

**Assessment of cognitive function and cerebral blood flow in patients undergoing aortic valve intervention**

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| **Chief Investigator** | *Nicholas Collins**Staff Specialist Cardiologist**John Hunter Hospital**c/- 58 Cleary Street**Hamilton NSW 2303.* |
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# Study Summary

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| Title | **Assessment of cognitive function and cerebral blood flow in patients undergoing aortic valve intervention** |
| Short Title | *TAVICOG study* |
| Protocol Number | *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* |
| Principal Investigator (PI) | *Dr Nicholas Collins**Staff Specialist Cardiologist**John Hunter Hospital**c/- 58 Cleary Street**Hamilton NSW 2303, Australia**Tel: +61 0411 987 025* *Email: Nicholas.Collins@hnehealth.nsw.gov.au* |
| Co-investigator 1 | *Dr Rachel Wong**NHMRC Dementia Research Fellow**Clinical Nutrition Research Centre**University of Newcastle**School of Biomedical Sciences & Pharmacy**Medical Sciences Building, MS 514**Callaghan NSW 2308**Tel: +61 02 4921 6408**Email:* *Rachel.Wong@newcastle.edu.au* |
| Co-investigator 2 | *Dr Rohan Bhagwandeen**Cardiologist**64 Denison St, Hamilton East NSW 2303**Tel: 61 02 4929 2444**rohanb@newcastleheart.com.au* |
| Co-investigator 3 | *Ms Brooke Keeble**TAVI Coordinator, Lake Macquarie Private Hospital**Gateshead, Newcastle NSW 2290**Tel: 61 02 4929 2444**Email: Brooke.Keeble@health.nsw.gov.au* |
| Co-investigator 4 | *Dr Max Ray**Cardiology Advanced Trainee, Cardiovascular Department**John Hunter Hospital* *Lookout Road**New Lambton Heights NSW 2305**Tel: +61 02 4921 4205**Email: Max.Ray@health.nsw.gov.au* |
| Co-investigator 5 | *Professor Andrew Boyle**Professor of Cardiovascular Medicine & Head of Discipline**School of Medicine and Public Health**Hunter Medical Research Institute**New Lambton Heights NSW 2305**Tel: +61 02 4921 4205**Email: Andrew.Boyle@newcastle.edu.au* |
| Co-investigator 6 | *Emeritus Prof Peter Howe**Director, Clinical Nutrition Research Centre**University of Newcastle**School of Biomedical Sciences & Pharmacy**Medical Sciences Building, MS 122a**Callaghan NSW 2308**Tel: +61 402 159 039**Email: Peter.Howe@newcastle.edu.au* |
| Co-investigator 7 | *Assoc Prof Aaron Sverdlov**Cardiologist**John Hunter Hospital* *Lookout Road**New Lambton Heights NSW 2305**Tel: +61 02 4921 4205**Email: aaron.sverdlov@newcastle.edu.au* |
| Trial management at UoN | *Natasha Baker, Administration/Research Assistant and**Jay Jay Thaung Zaw, PhD Student/Research Assistant**Clinical Nutrition Research Centre**University of Newcastle**School of Biomedical Sciences & Pharmacy**Medical Sciences Building, MS 304**Callaghan NSW 2308**Tel: +61 02 4921 6419**Email: Natasha.Baker@newcastle.edu.au* *Natasha will prepare the ethics application and study documents and assist with scheduling and data entry.**Email: JayJay.ThaungZaw@uon.edu.au**Jay Jay will conduct the site visits, administering informed consent and all tests at the Clinic, MS 304. She will also conduct the data analysis.* |
| HNE Health | *Elizabeth Nyman, liaison with HNE Health**Clinical Trial Coordinator**Clinical Trials and Research Team | Cardiovascular Department**John Hunter Hospital, Locked Bag 1, HRMC NSW 2310**Tel 02 4921 4720 or 02 4985 5433 | Fax 02 4921 4210**elizabeth.nyman@health.nsw.gov.au* |
| Objectives | *To examine and compare cerebrovascular and cognitive function in patients undergoing surgical aortic valve intervention and patients undergoing transcatheter aortic valve intervention* |
| Number of Subjects | *15 adults undergoing surgical aortic valve intervention and 15 adults undergoing transcatheter aortic valve intervention* |
| Main Inclusion Criteria | *Adult patients with aortic stenosis planned for aortic valve intervention, having measurable ultrasound signal on either side of the head.*  |
| Study outcomes | *Measures of cerebrovascular function:** *Cerebrovascular responsiveness (CVR) to cognitive testing and photic stimuli – uses Transcranial Doppler (TCD) ultrasound to assess the ability of blood vessels to dilate.*

*Measures of cognitive function** *Composite scores of individual cognitive tests*

*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, cognitive outcomes and gait speed.*
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| Duration of administration | *N/A* |
| Reference therapy | *Nil* |
| Statistical Consideration | *Baseline data will be collated with the differences between groups compared using ANOVA continuous variables and chi-squared for categorical variables.**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.*  |

# Introduction

## Executive summary

Traditional aortic valve replacement surgery, while effective in relieving the haemodynamic effects of aortic valve dysfunction, is associated with significant morbidity and mortality. The advent of transcatheter aortic valve intervention has resulted in improved procedural results in those considered at high and intermediate risk for surgical intervention.

Given that the prevalence of aortic stenosis increases with age, it is well-understood surgery may negatively affect cognitive function. Transcatheter aortic valve replacement may improve cognition via the effect of improving cerebral perfusion following relief of valvular dysfunction which may result in superior cognitive function. In contrast, the procedural risks of atheroembolism and cerebral ischaemia may worsen cognitive function. Previous research in patients with congenital heart disease has demonstrated an association between impaired cerebrovascular blood flow responses to stimuli and cognitive function (1, 2).

Based on the association of cognitive impairment after surgical aortic valve intervention, we anticipate that patients undergoing transcatheter intervention will demonstrate preserved cognitive function with improvement in cerebral blood flow responses following relief of obstruction. Understanding the likelihood and magnitude of cognitive changes following valve interventions is essential to inform patients adequately of procedural risks and potential advantages compared to traditional aortic valve surgery, and to assess the efficacy of cerebral protective devices and techniques.

The outcome of the study would be an improved understanding of the effects of aortic valve intervention on cognitive performance and cerebral blood flow for clinicians and patients. Most adults who require aortic valve intervention are elderly and at risk for cognitive impairment. Quantifying the neurocognitive effect of surgical versus transcatheter aortic valve intervention is essential to inform patient decision making regarding the risks and potential advantages of each approach, and to assess the efficacy of cerebral protective devices.

## Rationale

Older adults with cardiac dysfunction are at heightened risk of cognitive impairment (3). Cardiac-related cognitive impairment may be partially attributed to vascular dysfunction in the systemic, but more so in the cerebral vessels. Cerebral vessel insufficiency contributes to cerebrovascular changes such as hypoperfusion, white matter lesions and silent brain infarctions, which have been linked to accelerated cognitive impairment (4). Patterns of cognitive impairment vary across cardiac diagnoses (5). Deficit in executive function is universal in all cardiac conditions (i.e. heart failure, coronary artery disease, arrhythmia, arterial fibrillation), and in common comorbidities such as anxiety, diabetes, hypertension and obesity. Next to deficits in executive function, impairments in the memory and psychomotor domains are also common (6). Studies have linked the impairments of these cognitive domains to poor neurovascular coupling capacity (7, 8).

Cognitive impairment in adults with cardiac dysfunction is often mild; hence, individuals are unlikely to seek immediate clinical attention. Nonetheless, this mild impairment means that the cognitive deficit is greater than otherwise for the individual’s age and education level. Although the individual is able to complete basic activities of daily living independently, the capacity to complete complex activities that require higher cognitive function may be compromised. This can include managing finances, meal preparation, driving, personal, home and community safety, and high-level self-management of chronic diseases, termed behaviour functional capacity (9). Unaware of their subtle cognitive deficits, patients may become less vigorous to medication adherence or lifestyle modification and miss healthcare visits. The cornerstone of effective management in cardiac dysfunction is the ability to self-care. As such, clinical management in this population must go beyond the traditional physical aspects of care to encompass cognitive outcomes into practice.

Aortic valve surgery to treat aortic stenosis is commonly performed in older adults >65 years old. A recent review reported a decline of more than half a standard deviation in cognitive function within the first month post-operation compared to before the surgery. Although their cognitive health recovered within six months after surgery, it was not fully restored to baseline levels. In fact, cognitive function was still at a quarter of a standard deviation lower at six months post-surgery (10). This rate of cognitive decline per unit of time is far higher than what is expected in normal ageing or in persons with mild cognitive impairment (11). Whether cognition is fully restored in patients after traditional aortic valve surgery is unknown.

Transcatheter aortic valve intervention has emerged as an alternative as it is less invasive and has less complications. Importantly, post-surgery cognitive deterioration was only found in 13% of the patients compared to the 38% of the patients who showed improvement, particularly in those who had pre-surgery cognitive impairment (12). The cognitive improvement was hypothesised to be due to improved haemodynamics after the intervention. However, to date, no studies have evaluated or compared the cerebrovascular hemodynamics and linked it to cognitive outcomes in patients who have undergone traditional or transcatheter aortic valve intervention.

## Clinical data

None

# Study Objectives

We aim to perform a prospective study of the relationship between changes in cerebral blood flow and cognitive function (neurovascular coupling) in a cohort of patients undergoing aortic valve intervention.

We aim to assess patients undergoing both transcatheter (TAVI) and traditional surgical aortic valve (SAVI) intervention to document changes in cerebral blood responses following aortic valve replacement by evaluating patients before and after valve intervention.

## Primary outcome

Within-individual pre-post difference in cerebrovascular responsiveness (CVR) to cognitive testing at the level of the middle cerebral artery (MCA)

## Secondary outcomes

Within-individual pre-post difference in:

- Basal cerebrovascular haemodynamics

- Cognitive function

- CVR to photic stimulation

- Mood and perceived quality-of-life

Differences between TAVI and SAVI groups in primary and secondary outcomes

# Methods and Procedures

## Study design

A pilot case-control study will use transcranial Doppler (TCD) ultrasound to document changes in blood flow velocity in the middle cerebral artery during cognitive testing to assess neurovascular coupling in 15 patients undergoing transcatheter aortic valve intervention (TAVI) and 15 patients undergoing surgical aortic valve implantation (SAVI).

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

## Participant recruitment

Recruitment for the project will commence following approval of the protocol by the Ethics committee. It is anticipated that the subject activity will last for one visit before the procedure and one visit post-procedure.

Interested participants will be referred to the study coordinator who will send a Patient Information Statement, Consent Form and Health Questionnaire to obtain demographic and medication details. This information will help determine the participant's suitability before the first visit and collect data for the reporting of participant characteristics.

## Study procedures – Screening and eligibility

Participants will attend the research clinic at the University of Newcastle, Callaghan Campus, for screening. If they are eligible, data collection for the 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 before 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 be required 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

Participants will arrive after at least an hour fast (no food or caffeinated beverage) at the research clinic located in the Medical Sciences Building, MS 304, for further screening to determine study eligibility. Anthropometric measurements of height, weight and waist circumference will be obtained before the clinic BP is assessed. Participants who exceed the BP inclusion limit will be excluded.

A headpiece supporting an ultrasound probe on each temporal region will be fitted to patients. 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 either MCA, the participant will be excluded from the study. Otherwise, the participant will be assessed. The ultrasound will continuously record changes in the blood velocities in the MCA during the cognitive test battery.

After the cognitive tests, the investigator will adjust the ultrasound probes to locate the posterior cerebral arteries. Once a suitable blood flow signal is located, participants 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.

Participants will be reassessed within three to six months after their aortic valve procedures.

## Outcome Assessments

Patients will be assessed before aortic valve replacement and in the post-operative period to document changes in cognitive performance and associated abnormalities in cerebral blood flow response to cognitive and photic stimuli.

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. 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

A battery of seven cognitive tests will be administered and continuous recording of mean cerebral blood flow velocities in the MCA will be recorded simultaneously. The duration of the test battery is expected to last 35 minutes.

Global cognition

The Addenbrooke’s Cognitive Examination-III (ACE-III) is a brief cognitive test that assesses five cognitive domains: attention, memory, verbal fluency, language and visuospatial abilities. The total score is 100 with higher scores indicating better cognitive functioning. Administration of the ACE-III takes, on average, 10 minutes (13).

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).

Spatial Forward 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.

Controlled Oral Word Association Test

This set of verbal fluency tasks evaluate the spontaneous production of words under restricted search conditions. For phonemic fluency, individuals are given 1 min to name as many words as possible beginning with one of the letters F, A, S or C, F, L. For semantic fluency, individuals are given 1 min to name as many items of a category as possible. The most common category is “animals”. The administration of phonemic and semantic fluency takes approximately 5 minutes.

Digit Symbol Coding

A pen and paper assessment where numbers 1 to 9 were coded with a different symbol. The task was to write down as many correct symbols against each random number as fast and as accurately as possible in 90 sec.

Psychomotor speed

The 9-hole Pegboard Dexterity test assesses fine motor dexterity, which is a central component of hand function and relates to both the speed and accuracy of hand movements during the manipulation of objects. The participant will be asked to pick up the pegs one at a time using the right hand and place them in the holes one at a time until all nine holes are filled, then remove them one by one. This task will be repeated on the left hand. They will be assessed on the time taken to complete this task.

Pattern Comparison Processing Speed Test (NIH-ToolBox)

This test is designed to measure processing speed. The test itself takes less than 9s 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.

### 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 (4). While it does provide an insight on cognitive function, this assessment may be used as a surrogate in time-constrained clinical settings if the results are related to cognitive performance.

Following the cognitive assessments, mean blood flow velocities in the PCA will be recorded during 60 sec of eyes open, followed by a 30 sec of eyes shut and 30 sec with eyes open. 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.

### Mood and functional capacity

#### Depressive symptoms

The Center for Epidemiologic Studies Depression Scale (CES-D) (14) is a commonly used tool to characterize depressive symptoms in the general population. The 20-item self-administered scale measures the major depressive symptomatology, including depressive mood, feelings of guilt and worthlessness, psychomotor retardation, loss of appetite and sleep disturbances. These will be administered on paper.

#### The State-Trait Anxiety Inventory

The State-Trait Anxiety Inventory (STAI) is a commonly used measure of trait and state anxiety. Form Y, its most popular version, has 20 items for assessing trait anxiety and 20 for state anxiety. State anxiety items include: “I am tense; I am worried” and “I feel calm; I feel secure.” Trait anxiety items include: “I worry too much over something that really doesn’t matter” and “I am content; I am a steady person.” All items are rated on a 4-point scale (e.g., from “Almost Never” to “Almost Always”). Higher scores indicate greater anxiety.

#### Quality-of-life

The short-form 36 (SF-36) is a multi-purpose short-form health survey that measures an individual’s perception of functional health and physical and mental-wellbeing

## Reimbursement

Participants who complete the study will each receive $10 per visit to cover their travel expenses. Dependant participants requiring a taxi service will not receive the cash payment, rather their transport costs will be covered by a taxi cabcharge card up to the value of $40 per visit. There will be no reimbursement for participants who did not attend the CNRC.

## Subject selection and withdrawal

### Inclusion Criteria

* 15 patients with aortic stenosis undergoing surgical aortic valve intervention and 15 patients undergoing transcatheter aortic valve intervention
* Age > 18 years

### Exclusion Criteria

* Unable to obtain a measurable signal in either left or right MCA
* Uncontrolled hypertension (>160/100mmHg)
* 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 a Serious Adverse Event.
* The patient does not have an aortic valve intervention as planned.
* 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 planned to undergo surgical aortic valve intervention and 15 patients to undergo transcatheter aortic valve intervention.

## Statistical Methods

Baseline demographics and clinical data will be collated with differences between the transcatheter (TAVI) and surgical (SAVI) groups compared using Students t-test for continuous variables and chi-square tests for categorical variables.

# 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 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.

Prior to each visit to the research unit, the participants will be asked if they have any symptoms related to SARS-COV2, or have been in contact with a known case, or are undergoing isolation, or have travelled interstate in the past two weeks. Participants who have even a slight symptom will be asked to reschedule their visit and/or seek medical advice promptly.

## 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 procedures. 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 procedures 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 enrolment.

In the event of a medical emergency, we will ring 000 and contact Campus Security, who will direct emergency services to our location. All security staff are trained in first aid. The building’s local first aid person, on level 6, will also be called upon to assist if required.

If the event is not life threatening, we will advise the participant to see their GP as soon as possible. A Health Service clinic is also available on campus if required.

# 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 the Doppler device switched on only during recording.

Mental tests

We are mindful of the study participants’ mental health in response to the SARS-CoV2 crisis. They will be given opportunities to discuss any concerns relating to the research procedures prior to an appointment. They will be assured of the research unit’s guidelines and procedures for handling the health and safety of staff and participants.

Some participants may feel mildly distressed when completing the cognitive tests, as many of the tasks require them 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 normal 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.

Exposure to COVID-19 (SARS-CoV-2)

It is possible that the study participants are in the higher risk group for COVID-19 (e.g. over 65 years old with underlying medical conditions). To minimise their risk of exposure, the research will be conducted in facility that allows a 4-square metre space per person. However, the nature of data collection for TCD assessments does not allow a 1.5 m distance separation to be in place. As such, additional precautions are made to reduce this risk. They include:

* Study participants must confirm that they don’t have any symptoms, current isolation restrictions or interactions with others diagnosed with the virus, on each occasion before they attend on-site.
* Study participants with a COVID-19 Safe App on their smart phone must ensure that the app is open with Bluetooth switched on. Research staff will do the same.
* If a study participant is observed to be sick or displaying any symptoms whilst onsite they will be politely advised to return home and seek medical advice
* We will ensure that research staff do not come to work if they have any symptoms, current isolation restrictions or interactions with others diagnosed with the virus.
* All study participants will be required to sanitise their hands with the hand sanitizer provided immediately as they arrive and when they depart.
* We will clean the room including surfaces and equipment with 70% alcohol wipes or use spray bottles of a suitable disinfection agent and paper towel after each appointment and allow at least a 30-min interval between visits.
* We will ensure that both the staff and study participants adhere to basic personal infection controls such as no touching the face, coughing/sneezing protocols, no pens in the mouth, no chewing nails, no finger-lick paper-flick, avoiding sharing phones/workstations without wiping over between users etc.

# 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 authorised 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 fields of cardiology and neuroscience.

# Archiving

Archiving of all study materials will commence once the trial analysis has been completed. 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.

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