

**Clinical Research Protocol**

***neurovascular function and cognition in adult patients with complex congenital heart disease***

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| **Funder:** | *John Hunter Hospital Charitable Trust* |
| **Protocol Number:** | *1.1* |

**Initial version: 28-Feb-2017**

**Amended: 1 May 2017**

**Amended:** [date]

# Study Summary

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| Title | ***Neurovascular function and cognition in adult patients with complex congenital heart disease*** |
| Short Title | *CoCo Heart Disease* |
| Protocol Number | *1.1* |
| Phase | *2* |
| Methodology | *Cross-sectional study* |
| Study Duration | *9 months* |
| Study Centre(s) | *Clinical Nutrition Research Centre*  *University of Newcastle, Callaghan Campus*  *Medical Sciences Building MS 304* |
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| Objectives | *To examine cerebrovascular and cognitive function in patients with complex congenital heart disease using transcranial Doppler (TCD) ultrasound.* |
| Number of Subjects | *15 adults with complex congenital heart disease and 15 age-gender matched adults without heart disease* |
| Main Inclusion Criteria | *Adult patients with complex congenital heart disease, having measurable ultrasound signal on both sides of the head. Control participants should be healthy and without heart disease.* |
| Study outcomes | *Measures of cerebrovascular function:*   * *Cerebrovascular responsiveness (CVR) to cognitive testing and photic stimuli (uses TCD Doppler ultrasound to assess the ability of blood vessels to dilate).*   *Measures of cognitive function*   * *Composite scores of individual cognitive tests*   *Measure of gait speed*   * *Speed of gait at 4m and at 20m*   *Relationships between cerebrovascular function and cognitive outcomes*   * *The responsiveness of cerebral blood flow and the participants’ cognitive performance will be used to compare between groups and to determine the correlation between blood flow in the brain and cognitive outcomes and gait speed.* |
| Duration of administration | *N/A* |
| Reference therapy | *Nil* |
| Statistical Consideration | *Participant characteristics will be used as covariates if they are significantly correlated with the outcome measures. A two-sample t-test will be used to compare the group differences in outcome measures. Where appropriate, Bonferroni adjustments will be made to allow for multiple comparisons.* |

# Introduction

## Background

Patients born with congenital heart disease now expect excellent survival into adulthood, such that the number of adults with congenital heart disease now exceeds the number of affected children. While survival into adult life is excellent, there is increasing understanding of adverse sequelae complicating complex forms of congenital heart disease, which influence late morbidity and quality of life. In particular, the recognition of cognitive impairment is increasingly relevant with understanding of possible mechanisms limited.

Poor cerebral perfusion has been associated with cognitive impairment in late life. While the presence of cognitive impairment is recognised in patients with congenital heart disease compared to the general population, the underlying mechanisms remain unclear. Impaired executive function has been attributed to the effects of surgery and the underlying cardiac lesions on neurodevelopment; based on these findings, abnormal cerebral perfusion may potentially contribute. Neuronal activation promotes the endothelium to release nitric oxide, resulting in dilatation of local arterioles, which is reflected in increased blood flow in the larger vessels. Impaired vasodilation may reduce the normal perfusion increase during neuronal activation potentially contributing to poor cognitive performance. Even in healthy older women, early cerebrovascular deficits predicted cognitive dysfunction (1).

## Preclinical Data to Date

None

## Clinical Data to Date

In a proof-of-concept cross-sectional comparison between patients with previous surgical repair of aortic coarctation and controls, we have shown impairment of cerebrovascular responsiveness to hypercapnic challenges in the middle cerebral artery and advanced intracranial stiffness in the patient group. Furthermore, these patients also exhibited abnormalities of neurovascular coupling, as measured by photic stimulation in the posterior cerebral artery (paper accepted 8th April 2017 in the Journal of the European Paediatric Cardiology Society). Research on the neurocognitive sequelae such as neurovascular and cognitive functioning or dementia risk in patients with complex congenital heart disease is limited. We now want to investigate whether there are associations between abnormal cerebral perfusion and cognitive function in older adults with complex congenital heart disease.

# Study Objectives

To document the presence of abnormalities of neurovascular coupling as a marker of cognitive impairment in a cohort of patients with complex congenital heart disease in a cross-sectional investigation.

## Primary outcome

Cerebrovascular responsiveness (CVR) to cognitive testing at the level of the middle cerebral artery (MCA)

## Secondary outcomes

- CVR to photic stimulation

- Basal cerebrovascular hemodynamics

- Cognitive performance

- Gait speed

The outcome of this study would be an improved understanding among physicians of the presence of any abnormalities in cerebral blood flow in these patients. As these adults may require late interventions to maintain cardiac status, which predispose to further cognitive deficits, utilisation of methods with the ability to detect subclinical abnormalities of cerebral blood flow is critical; such tools may allow for early intervention where appropriate, document changes after procedures and measure efficacy of interventions designed to minimise cerebral injury during complex cardiac surgical procedures.

# Methods and Procedures

## Study Design

A cross-sectional investigation of cerebrovascular and cognitive function in adult patients with complex congenital heart disease.

The study will be conducted according to International Conference on Harmonization guidelines for Good Clinical Practice and University of Newcastle research policies and procedures.

## Participant recruitment

Recruitment for this project will commence following approval of the protocol by the Human Ethics Committee of University of Newcastle. It is anticipated that the subject activity will last for one visit. Control participants will be recruited from the Hunter Region in NSW using media advertising approved by the University of Newcastle Media and Marketing Department. Recruitment flyers will also be placed on noticeboards at the University of Newcastle, local pharmacies, local pathology centres (with permission). Participants will also be recruited from the Hunter Medical Research Institute (HMRI) Volunteer Register. Recruitment for volunteers for the control group will commence after we have completed data collection in the patient group. Participants in the patient group will be referred to the CNRC by the chief investigator.

Interested participants will contact the study coordinator who will send a Participant Information Statement, Consent Form and Health, Diet & Lifestyle Questionnaire for the purpose of obtaining demographic and lifestyle details. This is to help determine the participant’s suitability before visiting the CNRC and to collect data for the reporting of participant characteristics (i.e. whether participant meets the specific study inclusion).

## Study procedures- Screening and eligibility

Volunteers will be required to attend the CNRC for screening. If they are eligible, data collection for our outcome assessments will continue at the same visit.

### Obtaining informed consent

According to GCP-guidelines and also the Declaration of Helsinki, written informed consent must be obtained from subjects prior to participation in the trial. Subjects will voluntarily confirm their willingness to participate in the trial, after having been informed in writing and verbally of all aspects of the trial that are relevant to the subject's decision to participate. Subjects will be informed about requirements concerning data protection and have to agree to the direct access to their individual data. Subjects will sign an informed consent form for study participation. The informed consent form has to be signed and personally dated by the subject or legal guardian and the Investigator. Before informed consent is obtained, the subject has to be provided sufficient time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial will be answered to the satisfaction of the subject. The original signed informed consent form will be kept with the study documentation. A copy of the signed informed consent document and participant information sheet must be given to the subject.

### Assessment of eligibility at visit to clinic

Participants will arrive at the CNRC for further screening to determine study eligibility. Anthropometric measurements of height, weight and waist circumference will be obtained before clinic BP is assessed to determine compliance with the study’s blood pressure criteria.

Participants will then be fitted with a headpiece supporting an ultrasound probe on each temporal region. An investigator will adjust the probes until a measurable blood flow signal is obtained in each MCA. If the investigator is unable to obtain a blood flow signal in both MCAs, the participant will be excluded from the study. Otherwise, the participant will be assessed. The ultrasound will continuously record the changes in blood flow velocities in the MCA during a cognitive test battery. After the cognitive test, the investigator will adjust the ultrasound probes to locate the posterior cerebral arteries [either the posterior cerebral arteries (PCA) or the basilar artery (BA)] on either side of the temporal window. Due to the anatomical depth of the BA, the transforaminal (occipital) window is usually the site of insonation; however, it may be possible to detect a blood flow signal from the transtemporal window (same window as the MCA). In the event that the BA cannot be detected, the posterior cerebral artery will be located. Studies have confirmed that the PCA and BA responsiveness to hypercapnia is similar and therefore can be used as its own surrogate (1). Once a suitable blood flow signal is located, participant will be asked to open and close their eyes as guided by the investigator. Participants will not be excluded if blood flow signals from the posterior arteries are not found. A walking test will be administered as the last assessment

## Outcome assessments

### Blood Pressure (BP)

Seated BP will be assessed after resting in a seated position for 10 min. Four consecutive BP and HR readings will be taken at 5-minute intervals by automated oscillometry using a standard BP cuff over the left brachial artery (to assess BP). BP measurements will be performed by a single investigator, in accordance with the procedures outlined by the Joint National Committee on Prevention, Evaluation and Treatment of High Blood Pressure (VI): US Dept of Health and Human Services. Discarding the first reading, an average of the remaining measurements will be recorded for analysis.

### Cerebral artery stiffness (extent of arterial hardening) using pulsatility index (TCD)

Resting cerebral blood flow pulsatility and resistive index of the MCA will be determined during the basal blood flow recordings.

### Cognitive test battery

The neuropsychological test battery will consist of the National Institute of Health (NIH) Toolbox battery of cognitive function, which has been normed and validated across the lifespan (3), with additional tests of the executive function (Trail Making Task) and working memory (N-back Test and Spatial Span Test). The NIH test battery and Spatial Span Test will be delivered via an iPad and will assess domains of language, attention, information processing speed, working and episodic memory.

Trail Making Task will be assessed by pen-paper modality and will comprised of part A and part B. Trail Making Task, Part A, measures the ability to scan and to connect 25 numbers/letters consecutively that are placed randomly on a page (i.e. 1-2-3-4… or A-B-C-D…). This process requires both working memory and processing speed, which is found to be less efficient with age. Part B of the task assesses cognitive flexibility and processing speed, a process generally referred to as executive control, while alternating between connecting a number and letters in sequence with speed and accuracy (e.g. 1-A-2-B-3-C…). Time taken to complete Parts B and A forms an interference ratio score (B:A).

N-Back task will be presented on a computer screen. Targets and non-targets of digits will appear at a fast rate. The participant has to press a button whenever they see the target. In the 1-back condition, the target is any number identical to the trial preceding it. In the 2-back condition, the target is any number identical to the one presented two trials back. In the 3-back condition, the target is any number identical to the one presented three trials back. The task will consist out of 6 randomized blocks, each condition has 2 blocks. The blocks will last for 1.5 minutes and consist out of 30 trials. Errors and missed targets will be scored.

Spatial Span test

This test assesses working memory capacity. A random number of white squares are presented on the screen, some of which will briefly change colour in a variable sequence. The participant must then touch the boxes, which changed colour, in the same order that they were displayed by the iPad. The number of boxes increases from two at the start of the test to nine at the end. The longest sequence successfully recalled and time taken will be recorded.

### NIH Toolbox battery of cognitive test

De-identified results are stored in the device and will be transferred securely and backup on the University’s Network Drive and OwnCloud Drive.

Picture Vocabulary Test

The participant is presented with four pictures on the iPad screen and an audio recording saying a word. The participant is instructed to touch the picture that most closely shows the meaning of the word. After the participant makes a choice, another set of pictures automatically appears with the next item and associated audio files. The specific words presented depend on the participants’ performance. For most participants, the measure will last approximately five minutes and will contain 25 items. The iPad will administer each item one by one, in an untimed fashion, until the test is completed.

Flanker Inhibitory Control and Attention Test

This test is a measure of inhibitory control and attention. The Flanker requires the participant to focus on a particular stimulus while inhibiting attention to the stimuli flanking it. Participants are instructed to choose one of two buttons on the screen that corresponds to the direction in which the middle arrow is pointing. On congruent trials, all the arrows are pointing in the same direction. On incongruent trials, the flanking arrows are pointing in the opposite direction of the middle arrow. Congruent and incongruent trials are mixed. The word *middle* will appear on the screen. Participants will be instructed to select the button that matches the way the MIDDLE arrow is point and place their index finger on the Home Base after they have responded. There will be 20 trials in this test.

List Sorting Working Memory Test

This task assesses working memory and will require participants to recall and sequence differences to visually and orally presented stimuli. Picture of different foods and animals are displayed with both an accompanying audio recording and written text that names the item. In the1-list condition, the participant is asked to say the item back to the examiner in size order from smallest to largest. The test begins with two objects. The participant must succeed at one of the first two object items to continue. In the 2-list condition, participants are presented both food and animals and are first asked to say the food objects in size order and then the animal objects in size order.

Dimensional Change Card Sort Test

This task is a measure of cognitive flexibility and attention. Two target pictures are presented that vary along two dimensions (e.g. shape and colour). Participants are asked to match a series of bivalent test pictures (e.g. yellow balls and blue trucks) to the target pictures, first according to one dimension (e.g. colour) and then, after a number of trials, according to the other dimension (e.g. shapes). The relevant dimension for sorting is indicated by a cue word (e.g. ‘shape’ or ‘colour’) that appears on the screen for all participants. Participants must get at least three out of four practice trials correct to advance to the test. There will be a total of 30 mixed items.

Pattern Comparison Processing Speed Test

This test is designed to measure processing speed. The test itself takes less than 9-s and requires participants to discern whether two side-by-side pictures are the same or not by pressing ‘yes’ or ‘no’ on the buttons on the screen. There are a maximum of 130 items or a maximum response time of 85 seconds.

Picture Sequence Memory Test

In this measure of episodic memory, sequences of pictured objects and activities are presented in a particular order. The participants are asked to reproduce the sequence of pictures that is shown on the screen. Participants will respond by dragging the pictures from the yellow box on the screen to the grey boxes on the screen.

### Response of cerebral blood flow using transcranial Doppler (TCD) ultrasound to photic stimuli (assesses for the presence of neurovascular coupling abnormalities)

Increase in blood flow velocity in the posterior cerebral artery (PCA) in response to photic stimulation is a robust activation paradigm that allows for the assessment of the relationship between local neuronal activities and regional blood flow in the cortex (2). While it does provide an insight on cognitive function, this assessment may be used as a surrogate in time-constraint clinical settings if the results are related to cognitive performance. Following the cognitive assessments, this protocol will take place in a quiet, dark room and a monitor will be placed 0.3m in front of the seated participant. Mean blood flow velocities in the PCA will be recorded continuously during the stimulation period that will comprised of two continuous cycles of 20-sec of checkerboard stimulus presented on the monitor with eyes open, followed by 20-sec of eyes shut. The protocol will be repeated after a 5-min interval. Responsiveness to photic stimulation will be calculated as the percentage increase of peak mean blood flow velocity over baseline velocity. In addition to group-wise comparisons, the data from the photic protocol will be used in correlational analyses between cerebrovascular responsiveness to cognitive test battery and cognitive performance.

### Gait speed

The measure of gait speed will be administered twice in an open hallway. A practice trial precedes the timed trials. Volunteers will walk at her normal pace for four metres and 20 metres. The timing starts when the volunteer crosses over the start line and timing stops when one of the volunteer’s feet is completely across the finish line.

## Reimbursement

Participants who complete the study will each receive $30 as a compensation for their time and expenses. There will be a $10 pro rata payment for participants who attend the visit but are excluded during screening. There will be no reimbursement for participants who did not attend the CNRC.

## Subject Selection and Withdrawal

### Inclusion Criteria

* 15 patients with complex congenital heart disease and 15 healthy age-gender matched controls.
* Age > 18 years

### Exclusion Criteria

* Unable to obtain a measurable signal in both left and right MCA
* History of cerebrovascular events, including transient ischemic attack.
* Uncontrolled hypertension (>160/100mmHg) (measured at the visit to CNRC)
* Pregnant women and people highly dependent on medical care.

### Early Withdrawal of Subjects

Participants have the right to withdraw from the study at any time for any reason, without being obliged to give reasons and without penalty or loss of benefits they are entitled to. The investigator also has the right to withdraw participants from the study if it is in their best interest. Participants who withdraw prematurely from the study will not be replaced. However, data collected will be used in the data analysis.

Participants will be discontinued from the study if:

* The participant experiences an Adverse Event.
* The participant or the participant’s attending physician requests that the participant be withdrawn from the study.
* The participant does not meet the enrolment criteria.
* The participant is unwilling to comply to study protocol.

# Statistical Plan

## Sample Size Determination

As this is an exploratory study, we will recruit 15 participants with complex congenital heart disease and 15 healthy controls

## Statistical Methods

Participant characteristics (body mass index, waist circumference, clinic BP, medication use, history of sleep apnoea or myocardial infarction) will be used as covariates. Age and gender may be added as covariates if they are significantly correlated with the outcome measures. Echocardiography and cross sectional imaging (CT/MRI aorta), where available, will be assessed.

Participant characteristics will be used as covariates if they are significantly correlated with the outcome measures. A two-sample t-test will be used to compare the group differences in outcome measures. Linear regressions will determine if there are relationships between gait speed and cerebrovascular function and cognitive performance. Where appropriate, Bonferroni adjustments will be made to allow for multiple comparisons.

# Safety and Adverse Events

## Safety evaluation

Investigators are responsible for monitoring the safety of participants who have entered this study and Dr Nicholas Collins will be alerted to any event that seems unusual, even if this event seems to be an unanticipated benefit to the participant. A health, diet and lifestyle questionnaire will be completed by the participants along with a signed informed consent, which will include medical conditions, current medication and dietary supplement use. The investigator will go through each response on the questionnaire with the participant at the start of the visit. Any adverse events that occur during the study will be reported to Professor Nicholas Collins and to the HNE and UoN Human Research Ethics Committees.

## Adverse Events

An Adverse Event (AE) is defined as any untoward medical occurrence in a participant during the assessments conducted at each clinic visit and during the study intervention that may or may not be related to the study protocol and/or investigational product. A Serious Adverse Event (SAE) is defined as any untoward serious medical occurrence at any dose that results in death, or is life-threatening or required inpatient hospitalisation, or results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect, or is a medically important event or reaction.

The study coordinator will inform the principal investigator of all AEs and SAEs, who will then notify the relevant bodies. Depending on the nature of AE or SAE, it may be necessary for treatment to cease and/or for the participant to be withdrawn from the study.

All SAE that may be related or unrelated to the investigational product will be documented in the SAE Form, Case Report Form and will be reported immediately to the HNE and UoN Human Research Ethics Committees and the sponsor. Any unforeseen AE, or complaints from participants in the research, or about the research, will be documented in the AE Form and Case Report Form and will be reported to the HNE and UoN Human Research Ethics Committees as soon as possible.

All adverse events must be documented and followed up until the AE outcome has been established or the condition is stabilised, even after the subject has completed his/her study treatment.

# Risks

TCD and CVR assessments – A semi-rigid headpiece will be fitted onto the participant’s head. The fitting should be snug but not overly tight such that it would cause severe discomfort. Participants will advise the investigators should the discomfort become unacceptable. The 2Mhz probes will be fixed at the participants’ temporal window. To minimise exposure, the minimum settings will be used and Doppler device switched on only during recording.

Mental tests

Some participants may feel mildly distressed when completing the cognitive tests, as many of the tasks require you to respond quickly or complete a number of tasks simultaneously. However, all volunteers should feel assured that high performance levels on the tests are not expected. Should a participant become upset or distressed before or any time during these tests, they will be advised to inform the investigator.

Performing below one’s usual standard on mental tests is quite common, especially at the first visit to the study site. This may be due to a variety of reasons such as unfamiliarity with the environment, misunderstanding of test instructions, lack of sleep, tiredness, hunger, etc. If participants score below the range of scores on the mental test at screening, they will have the opportunity to return at another scheduled day for retesting. However, if participants have previous or on-going concerns with their memory or mental performance, they will be advised to seek advice from their GP before study participation.

Light stimulation

There may be a chance of visual fatigue from exposure to light emitting from a computer monitor. To minimise risk, participants will keep their eyes on the screen for no more than 1 minute.

Walking test

There is a slight risk of losing one’s balance, rolling of the ankles or slipping in the walking test. Proper footwear (i.e. flat shoes or athletic shoes) must be worn for the locomotive test. The investigator will also walk alongside the participant if they feel unsteady on their feet. The open hallway is brightly lit, dry and free from obstacles before test commencement. Participation in this walking test is optional.

# Privacy and Confidentiality

Any information collected by the investigators which might identify participant will be stored securely and only assessed by the investigators and the authorized auditor. When a participant expresses initial interest in the study, a numeric identification code will be assigned to the volunteer. This numeric identification code will be used in all hard copies and electronic records of the data collected from each volunteer. The Health, Diet and Lifestyle questionnaire which participants will return by post, or via email, will bear the numeric identification code and contact details. During statistical data analysis the database will be stored in a password protected computer file on a computer that is kept in a locked room. All data for the study will be retained on file by the principal investigators at the John Hunter Hospital, in a locked data storage site for a period of five years. Electronic files are secured by password only known to the investigators of this study. All records including electronic files will be destroyed and deleted after five years.

## Quality Control and Quality Assurance

Data collection will be monitored internally by trial investigators. The overall conduct of the clinical trial will be managed by a certified clinical research coordinator, Dr Rachel Wong.

## Disclosure, Publication and Confidentiality

Confidentiality of participants will be maintained. Participant identity will be limited to authorised staff working on this study. However, in the event of an official audit and inspection, the authorised auditor will have access to the source documents for source data verification at the research site only.

Participants will be assigned a unique participant identification code. All data collected for the purposes of this study will be kept a separate folder and participants will not be identified from these folders. Prior to data archiving, the first page of the Health, Diet and Lifestyle Questionnaire containing participant’s contact details will be removed from the rest of the document and destroyed according to the University’s secure data disposal procedures.

With the participant’s consent, the study investigators may contact their nominated GP regarding their study participation if necessary. However, all participants are advised to discuss their involvement with their GP personally.

All individual data sets will be retained by the study investigators. Individual volunteers will not be identified in any reports arising from the study.

At the conclusion of the study, participants will be given an overall group summary of findings.

# Study Reports and Publications Plans

If successful, there is potential to submit manuscripts for publications in high-ranked journals in the field of cardiology and neuroscience.

# Archiving

Archiving of all study materials will commence once The study investigators must archive the protocol, documentation, approvals and all other essential documents related to the study including certificates that satisfactory audit and inspection procedures have been carried out. Copies of all human study material will be archived at the off-site location appointed by the John Hunter Hospital for a period of at least five years (or more when legally required). All documents must be archived in a secure place and treated as confidential material.

# References

1. Wong RHX, Evans HM, Howe PRC. Poor cerebrovascular function is an early marker of cognitive decline in healthy postmenopausal women. Alzheimer's & Dementia: Translational Research & Clinical Interventions. 2016;2(3):162-8.

2. Aaslid R. Visually Evoked Dynamic Blood-Flow Response of the Human Cerebral-Circulation. Stroke. 1987;18(4):771-5.

3. Weintraub S, Dikmen SS, Heaton RK, Tulsky DS, Zelazo PD, Slotkin J, et al. The Cognition Battery of the NIH Toolbox for Assessment of Neurological and Behavioral Function: Validation in an Adult Sample. J Int Neuropsych Soc. 2014;20(06):567-78.