total Time, Efficiency Score (Total Correct/Total Time to Complete). Higher scores indicate better executive function. *Main outcome definition: Efficiency Score (continuous)*	Administration time: 5 mins

Construct	Instrument#^	Number of Items	Scoring and Interpretation	Comments
Attention - Visual	Test of Everyday Attention for Children, 2nd Edition (TEA-Ch2) (12)	5 trials	Scaled scores have a mean of 10 and SD of 3 (Range 1-19). Percentile ranked score. Higher scores indicate better attention. *Main outcome definition: Attention Score (continuous)*	Balloon Hunt and Balloons 5 subtests only. Administration time: 7 mins
Language	Clinical Evaluation of Language Fundamentals – Australian and New Zealand 5th Edition Screening Test (CELF-5 A&NZ Screening Test) (13)	13	Total Score: sum of the child's score points. Total score compared to a research-based criterion score appropriate for the child's age. Age 5:0-8:11 have one criterion score. Higher scores indicate better language. *Main outcome definition: Total Score (continuous)*	Word structure, Word Classes, Following directions and Recalling sentences subtests only. Administration time: 10-15 mins
Attention	Conners Kiddie Continuous Performance Test, 2nd Edition (K-CPT 2) (14)	Up to 200 trials	Higher scores indicate poorer attention. *Main outcome definition: Composite Attention Score*	4 domains of attention: Impulsivity, Inattentiveness, Sustained attention, and Vigilance. Administration time: 7 mins

Construct	Instrument#^	Number of Items	Scoring and Interpretation	Comments
Memory	Wide Range Assessment of Memory and Learning, 3rd Edition (WRAML3) (15)	4 stories 85 questions	Scaled score, M=10, SD=3. Subtest scaled scores derived from the total raw scores on a given subtest- and describe the overall performance on that subtest. Story Memory – story memory total raw score. Story Recognition – story memory recognition total raw score. Higher scores indicate better memory. *Main outcome definition: Verbal Memory Score (continuous)*	Story Memory subtest only. Administration time: 20 mins
Memory	Working Memory Test Battery for Children (WMTB-C) (16)	9	Trials Correct Score: Total number of correct trials achieved before testing is discontinued. Higher scores indicate better memory. *Main outcome definition: Total Trials Correct (continuous)*	Digit Recall subtest only. Administration time: 5 mins
Parent-completed Online Measures				
Social behavior/Autism	Social Responsiveness Scale, 2nd Edition (SRS-2) (17)	65	Each item scored on a 4-point Likert scale: 1 = Not true to 4 = Almost always true. Scores: Total, Treatment subscales, DSM-5 compatible subscales. Higher scores indicate clinically significant deficiencies in social behavior *Main outcome definition: Total Score (continuous)*	Administration time: 15-20 mins

Construct	Instrument#^	Number of Items	Scoring and Interpretation	Comments
ADHD	ADHD Rating Scale, 5th Edition (ADHD-RS-5) (18)	18	Each item scored on a 4-point Likert scale. Scores: Total, Inattention and Hyperactivity-Impulsivity. Total raw score: Sum of inattention and hyperactivity subscale raw scores. Converted to total percentile score. Higher scores indicate more impairment in attention. *Main outcome definition: Total Percentile Score (continuous)*	Administration time: 5 mins
Social functioning	Adaptive Behavior Assessment System, 3rd Edition (ABAS-3) (19)	46	Each item is scored on a 4-point Likert scale: 0 = Is not able to do this behavior to 3 = Always (or almost always) Standard Score for Social Adaptive domain compared to norms. Mean of 100 and SD of 15. Lower scores indicate lower adaptive behaviors. General Adaptive Composite Score: Composed on all measured skill areas, providing an overall estimate of adaptive behavior. Higher scores indicate better social functioning. *Main outcome definition: General Adaptive Composite Score (continuous)*	Leisure and Social subscales only Administration time: 10 mins One age-appropriate questionnaire 5-21 years.

Construct	Instrument[#^]	Number of Items	Scoring and Interpretation	Comments
Fatigue	Pediatric Quality of Life Inventory (PedsQL) Multidimensional Fatigue Scale – Full scale (6)	18	Each item scored on 5-point Likert scale: 0 = Never a problem to 4 = Almost always a problem. Total score: Sum of general, sleep/rest and cognitive fatigue. Higher scores indicate lower problems. *Main outcome definition: Total Fatigue Score (continuous)*	Administration time: 5 mins Four age-appropriate questionnaires 2 – 18 years. Domains: General fatigue, Sleep/rest fatigue, and Cognitive fatigue.
Parent-Child Attachment	Attachment Relationship Inventory-Caregiver Perspective (ARI-CP 2-5) (20)	48	Each item scored on a 6-point Likert scale: 1 = Not at all applicable to 5 = Fully applicable. Four subscales (secure, avoidant, ambivalent, disorganized). Scale scores represent the sum scores of all items of the scale. Higher scores indicate better attachment. *Main outcome definition: Global Attachment Score (continuous)*	Administration time: 5 mins

[#]All measures used in accordance with associated user manuals; [^]Order of administration of questionnaires standardized; [a] Depending on age.

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Standard Protocol Items for Observational Studies (SPIROS)

Table 1: Checklist of preliminary items

Section and topic	Description / sub-categories	Addressed on page number
i) General Information		
Title	Descriptive title identifying study design	Page 1
Protocol version	Version or amendment number and date and summary of changes	NA
Protocol summary	Brief summary of protocol research	Pages 6-8
Sponsor and partner institute name	Name of sponsor and participating institutes (if applicable)	Page 12
Investigators name	Name of principal and co investigators.	Pages 1-4
Affiliation of investigators	Affiliated institutions of investigators	Pages 1-4
Principal researcher contact detail	Name, email address, affiliation of Principal researcher for correspondence.	Corresponding author page 4
Table of content	Table of content	NA
Page number	Page number on each page of protocol	Pages 1-49
List of Abbreviations	A detailed List of all abbreviations used in protocol with full form.	NA
ii) Introduction		
Background of study	Scientific background of study	Pages 9-11
Review of prior research	Summary of all previous relevant research	Pages 9-11

Rationale of study	Justification for conducting the study	Page 11
Aim	Broader aims and specific objectives of the study	Pages 12
Objective of study	Primary and secondry objectives of study	Page 12
Prespecified hypothesis	Prespecified null or alternative hypothesis	NA
iii) Methods		
Study design	Description of type/design of study	Page 12
Study setting	Description of setting, locations, relevant dates, including periods of recruitment/survey, exposure, follow-up, and data collection. Schedule of study procedure – Figure or table	Pages 13 Tables 1-2
Sample size	Estimated number, calculation and assumptions Power calculation	Page 35 NA
Sampling procedure	Description of sampling strategy to ensure representativeness and control of potential bias	Page 13
Participants	**Cohort study**—eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. For matched studies, give matching criteria and number of exposed and unexposed **Case-control study**—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls For matched studies, give matching criteria and the number of controls per case	Pages 13-15 Tables 1-2 NA

	Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	• All outcomes • Exposures- definition of exposure of interest, • Predictors • Potential confounders • Effect modifiers	Page 15 Tables 1-2
Data Sources/ Measurement	• For each variable of interest, give sources of data and details of methods of assessment (measurement). • Describe comparability of assessment methods if there is more than one group • Data collection points table • Blinding procedure	Page 16-19, 21 Tables 1-2 NA NA NA
Bias	Describe any efforts to address potential sources of bias More specifically- • Information bias • Selection Bias • Control for confounding	Pages 16-19, 21
Statistical analysis plan	• Method of primary / secondary outcomes and additional analysis • Handling of missing data • Post-hoc analysis	Pages 16-19 Pages 16-19 NA

Handling of withdrawals and lost to follow up	Describe the procedures to be followed when a participant ceases participation in the study prematurely or is lost to follow up	Pages 14-15, 16-19
Replacements	Provide information on whether or not participants who discontinue the study will be replaced via additional recruitment to maintain the required sample size.	NA
Outcome	Define and describe all primary and secondary outcome or lost to follow up	Pages -16-19 Tables 1-2
Database management	• Detail plan of database management including: • Data collection (electronic or paper based), • Source data • Data entry • Data editing • Coding • Data storage • Record retention • Data confidentiality	Page 22
Validation of instrument	Reliability / validity of instrument or plan to establish validation	Page 14-15 Tables 1-2
Follow up	Plan of follow up and addressing lost to follow up	Page 15; Tables 1-2
Quality control	• Method of quality control • Monitoring (internal and external) • Training of surveyors	Pages 22 Pages 22 Pages 22
Quality assurance	Plan of quality assurance	Pages 22

Expected outcome /results	A brief description of expected outcome or results	Pages 21
iv) Ethical consideration		
Ethical approval	Whether it has been obtained and name of ethical committees. If approval not sought , Reason	Page 22
Agreement and consent	Method of taking consent. Reason if consent not sought	Pages 14-15, 22
Risk / Harm to participants	Any potential risk or harm to study participants	NA
Adverse event and Severe adverse event reporting	Outline how Adverse Event and Severe adverse event information will be collected.	NA
v) Reporting and dissemination		
Protocol amendments	Methods of communicating to investigators/IRBs and documenting	Pages 22
Dissemination	How results will be disseminated to participants, practitioners, public	Page 22
Publication Plan	Who has right to publish; restrictions; authorship guidelines Open Access	NA
Reporting of early stopping	Dissemination of results if trial is stopped early (for any reason)	NA
vi) Others		
Limitations	Limitations of proposed study, including risk of bias	Page 21
Strength of study	Highlight strengths of proposed study	Page 21
References	List of references cited in protocol	Pages 24-30

Data collection forms	Summary table of all forms used for data collection at each point of study	Tables 1 and 2
Informed consent forms	Sample of informed consent form, translated into local language	NA
Funding	Source of funding and the role of the funders for the present study	Page 5
Acknowledgement for protocol development	Acknowledgement of persons involved in protocol preparation	Page 23
Data sharing policy	To describe how data will be made available in public domain.	NA
Contributions of authors to protocol	Listed authors should have participated sufficiently in prepartion of protocol with details of their contribution.	Page 23
Trial registry	For observational studies also registered as trial	Page 7
Annexures	Data collection form /instruments Informed consent form Standard operating procedures (SOPs) Detailed Statistical analysis plan (SAP)	NA NA Tables 1-2 NA

BMJ Open

A Longitudinal Cohort Study Investigating Neurodevelopmental and Socio-emotional Outcomes in School-Entry aged Children after Open Heart Surgery in Australia and New Zealand: The NITRIC Follow-up Study Protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-075429.R2
Article Type:	Protocol
Date Submitted by the Author:	08-Aug-2023

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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Cardiovascular medicine, Intensive care
Keywords:	Congenital heart disease < CARDIOLOGY, Paediatric intensive & critical care < ANAESTHETICS, Developmental neurology & neurodisability < PAEDIATRICS, Paediatric cardiology < CARDIOLOGY, Paediatric cardiac surgery < PAEDIATRIC SURGERY

Title Page:

A Longitudinal Cohort Study Investigating Neurodevelopmental and Socio-emotional 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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Competing Interests Statement:

None declared.

Key words: child; congenital heart disease; cognition; behavior; neurodevelopment; trajectories; phenotype; preschool; school readiness; screening; latent effects

Funding: This work is supported by grants from the Medical Research Future Fund (ARGCHDG000036), Australia; the Children's Hospital Foundation, Australia; the Starship Foundation (SF4226), New Zealand; and the Green Lane Research and Educational Fund (21/22/4158), New Zealand. VA is supported by a National Health and Medical Research Council (Australia) Investigator Grant. The funding sources were not involved in study design, analyses, nor interpretation of the results.

Word Count: 3571

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 standardized 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 randomized 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 behavior 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 5 sites in Australia and New Zealand will be eligible. Follow-up assessments will occur in two stages: i) annual online screening of global neurodevelopment, socioemotional and executive functioning, health-related quality of life and parenting stress at ages 2-5 years; and ii) 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 (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.

Registration details: 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

ARTICLE SUMMARY

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.

- The NITRIC Follow-Up Study data will be combined with prospective well characterized datasets on clinical, socioeconomic, and biological variables, including multi-omics obtained pre and post CPB.

- CHD families, clinicians and other stakeholders have co-designed the NITRIC Follow-Up sSudy 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.

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 pediatric 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 amongst 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, visuo-spatial and visuo-motor challenges, attention deficits, motor delays, socioemotional problems, secondary learning disabilities and reduced quality of life (QoL) (6, 7). Early post-operative 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 quality of life, with long-lasting 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 (e.g., 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 quality of life (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. Whilst 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 intelligence quotient 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 (CNOC), an international multidisciplinary group committed to optimizing neurodevelopmental outcomes for children with CHD, has recently recommended for future research to prioritize 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 CPB surgery and represents the largest randomized 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 to 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 characterized 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 standardized 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 multicenter, 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 pediatric 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 to 2 years) and the four-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 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 timepoint. 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 (SEIFA IRSD) deciles and The New Zealand Index of Deprivation (NZDep) derived from the postcode recorded at 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 [ARIA]) 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 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 individualized 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 minutes 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. Supplemental Table S1 details the questionnaires included in annual screening assessments to be completed by parents. These measures assess child neurodevelopment, socioemotional status, quality of life, parent emotional well-being and parenting stress. We will also collect health service utilisation 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 & Primary Scale of Intelligence) tool administered first. Missing data (due to child or parent disability or lack of cooperation) will be recorded and categorized. 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, seven 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 (Supplemental Tables S1 and S2) will be presented at each timepoint with the point estimate and measure of variation. In addition to continuous outcome measures, secondary analyses will use cut-offs to categorize 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 [ASQ] Total Score, Strengths and Difficulties Questionnaire [SDQ] Total Difficulties Score, and Behavior Rating Inventory for Executive Function for Pre-schoolers [BRIEF-P] 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 chi-squared 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 firstly 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 Supplemental Table S2) will be used to derive neurodevelopmental and socioemotional phenotypes. These will include the language, attention, executive functioning, and memory, and social behavior 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 firstly 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 datasets 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 (e.g., Silhouette index, Gap index, Dunn index), and one set of phenotypes from the multiple imputed datasets used for the remaining analyses. Graphical methods will be used to describe and visualize the composition of the phenotypes. Latent class analysis will then be used to assess the reproducibility of the phenotypes within the entire dataset.

Structural Equation Modelling

Structural equation modelling (SEM) 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 aged five. 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- and post-surgery samples and metabolomics data and proteomics data will be generated on subset of 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 datasets to derive a combination biomarker (including gene expression, metabolites and proteins) to predict short-term and long-term patient outcomes.

Feasibility and Engagement

To maximize follow-up rates, we have developed detailed standardized 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 (e.g. 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 (i.e. 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 summarized 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. Firstly, 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 (albeit positively); hence the collection of healthcare utilization data is an important inclusion in this study. Follow-up timing may range amongst 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 characterized datasets on clinical, socioeconomic, and biological variables, including multi-omics obtained pre- 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 quality of life measures, we will undertake the largest population-based follow-up cohort of infants undergoing CPB for CHD and collect extensive patient- and family-centered outcomes between 2 and 5 years of age. Through the combination with biochemical data obtained pre- and post-CPB, the program will seek to unravel links between early host response to CPB and late outcomes. As a result, this study will assist us in identify 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™ 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 centralized, and site monitoring of recruitment and survey completion rates. Following principles of the International Council of Harmonisation, Good Clinical Practice (ICH-GCP) 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 program meetings will be convened during the study to update all program 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 21st December 2020) and New Zealand Health and Disability Ethics Committee (21/NTA/83; original submission approved 6th September 2021). Recruitment commenced on May 10th, 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 (FOAM) resources to generate discussion and disseminate the outcomes of the study.

Author Statement:

DAL, VA, WB, KG and LJS conceived the study, developed the protocol, co-wrote the first draft of the manuscript, and approved the final draft. All other authors (LHC, NTS, KRC, ADM, SB, CFP, KM, NP, PJA, NB, BR, HB, KM, JCF, CS, SR, JB, SE, MSF, BWA, PV, DY, DA, MMHC, CPB, TLG, AI, IAN, JA) assisted with development of the interventions and methods, outcomes, and materials, reviewed the manuscript, and approved the final version.

Acknowledgements:

We would like to thank the families who have generously participated in the development of the methods and family materials, and who will participate in the study.

Patient and public involvement:

Patients and/or the public were involved in the design, conduct, reporting, and dissemination plans of this research. Refer to the Methods section for further details.

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Supplemental materials for:
A Longitudinal Cohort Study Investigating Neurodevelopmental and Socio-emotional 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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Table of Contents:

Table S1. Parent-completed online screening assessments conducted at 2- to 5-years of age

Construct	Instrument[#^]	Number of Items	Scoring and Interpretation	Comments
Child-focused Measures[§]				
Neurodevelopment	Ages and Stages Questionnaire, 3rd Edition (ASQ-3) (1)	30	Each item scored: Yes, Sometimes, or Not yet. Above, close to, and below cut-off scores provided based on aged norms for each domain. Domain scores added to create total score. Higher scores indicate better neurodevelopment. *Main outcome definition: Total ASQ-3 Score (continuous)*	5-10 mins to complete. 21 age-appropriate questionnaires for 1-66 months. Domains: communication, gross motor, fine motor, problem-solving and personal-social.
Socioemotional Behavior	Strengths and Difficulties Questionnaire (SDQ) (2)	25	Each item scored on a 3-point Likert scale: Not true, somewhat true, certainly true. Scale scores derived for Emotional problems, Conduct problems, Hyperactivity, Peer problems, Prosocial, and Total Difficulties, compared to aged norms. Higher scores indicate better socioemotional behavior. *Main outcome definition: Total Difficulties Score (continuous)*	5-10 mins to complete. Two age-appropriate questionnaires for 2-17 years. Domains: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, prosocial behaviors.
Health Related Quality of Life (HRQoL)	Pediatric Quality of Life Inventory (PedsQL) (3, 4)	23-38[a]	Each item scored on a 5-point Likert scale: 0 = Never a problem to 4 = Almost always a problem. Psychosocial Health Summary Score, Physical Health Summary Score, and Total Score, compared to aged norms. Higher scores indicate better HRQoL. *Main outcome definition: Total PedsQL Score (continuous)*	5 mins to complete. Five age-appropriate questionnaires for 1 month – 18 years. Domains: physical, emotional, social, and school functioning.

Construct	Instrument[#^]	Number of Items	Scoring and Interpretation	Comments
Executive Functioning	Behavior Rating Inventory for Executive Function for Pre-schoolers (BRIEF-P) (5)	63	Each item scored. Inhibitory Self-Control Index, Flexibility Index, Emergent Metacognition and Global Executive Composite score, compared to aged norms. The recommended cut-off for clinical significance is ≥ 65. Lower scores indicate better executive functioning. *Main outcome definition: Global Executive Composite Score (continuous)*	10-15 mins to complete. One questionnaire 2 - 5 years 11 months. Domains: inhibit, shift, emotional control, working memory, plan/organize.
Fatigue	The Pediatric Quality of Life Inventory (PedsQL) Multidimensional Fatigue Scale (6)	6	Each item scored on 5-point Likert scale: 0 = Never a problem to 4 = Almost always a problem. Total score compared to aged norms. Higher scores indicate lower problems. *Main outcome definition: Total General Fatigue Score (continuous)*	General Fatigue subscale only 2 minutes to complete. Four age-appropriate questionnaires for 2 – 18 years. Domains: General fatigue, Sleep/rest fatigue, and Cognitive fatigue.
Healthcare Utilisation	Developed by research team.	12	*Main outcome definition: Total parent-reported utilisation of in- and out-patient visits and costs (continuous)*	2 minutes to complete. Domains: Visits to healthcare professionals and facilities, and finances relating to appointments and care
Parent-focused Measures				
Emotional Wellbeing	The Kessler-6 (K6) (7)	6	Items are scored on a 5-point Likert scale (1= 'none of the time' to 5 = 'all of the time'). Total score ranged from 0-24, with higher scores representing higher levels of psychological distress such as anxiety and depression. *Main outcome definition: Total K6 Score (continuous)*	1 minute to complete

Construct	Instrument[#^]	Number of Items	Scoring and Interpretation	Comments
Parenting Stress	The Parenting Stress Index-4 Short Form (PSI-4-SF)(8)	36	Items are scored on a 4-point Likert scale: 1 = Strongly agree to 5 = strongly disagree. A percentile score on Total stress ≥ 91% indicates clinically significant levels of stress. Higher scores indicate more parenting stress. *Main outcome definition: Total PIS-4-SF Percentile Score (continuous)*	10 minutes to complete. Domains: Parental distress, Parent-child dysfunctional interaction, and Difficult child

[#]All measures used in accordance with associated user manuals; [^]Order of administration of questionnaires standardized; [§] All child-focused measures validated for use as parent-reported; [a] Depending on age.

Table S2. Face-to-face neurodevelopmental assessment at 5-years of age

Construct	Instrument[#^]	Number of Items	Scoring and Interpretation	Comments
Face-to-Face Measures				
Cognition	Wechsler Preschool & Primary Scale of Intelligence – 4th Edition Australia and New Zealand Standardised Edition (WPPSI-IV A&NZ) (9)	15 subtests	Three levels of interpretation: Full Scale, Primary Index scales, and Ancillary Index scales. The Full Scale and all indexes have a mean score of 100 and SD of 15. Higher scores indicate higher cognition. *Main outcome definition: Full Scale IQ (continuous)*	Block design, Information, Matrix reasoning, Bug search, Picture memory, Similarities, Cancellation and Zoo location subtests only. Administration time: 45-60 mins
Motor function	Movement Assessment Battery for Children, 2nd Edition (MABC-2) (10)	8 tasks	8 Task standard scores and a Total test score. Manual dexterity component score: sum of standard scores of MD1, MD2 and MD3. Higher scores indicate better motor function. *Main outcome definition: Manual Dexterity Component Score (continuous)*	Posting coins, Threading beads and Drawing trail 1 subtests only. Administration time: 10 mins
Executive Function	Day/Night Task (11)	16 cards	Total correct, Total Self Corrections, Total Time, Efficiency Score (Total Correct/Total Time to Complete). Higher scores indicate better executive function. *Main outcome definition: Efficiency Score (continuous)*	Administration time: 5 mins

Construct	Instrument#^	Number of Items	Scoring and Interpretation	Comments
Attention - Visual	Test of Everyday Attention for Children, 2nd Edition (TEA-Ch2) (12)	5 trials	Scaled scores have a mean of 10 and SD of 3 (Range 1-19). Percentile ranked score. Higher scores indicate better attention. *Main outcome definition: Attention Score (continuous)*	Balloon Hunt and Balloons 5 subtests only. Administration time: 7 mins
Language	Clinical Evaluation of Language Fundamentals – Australian and New Zealand 5th Edition Screening Test (CELF-5 A&NZ Screening Test) (13)	13	Total Score: sum of the child's score points. Total score compared to a research-based criterion score appropriate for the child's age. Age 5:0-8:11 have one criterion score. Higher scores indicate better language. *Main outcome definition: Total Score (continuous)*	Word structure, Word Classes, Following directions and Recalling sentences subtests only. Administration time: 10-15 mins
Attention	Conners Kiddie Continuous Performance Test, 2nd Edition (K-CPT 2) (14)	Up to 200 trials	Higher scores indicate poorer attention. *Main outcome definition: Composite Attention Score*	4 domains of attention: Impulsivity, Inattentiveness, Sustained attention, and Vigilance. Administration time: 7 mins

Construct	Instrument#^	Number of Items	Scoring and Interpretation	Comments
Memory	Wide Range Assessment of Memory and Learning, 3rd Edition (WRAML3) (15)	4 stories 85 questions	Scaled score, M=10, SD=3. Subtest scaled scores derived from the total raw scores on a given subtest- and describe the overall performance on that subtest. Story Memory – story memory total raw score. Story Recognition – story memory recognition total raw score. Higher scores indicate better memory. *Main outcome definition: Verbal Memory Score (continuous)*	Story Memory subtest only. Administration time: 20 mins
Memory	Working Memory Test Battery for Children (WMTB-C) (16)	9	Trials Correct Score: Total number of correct trials achieved before testing is discontinued. Higher scores indicate better memory. *Main outcome definition: Total Trials Correct (continuous)*	Digit Recall subtest only. Administration time: 5 mins
Parent-completed Online Measures				
Social behavior/Autism	Social Responsiveness Scale, 2nd Edition (SRS-2) (17)	65	Each item scored on a 4-point Likert scale: 1 = Not true to 4 = Almost always true. Scores: Total, Treatment subscales, DSM-5 compatible subscales. Higher scores indicate clinically significant deficiencies in social behavior *Main outcome definition: Total Score (continuous)*	Administration time: 15-20 mins

Construct	Instrument#^	Number of Items	Scoring and Interpretation	Comments
ADHD	ADHD Rating Scale, 5th Edition (ADHD-RS-5) (18)	18	Each item scored on a 4-point Likert scale. Scores: Total, Inattention and Hyperactivity-Impulsivity. Total raw score: Sum of inattention and hyperactivity subscale raw scores. Converted to total percentile score. Higher scores indicate more impairment in attention. *Main outcome definition: Total Percentile Score (continuous)*	Administration time: 5 mins
Social functioning	Adaptive Behavior Assessment System, 3rd Edition (ABAS-3) (19)	46	Each item is scored on a 4-point Likert scale: 0 = Is not able to do this behavior to 3 = Always (or almost always) Standard Score for Social Adaptive domain compared to norms. Mean of 100 and SD of 15. Lower scores indicate lower adaptive behaviors. General Adaptive Composite Score: Composed on all measured skill areas, providing an overall estimate of adaptive behavior. Higher scores indicate better social functioning. *Main outcome definition: General Adaptive Composite Score (continuous)*	Leisure and Social subscales only Administration time: 10 mins One age-appropriate questionnaire 5-21 years.

Construct	Instrument[#^]	Number of Items	Scoring and Interpretation	Comments
Fatigue	Pediatric Quality of Life Inventory (PedsQL) Multidimensional Fatigue Scale – Full scale (6)	18	Each item scored on 5-point Likert scale: 0 = Never a problem to 4 = Almost always a problem. Total score: Sum of general, sleep/rest and cognitive fatigue. Higher scores indicate lower problems. *Main outcome definition: Total Fatigue Score (continuous)*	Administration time: 5 mins Four age-appropriate questionnaires 2 – 18 years. Domains: General fatigue, Sleep/rest fatigue, and Cognitive fatigue.
Parent-Child Attachment	Attachment Relationship Inventory-Caregiver Perspective (ARI-CP 2-5) (20)	48	Each item scored on a 6-point Likert scale: 1 = Not at all applicable to 5 = Fully applicable. Four subscales (secure, avoidant, ambivalent, disorganized). Scale scores represent the sum scores of all items of the scale. Higher scores indicate better attachment. *Main outcome definition: Global Attachment Score (continuous)*	Administration time: 5 mins

[#]All measures used in accordance with associated user manuals; [^]Order of administration of questionnaires standardized; [a] Depending on age.

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Standard Protocol Items for Observational Studies (SPIROS)

Table 1: Checklist of preliminary items

Section and topic	Description / sub-categories	Addressed on page number
i) General Information		
Title	Descriptive title identifying study design	Page 1
Protocol version	Version or amendment number and date and summary of changes	NA
Protocol summary	Brief summary of protocol research	Pages 6-8
Sponsor and partner institute name	Name of sponsor and participating institutes (if applicable)	Page 12
Investigators name	Name of principal and co investigators.	Pages 1-4
Affiliation of investigators	Affiliated institutions of investigators	Pages 1-4
Principal researcher contact detail	Name, email address, affiliation of Principal researcher for correspondence.	Corresponding author page 4
Table of content	Table of content	NA
Page number	Page number on each page of protocol	Pages 1-49
List of Abbreviations	A detailed List of all abbreviations used in protocol with full form.	NA
ii) Introduction		
Background of study	Scientific background of study	Pages 9-11
Review of prior research	Summary of all previous relevant research	Pages 9-11

Rationale of study	Justification for conducting the study	Page 11
Aim	Broader aims and specific objectives of the study	Pages 12
Objective of study	Primary and secondry objectives of study	Page 12
Prespecified hypothesis	Prespecified null or alternative hypothesis	NA
iii) Methods		
Study design	Description of type/design of study	Page 12
Study setting	Description of setting, locations, relevant dates, including periods of recruitment/survey, exposure, follow-up, and data collection. Schedule of study procedure – Figure or table	Pages 13 Tables 1-2
Sample size	Estimated number, calculation and assumptions Power calculation	Page 35 NA
Sampling procedure	Description of sampling strategy to ensure representativeness and control of potential bias	Page 13
Participants	**Cohort study**—eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. For matched studies, give matching criteria and number of exposed and unexposed **Case-control study**—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls For matched studies, give matching criteria and the number of controls per case	Pages 13-15 Tables 1-2 NA

	Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	
Variables	• All outcomes • Exposures- definition of exposure of interest, • Predictors • Potential confounders • Effect modifiers	Page 15 Tables 1-2
Data Sources/ Measurement	• For each variable of interest, give sources of data and details of methods of assessment (measurement). • Describe comparability of assessment methods if there is more than one group • Data collection points table • Blinding procedure	Page 16-19, 21 Tables 1-2 NA NA NA
Bias	Describe any efforts to address potential sources of bias More specifically- • Information bias • Selection Bias • Control for confounding	Pages 16-19, 21
Statistical analysis plan	• Method of primary / secondary outcomes and additional analysis • Handling of missing data • Post-hoc analysis	Pages 16-19 Pages 16-19 NA

Handling of withdrawals and lost to follow up	Describe the procedures to be followed when a participant ceases participation in the study prematurely or is lost to follow up	Pages 14-15, 16-19
Replacements	Provide information on whether or not participants who discontinue the study will be replaced via additional recruitment to maintain the required sample size.	NA
Outcome	Define and describe all primary and secondary outcome or lost to follow up	Pages -16-19 Tables 1-2
Database management	• Detail plan of database management including: • Data collection (electronic or paper based), • Source data • Data entry • Data editing • Coding • Data storage • Record retention • Data confidentiality	Page 22
Validation of instrument	Reliability / validity of instrument or plan to establish validation	Page 14-15 Tables 1-2
Follow up	Plan of follow up and addressing lost to follow up	Page 15; Tables 1-2
Quality control	• Method of quality control • Monitoring (internal and external) • Training of surveyors	Pages 22 Pages 22 Pages 22
Quality assurance	Plan of quality assurance	Pages 22

Expected outcome /results	A brief description of expected outcome or results	Pages 21
iv) Ethical consideration		
Ethical approval	Whether it has been obtained and name of ethical committees. If approval not sought , Reason	Page 22
Agreement and consent	Method of taking consent. Reason if consent not sought	Pages 14-15, 22
Risk / Harm to participants	Any potential risk or harm to study participants	NA
Adverse event and Severe adverse event reporting	Outline how Adverse Event and Severe adverse event information will be collected.	NA
v) Reporting and dissemination		
Protocol amendments	Methods of communicating to investigators/IRBs and documenting	Pages 22
Dissemination	How results will be disseminated to participants, practitioners, public	Page 22
Publication Plan	Who has right to publish; restrictions; authorship guidelines Open Access	NA
Reporting of early stopping	Dissemination of results if trial is stopped early (for any reason)	NA
vi) Others		
Limitations	Limitations of proposed study, including risk of bias	Page 21
Strength of study	Highlight strengths of proposed study	Page 21
References	List of references cited in protocol	Pages 24-30

Data collection forms	Summary table of all forms used for data collection at each point of study	Tables 1 and 2
Informed consent forms	Sample of informed consent form, translated into local language	NA
Funding	Source of funding and the role of the funders for the present study	Page 5
Acknowledgement for protocol development	Acknowledgement of persons involved in protocol preparation	Page 23
Data sharing policy	To describe how data will be made available in public domain.	NA
Contributions of authors to protocol	Listed authors should have participated sufficiently in prepartion of protocol with details of their contribution.	Page 23
Trial registry	For observational studies also registered as trial	Page 7
Annexures	Data collection form /instruments Informed consent form Standard operating procedures (SOPs) Detailed Statistical analysis plan (SAP)	NA NA Tables 1-2 NA