TRIAL OF AN INDIVIDUALISED INTERVENTION FOR THE PREVENTION OF STROKE (TIIPS)

Study Protocol & Manual of Procedures

2021

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Document History

Version	Date	Author	Comments
1.0	10 February 2022	Rita Krishnamurthi	Draft 1 For submission to ethics
2.0	10 August 2022	Rita Krishnamurthi	Draft 2 for DSMC, corrections made to Outcomes table
2.0	19 August 2022	Rita Krishnamurthi	Draft 2, minor changes to coaching sessions as noted below (Section 7), HDEC, AUTEC approval numbers and ANZCTR numbers added
2.0	05 September 2022	Rita Krishnamurthi	Recommendations added based on first DSMC meeting on 22 Aug 2022. The recommendations are added to the Appendix of the Protocol.
2.0	5 December 2022	Rita Krishnamurthi	Inclusion criteria reviewed by trial Steering Committee and 4 changes recommended (pending HDEC ethics approval): (1) Removing upper age cut-off (currently >75 years) (2) Reducing the MoCA cognitive score cut-off for inclusion to ≥23, currently ≥26 (3) Inclusion of people with systolic blood pressure between 120 mm Hg and 129 mm Hg who are on blood pressure medication (currently include systolic blood pressure ≥130 mmHg (4) Increasing the time frame from stroke/TIA event onset to baseline 90 days (currently 4 weeks ± 2 weeks).
2.0	5 December 2022	Irene Zeng	Addition of Statistical Monitoring Guidelines (Section 8)

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6. Ethical approval and trial registration

HDEC Approval # 2022 AM 12456

AUTEC Approval # **22/206 Trial of an individualised intervention for the prevention of stroke (TIIPS)**

ANZTR Registration # ACTRN12622000939796 (registered 01/07/2022)

7. Protocol Updates

Date	Change	Reason	Comments
20.07.2022	The initial session will be conducted face-to-face and remaining coaching sessions via telephone. However, the second session may be in person if the coach deems it appropriate (reasons to be recorded in REDCap).	Allowing a second face to face session may be needed in some cases if the coach deems it appropriate	Coaches have been updated
15.12.2022	Inclusion criteria reviewed by trial Steering Committee and 4 changes recommended (pending HDEC ethics approval): (1) Removing upper age cut-off (currently >75 years) (2) Reducing the MoCA cognitive score cut-off for inclusion to ≥23, currently ≥26 (3) Inclusion of people with systolic blood pressure between 120 mm Hg and 129 mm Hg who are on blood pressure medication (currently include systolic blood pressure ≥130 mmHg (4) Increasing the time frame from stroke/TIA event onset to baseline 90 days (currently 4 weeks ± 2 weeks).	(1) Average age of stroke in European demographic is 75 and hence many are excluded. Increasing the age cut off and using the mRS score instead for including independent (2) A MoCA score of ≥23 was deemed acceptable by the SC and team neuropsychology expert. (3) Including those with BP in this range allows greater generalisability to the stroke population. (4) This will allow greater flexibility for recruitment	Ethics approval obtained

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TRIAL OF AN INDIVIDUALISED INTERVENTION FOR THE PREVENTION OF STROKE (TIIPS)

1. INTRODUCTION

BACKGROUND AND RATIONALE

TRIAL SUMMARY

1.1 THE IMPACT OF TIA/MINOR STROKE

Patients with Transient Ischaemic Attack (TIA) and minor (non-disabling; (NIHSS ≤ 3)[1] stroke are at high risk of secondary vascular events including major stroke, myocardial infarction (MI), cognitive deficits and death, with population-based studies reporting incidence of adverse outcomes as high as 25% within 90 days.[2] New vascular events, including fatal strokes, MI, and other cardiovascular deaths occur in up to 26% of patients within four years post-TIA.[3, 4] Increased risk is associated with unhealthy lifestyle and poor adherence to medications to treat elevated blood pressure, diabetes mellitus, and previous vascular disease.[3] ARCOS-IV[5] showed that age standardised incidence of first-ever TIA in NZ is one of the highest among developed countries at 50 [95%CI 46-55] per 100,000 persons in 2011-2012.[6] TIA occurred at a younger mean age in Māori and Pacific people (60 years), and Asian and other (including Middle Eastern and African) people (68 years) compared to Europeans (74 years).[6] ARCOS-IV also found a high prevalence of cardiometabolic risk factors (e.g. 65% had hypertension, 47% had elevated lipids and 27% had atrial fibrillation).

1.2 SECONDARY PREVENTION AFTER TIA/MINOR STROKE

There is ample evidence that modifying health behaviours for stroke and cardiovascular disease (CVD) prevention is feasible, improves health outcomes, reduces healthcare costs, can reduce individual risk of stroke by about 80%,[7] [8] and can reduce stroke incidence by about 50%.[9] Addressing health behaviours, including use of multifactorial lifestyle interventions,[10] can lead to clinically meaningful reductions in CVD and stroke.[11] Both TIA and minor stroke are highly preventable with medical management,[12-14] combined with education about stroke/TIA and the importance of medication adherence, and support for lifestyle behaviour change.[15-18] Current NZ stroke guidelines recommend behavioural counselling for diabetes, diet, exercise and smoking cessation for long-term self-management of risk factors.[19] However in NZ, management of TIA/minor stroke *remains inadequate*.[20] In addition, due to the transient nature of symptoms *patients do not recognise TIA as a significant medical event* with long-term health implications. Resultant delays in seeking medical treatment, low adherence to healthy lifestyle and prescribed medications, lead to *preventable major secondary events*.[21-23]

1.3 EFFICACY OF LIFESTYLE INTERVENTIONS IN STROKE/TIA

A recent systematic review including 15 trials on lifestyle interventions for secondary prevention following TIA or ischemic stroke, with the majority based on educational material, lifestyle advice, or exercise training,[24] showed a significant lowering of systolic blood pressure, but no significant effect on cholesterol or mortality. The authors recommended that future trials test interventions with at least 8 contact points,

using a theoretical framework,[25] including educational and behavioural interventions with at least a four-month follow-up, and considering factors such as self-efficacy to facilitate health behaviour change.[24] Well-designed health coaching interventions improve physical and mental health, and sustain changes in lifestyle-related behaviours in people with diabetes[26, 27] myocardial infarction,[28] and other chronic conditions.[103] Resultant health behaviour changes have the potential to be long-lasting.[29]

1.4 MEASURING CARDIOVASCULAR RISK.

Testing an intervention that targets brain and heart health requires an evidence-based, relevant and reliable measure to determine its efficacy. Hypertension or high blood pressure is the most significant risk factor for stroke. The landmark INTERSTROKE study conducted in over twenty-six thousand participants in 32 countries showed that a history of hypertension increased the risk of stroke by 2.64-fold, and was the most significant risk factor for stroke. [30] Moreover the Global Burden of Diseases studies have shown that high systolic blood pressure is the leading risk factor contributing to the burden of stroke with 79.6 million disability adjusted life years lost (DALYs), which equated to 55% of DALYs. [31, 32]. A meta-analysis of 48 randomised trials evaluating the effects of blood pressure lowering in the risk of major CVD events (including stroke) found that a reduction of 5 mm Hg systolic blood pressure was associated with an 11% reduction in major cardiovascular events in people with previous cardiovascular disease.[33]

A recent study from Finland examined the association of the LS7 with the risk of stroke men without a history of stroke. In terms of absolute blood pressure, the study found that average blood pressures were 138.2 ± 16.6 mm Hg in the poor, 132.0 ± 16.5 mm Hg in the average and 118.6 ± 12.4 mm Hg in the optimum categories of the LS7.[34] Thus, an improvement from poor to ideal blood pressures could reduce systolic blood pressure by up to 13 mm Hg. Th Novel Approach to Cardiovascular Health By Optimizing Risk Management (ANCHOR) trial demonstrated a 4.5 mm Hg reduction in systolic blood pressure using a behaviour change intervention in people with an increased risk of CVD. [35] While the incidence of stroke and new vascular events would be ideal primary outcomes, this outcome would require long term follow-up and a prohibitively large sample size [18, 24, 36]. Blood pressure is also considered as a practical paradigm for preventing cardiovascular disease and improving total health. [33] Given the increased risk of secondary events in this population, a 6 mm Hg difference in systolic blood pressure is plausible with an effective intervention.[37]

As well as improving blood pressure, a key secondary aim of the trial is to address multifactorial modifiable risk factors as a way to lower the risk of stroke and CVD. The INTERSTROKE study also found that overall there were ten potentially modifiable risk factors are collectively associated with about 90% of the population-attributable risk of stroke.[30] including lifestyle related risk factors such as physical activity, diet, and smoking. The Life's Simple 7 (LS7) was developed by the American Heart Association, (AHA), to predict ideal cardiovascular health using seven domains or metrics.[37-39] These are; blood pressure, cholesterol, glucose, body mass index, smoking, physical activity, and diet.[37] The LS7 is a simple scoring system to assess cardiovascular health with scores ranging from 0 to 14, with the overall LS7 score categorised as inadequate (0–4), average (5–9), or optimum (10–14) cardiovascular health (see Table 1). Inadequate and average scores on the LS7 have a high association with increased CVD/stroke risk and mortality.[38] Ideal levels of the Life's Simple 7 factors are defined as: non-smoker or quit >1 year ago; body mass index (BMI) of <25 kg/m2; ≥150 min/week of moderate+vigorous physical activity; 4 to 5 components of a healthy diet pattern; untreated total cholesterol of <5.2 mmol/L; untreated blood pressure of <120/80 mm Hg; and untreated fasting glucose of <5.6 mmol/L. The Reasons for Geographic and Racial Differences in Stroke study (REGARDS) found that in 22,914 people with no previous history of CVD, an improvement by one category (from inadequate

to average or average to optimum) or of the LS7 score was associated with a 25% lower risk of stroke, and that a 1-point higher LS7 score was associated with an 8% lower risk of stroke.[37] In the Atherosclerosis Risk in Communities (ARIC) study of 1277 individuals who experienced a MI, adverse outcomes were inversely related to mid-life LS7 scores using the LS7 scoring where two-points are given for each optimum domain.[40] A recent review suggested that "an integrated socio-behavioural and medical intervention to improve LS7 factors was a potent and likely cost-effective approach to cardiovascular and general health promotion and disease prevention".[41] The SUCCEED trial of a multi-component intervention to improve risk factor control did not see a significant difference in their primary outcome of blood pressure reduction but showed improvements in some lifestyle risk factors. [42]

1.5 HEALTH AND WELLNESS COACHING.

Health and Wellness coaching (HWC) is a multidimensional psychological behaviour change intervention aimed at improving self-management of lifestyle behaviour and maintaining health and wellbeing.[43] HWC is a goal-oriented, theory based,[25] client-centred partnership that has produced positive effects on health and enhanced well-being of patients with chronic disease.[44-46] HWC is a widely accepted and established intervention in the community,[47] and is of particular relevance to stroke prevention as it can address multiple risk factors. HWC fosters ongoing self-directed learning,[44] delivers a cost-effective[48] intervention in person or by telephone, and by medical or non-medical personnel, thus saving cost and increasing the scope of implementation. Individuals who receive HWC have increased perceived health status, improved medication adherence, and physical activity,[49, 50] with significantly improved health outcomes shown in patients following myocardial infarction.[51-53]

THEORETICAL FRAMEWORK

In the context of this study the health and wellness coaching intervention is aimed at behaviour change which improves and physical health as well as the mental wellbeing of participants. However, behaviour change is challenging, and influenced by of physical, psychological and psychosocial factors, which may change over time. Motivating individuals to change unfavourable health behaviours is a challenge for health professionals, but growing evidence suggests that involving people in their own decision-making results in more favourable outcomes.(Steenkiste, 2007 #78}

There are several theoretical models for health behaviour change that support the HWC intervention. These include the concept of self-efficacy [54] in the health belief model, which focuses on attitudes and beliefs as a way to explain behaviour for improving lifestyle changes. Fostering a sense of self-determination, self-responsibility and ownership enhances motivation, satisfaction and adherence to healthier lifestyle choices.[55]The transtheoretical model proposed by Prochaska suggests that health behaviour is an interaction of five stages of change, processes of change and self-efficacy.[56] In this model, it is suggested that individuals move through stages of change: pre-contemplation, contemplation, preparation, action, maintenance and termination. Change may occur at different rates for individuals and they may even move back and forth between stages, before achieving the final stage of termination. Self-change is a product of individuals doing the right thing (processes) at the right time (stages).

The HWC intervention is underpinned by a combination of these theoretical models, as HWC also encompasses the whole person and their beliefs, but it also considers the dynamic interaction between the person and their environment and all the factors that influence them.

1.6 Previous evidence for HWC for stroke preventions

We have recently completed (publication underway) a phase III randomised controlled trial (RCT) using HWC (PREVENTS study, n=320) [57] for ***primary*** stroke prevention in those with moderate and high risk of CVD (prior stroke or TIA excluded).

The study showed a significant difference in the change in LS7 score in the HWC group between baseline (7.08 [2.03]) and 9- months (7.39 [2.00]) compared to controls (baseline 7.15 [2.20], 9-months 7.15 [2.39]) (p=0.044). Among LS7 domains, regression analyses adjusting for age, sex and ethnicity showed statistically significant increases in scores (indicating a positive change) for blood pressure (p=0.005), and cholesterol (p=0.04). The absolute blood pressure increased in both groups, but the increase was greater in the control group (10.58mmHg) than the HWC group (4.36mmHg). Cholesterol, blood glucose and BMI values also showed greater decreases in the HWC group compared to controls. The trial also demonstrated high acceptability and feasibility of the HWC intervention, positive feedback from participants and low dropout.

2. TRIAL DESIGN

The **T**rial of an **I**ndividualised **I**ntervention for the **P**revention of **S**troke (TIIPS) is a phase III, prospective, open-label, single-blinded end-point randomised controlled trial of 360 participants. The participants will be recruited from Auckland -based public hospitals (Middlemore Hospital, North Shore Hospital, Waitakere, Auckland City and Waikato Hospital, Hamilton., including outpatient TIA clinics. The recruitment of participants from the existing health system will maximise the uptake of the intervention.

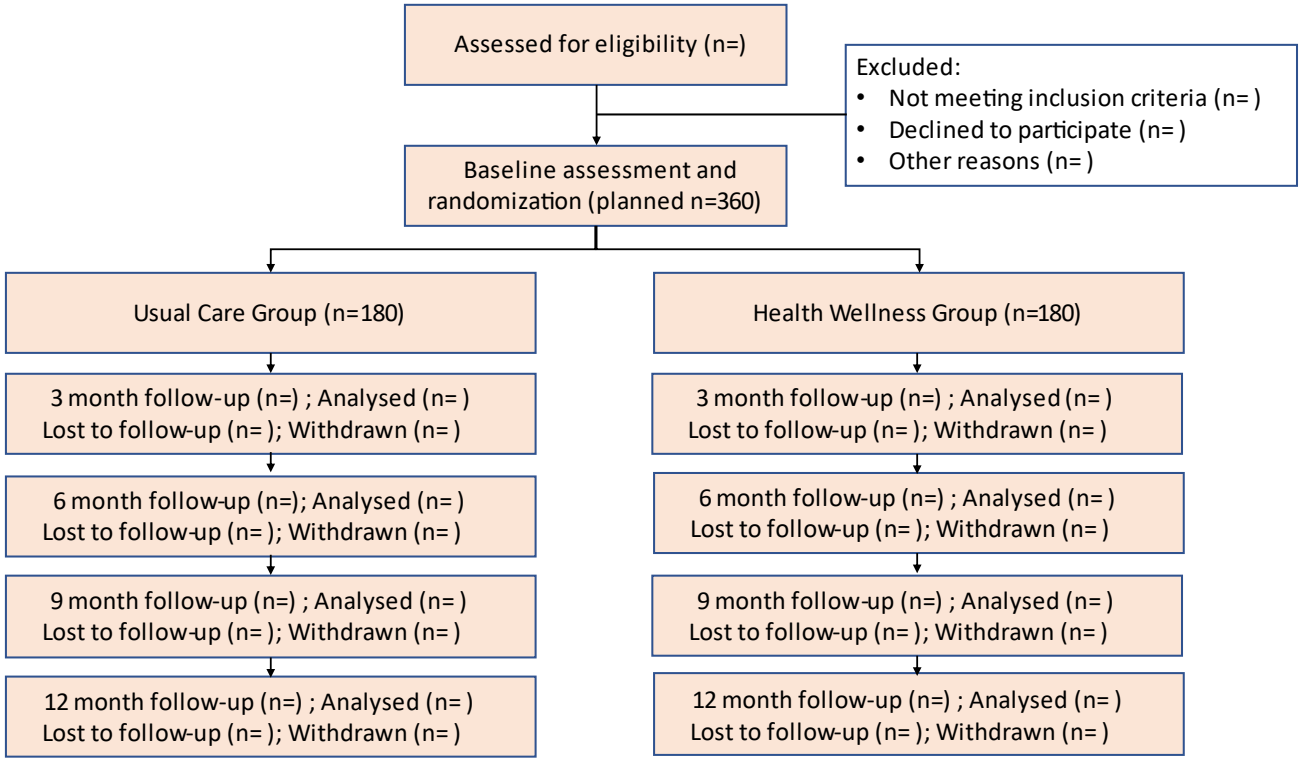
Sample size calculation and power analysis:

N= 360 participants are required to provide 85% power (two sided α=0.05) to detect at least a 6 mm Hg clinically significant difference in systolic BP (SBP) changes at 6 months from baseline, between the HWC and UC groups. This estimation assumes a 20% non-compliance/loss to follow-up. Based on our previous HWC trial (Prevents RCT on HWC for primary stroke prevention, publication in preparation) [57] data in NZ stroke patients (n=251, 9- month BP change in HWC patients is 4.4 mm Hg (SD:18) and in usual care patients is 10.6 mm HG (SD 22).

The sample size estimations used the proc power procedure of SAS – a statistical analysis software. Using the means of the SBP changes in the two groups and the pooled standard deviation (SD 20) from the previous HWC trial, the calculation indicates n=352. R software was also used for simulating changes in BP for the two groups and yielded a simulated type II error < 0.10 (statistical power > 0.90) when n=300 (simulation of 1000 and 10000 times). We adopted the simulated results because it uses two different group standard deviations, and it is under the budget limit control. After adjusted 20% attrition rate, the proposed sample size is n=360. With an attrition rate of 10% the required sample size is 317. The power calculation is also informed by literature that a 5mmHg reduction in SPB is clinically meaningful and leads to a 11% reduction in the incidence of stroke.

The results of the trial will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement as outlined in the below flowchart. If required, we will apply The CONSERVE 2021 Statemen; Guidelines for Reporting Trial Protocols and Completed Trials Modified, in the case of the study being affected COVID-19 Pandemic and Other Extenuating Circumstances.

CONSORT Chart



2.1 AIMS AND HYPOTHESES

The **primary aim** is to determine the effectiveness of HWC in improving blood pressure at 6 months post-randomisation.

The primary hypothesis is that HWC initiated within three months post minor stroke or onset of TIA will lead to clinically meaningful improvements in lifestyle behaviours resulting in a mean difference of 6 mm Hg change in blood pressure from Baseline to 6 months post-randomisation in the HWC compared to usual care. Recurrent TIA onset is included.

The primary end-point is the difference in the mean change from Baseline in systolic blood pressure at 6 months post-randomisation between UC and HWC. The study is powered to detect a mean difference in change of 6 mm Hg (SD±20 mm Hg) between HWC and UC groups at 6 months post-randomisation.

The **secondary aims** are to determine are to determine the effectiveness of HWC in improving

1. Overall cardiovascular disease (including stroke) risk at 6 months post-randomisation based on the LS7 compared to Baseline
2. Individual LS7 behavioural risk factors at 3-, 6- 9- and 12- months post-randomisation compared to Baseline
3. Awareness about stroke symptoms, risk factors and their management 6- and 12- months post-randomisation compared to Baseline
4. Quality of life, at 6- and 12- months post-randomisation compared to Baseline
5. Cognitive outcomes at 6-, and 12- months post-randomisation compared to Baseline
6. Mood outcomes compared to Baseline

7. Adherence to CVD medications at 3, 6-, and 9 and 12- months compared to Baseline
8. CVD/adverse outcomes at 12 months post randomisation.
9. Health and service costs at 12 months post randomisation
10. Productivity status at 12 months post randomisation

Secondary outcomes are:

1. systolic blood pressure, total cholesterol, blood glucose at 6-months post randomisation
2. change in proportion of participants in 'high' and 'intermediate' to 'low' risk on LS7 at 6-months post randomisation
3. Stroke risk from Stroke Riskometer – 5- year absolute and relative risk at 6- and 12-months post randomisation
4. Quality of life (EQ5D) at 6-months post randomisation
5. Stroke awareness at 6- and 12-months post randomisation
6. Cognitive assessment score (Montreal Cognitive Assessment) 6-months post randomisation
7. Medication adherence (Self-Efficacy For Appropriate Medication Use Scale (SEAMS)
8. CVD adverse outcomes (fatal and nonfatal stroke, TIA, myocardial infarction and heart failure, death attributable to CVD and all-cause mortality)
9. Healthcare and community service costs assessed as self-reported service use questionnaire at follow up. Productivity status will be self-reported and will include items regarding status (e.g., paid work, voluntary work, homemaker, student, unemployed), hours (e.g., full/part time), compared to hospitalisation pre-stroke status.

2.1 PARTICIPANT RECRUITEMENT

2.2.1 INCLUSION CRITERIA:

1. People aged between18 years or older diagnosed with TIA or minor stroke (excluding subarachnoid haemorrhage (SAH)) (National Institutes of Health Stroke Scale (NIHSS) score ≤ 4) and/or modified Rankin Scale (mRS) score 0-2 at discharge [1] or independent in activities of daily living in the past 90 days
2. Admitted to one of the three Auckland based hospitals, Waikato Hospital or identified via primary care for minor stroke or TIA
3. With at least 2 modifiable risk factors
4. With systolic blood pressure between 120-129 mm Hg and on blood pressure medications OR systolic blood pressure ≥130 mm Hg
5. Who can converse in English
6. Provides written informed consent

2.2.2 EXCLUSION CRITERIA

1. History of major stroke or myocardial infarction (verified through Clinical Portal medical records)
2. Planned carotid endarterectomy
3. Life-threatening conditions with a life-expectancy <5 years
4. Current (in the past year) significant clinical depression/anxiety (Hospital Anxiety and Depression questionnaire (HADS) ≥11 in either or both the depression and anxiety domains) (either in clinical records or at screening) OR psychiatric conditions (based on medical records),
5. History (past year) of alcohol or drug/substance abuse
7. Dependent on others (living in a rest-home/care facility)

8. Unable to have telephone assessments due to hearing difficulties
9. Significant cognitive impairment or pre-existing diagnosis of dementia e.g. ACE-R ≤82 (from clinical records), or at screening [MoCA (<23)]
10. Participation in another RCT or major research study

The majority of the inclusion and exclusion criteria will be determined by means of medical record/clinical portal screening, completed by hospital based research staff. If all the relevant information is not available, the initial section of the Baseline assessment will allow further screening to check for remaining criteria (e.g. cognitive impiarment or abnormal mood). Exclusion due to significant anxiety and depression [58, 59] or cognitive impairment [60] are necessary in order to recruit participants who will be able to engage effectively with the study over a period of 12 months.

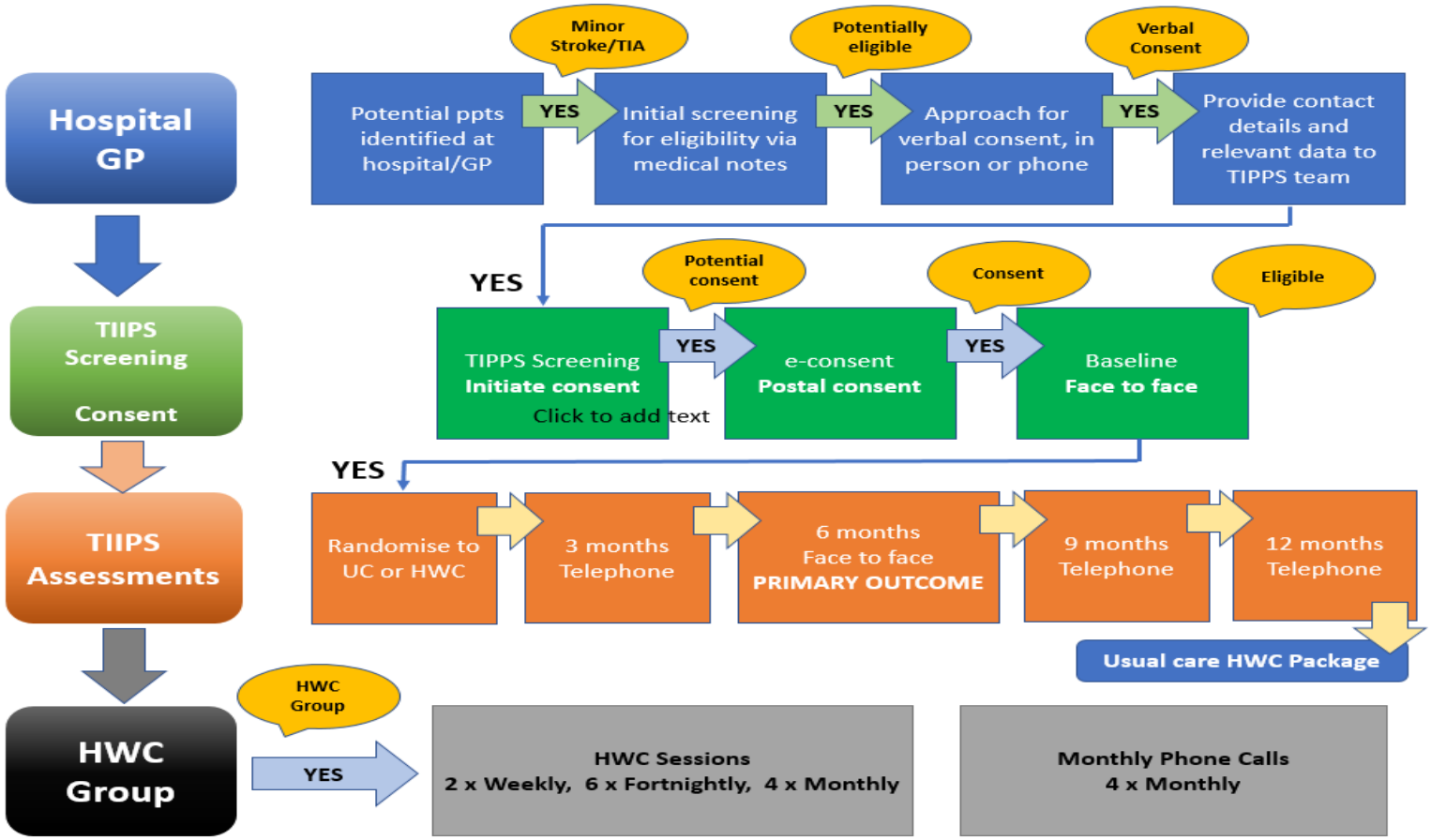
2.2.3 SCREENING

Screening will happen in two stages (see Flowchart Figure 1).

(1) Potential participants initially screened for eligibility based on the study inclusion and exclusion criteria (See **Appendix C** Case Record Forms, Screening Form) from hospital admission information at the public hospitals in Auckland. Those deemed to be potentially suitable will contacted by a hospital-based research assistant to briefly explain the study and for verbal consent to be contacted by a study research assistant.
(2) Those who agree to be contacted will be telephoned by a study research Officer (RO). The RO will provide a brief description of the study, and the screening form will be reviewed to confirm eligibility based available information. If a person is found to be ineligible, the reason will be explained and the participant thanked for their interest in participating in the trial.

STUDY PROCESSES FLOWCHART

Note: **HWC sessions** tailored to individual needs



3. STUDY PROCESSES

3.1 RECRUITMENT SITES

1 Auckland City Hospital, Grafton, Auckland City
2 Middlemore Hospital, Otahuhu, Auckland
3 Northshore Hospital, Takapuna, Auckland
4 Waitakere Hospital, Henderson, Auckland
5 Waikato Hospital

3.2 PARTICIPANT RECRUITMENT PROCEDURES

Trial participants will predominantly be recruited through hospital referrals. **H**ospital based RAs (**H**RA) based in the stroke wards and HRAs who have access to the Clinical portal and patient medical records will conduct daily searches of presentations and admissions to hospital with any diagnoses suggestive of stroke and/or TIA. For those patients with a diagnosis of stroke or TIA as confirmed by their treating physician, the RA will further search their records for the main eligibility criteria as listed in section 2.1. Those who meet the criteria will be approached either in-person if still in hospital or by telephone if discharged, by the HRA, for verbal consent to be contacted by a study RA for further information about the study. The HRA will provide the name and contact details (usually a landline or mobile number) of those who agree to be contacted to the **c**ommunity RA (**C**RA). The number of people who meet the initial screening criteria will be registered in the study database. Potential participants who are identified through GP practices will be approached by the GP or clinic nurse for verbal consent to approach the patient for their interest in the study. Those who consent to be contacted will be telephoned by a CRA in a similar manner as for hospital referrals. Confirmation of TIA/stroke diagnoses will be conducted by checking medical records and/or by the study neurologists.

3.3 CONSENTING

The RO will contact those who have provide verbal consent for initial contact, will be telephoned by a RO to explain the study in detail and to answer any questions. Participants will be informed of their choice to participate and to withdraw at any time, will have a chance to ask any questions. Following this, those who agree to participate will be asked to send a signed copy of the PISC to the research team via post, e-mail or electronic scanning (e-consent). The signed consent form will be countersigned by a research assistant as the person who explained the study to the participant. A copy of the signed consent form will be retained by the study participant, and an e-copy will be retained by the study team in the REDCap database. Eligible participants will be registered on the TIIPS REDCap database and assigned a unique participant ID.

3.4 ASSESSMENTS

There will be a total of five assessments: baseline, 3, 6, 9 and 12 months. Eligible participants will be contacted by CRAs to book appointments for assessments. The baseline and 6- month assessments will be conducted face to face to allow the measurement of the primary outcome metrics for the LS7 (height, weight, blood pressure, blood glucose and blood cholesterol) as well as cognitive assessments. The 3-, 9- and 12-months assessments will be conducted over telephone, at a suitable time.

For face-to-face assessments, the participant will have the option of attending a clinic at one of the three locations at the AUT campuses (AUT North, City , South or Waikato). Participants travelling to clinics will be provided a petrol or supermarket voucher (NZ $20) for parking or travel costs.

Participants who are unable to travel to clinic sites will be offered a home visit to conduct the baseline and 6-month assessments.

Assessments needed to check final eligibility will be conducted first. (1) Blood pressure will be assessed first, and if eligible, (2) the MoCA test will be conducted. If the cut-off for inclusion is met, (3) the HADs assessment will be conducted. The remaining assessments will be conducted of the criteria for HADs cut-off is also met. If at any of the three stages, the inclusion criteria of the study are not met, the participant will be informed, thanked for their time and provided with their voucher for participating in the study.

1. COVID-19 OUTBREAK RELATED RESTRICTIONS

The research Protocol may need to be amended should there be a COVID outbreak and government-imposed restrictions. The pandemic may result in the reduced ability to recruit participants, and conduct face to face assessments. The trial will follow the NZ government guidelines and AUT policies. The ethics committees will be informed of any significant changes and approvals for amendments will be sought as required.

COVID-10 Protection Framework Requirements

Research guidelines at AUT at the Red level of the Protection Framework are outlines at the weblink https://auti.aut.ac.nz/resch/duringcovid-19/Pages/default.aspx. All RAs who will be contacting participants in-person will be required to be fully vaccinated against COVID-19, and will be required to wear medical masks during all in-person assessments. Gloves and eye protection will be worn during blood sample collection.

3.5 CASE RECORD FORMS AND QUESTIONNAIRES

2. LIST OF QUESTIONNAIRES

Table 1. List of outcome measures

Outcome measure	Baseline	3	6	9	12
Demographic Factors: Age, sex, ethnicity, employment, education, marital status	✓				
Event type - stroke and pathological subtypes, or TIA and event date (physician diagnosed)	✓				
NIHSS or mRS (if available)	✓				
Hospitalization details: hospital, date of admission, date of discharge	✓				
Event details (revascularization and planned procedures) from medical records	✓				
Hospital Anxiety and Depression Scale	✓	✓	✓	✓	✓
Stroke awareness (recognition of risk factors, knowledge of actions) [61]	✓		✓		✓

Quality of life (EQ-5D-5L)	✓		✓		
Life Satisfaction Sliding Scale	✓	✓	✓	✓	✓
Satisfaction with life scale	✓	✓	✓	✓	✓
Cognitive functioning by MoCA	✓		✓		
Medication adherence and self-efficacy (SEAMS)	✓	✓	✓	✓	✓
Physical measurements (non-fasting blood test, SBP/DBP, BMI, HR)*	✓		✓		
Absolute and relative 5-year risk of stroke (as measured by Stroke Riskometer app)	✓		✓		
Lifestyle factors (Diet score, physical activity, smoking, alcohol)	✓	✓	✓	✓	✓
CVD outcomes, recurrent events, hospitalisation (stroke, CVD events) self-report and/or from clinical records	✓	✓	✓	✓	✓
Health and Service costs: NMDS (NZ)		✓	✓	✓	✓
Productivity level NMDS (NZ)		✓	✓	✓	✓
Participant feedback questionnaire – Intervention group only		✓	✓		

Items will include demographic factors, medical history, lifestyle risk factors, awareness of stroke risk factors, warning signs, symptoms and actions;[64] depression screening test (Hospital Anxiety and Depression Scale) health related quality of life (EQ-5D-5L),[62] health-care resource use questionnaire, cognitive assessment (Montreal Cognitive Assessment MoCA) and participant satisfaction questionnaires. See 2 for details of measures collected at each timepoint. Life's Simple 7 score will be calculated from corresponding measurements of smoking, BMI, physical activity, healthy diet score, blood total cholesterol, glucose level and BP

).[37]

Table 2. Life's Simple 7

Modifiable factors	Poor health	Intermediate health	Ideal health
Smoking status	Current smoker	Former ≤ 12 months	Never or quit > 12 months
Body mass index	≥ 30 kg/m^2	25–29.9 kg/m^2	< 25 kg/m^2
Physical activity	No physical activity	1–3 times, less than 2.5 hours per week	≥ 4 times per week, 2.5 hours or more
Healthy diet score	0–1 component	2–3 components	4–5 components
Total cholesterol	≥ 240 mg/dL	200–239 mg/dL or treated to goal	< 200 mg/dL
Blood pressure	SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg	SBP 120–139 mm Hg or DBP 80–89 mm Hg or treated to goal	SBP < 120 mm Hg and DBP < 80 mm Hg
Blood glucose	≥ 126 mg/dL	100–125 mg/dL or treated to goal	< 100 mg/dL

3. ASSESSMENT INFORMATION

The Primary Outcome measure of **blood pressure** will be collected as part of the LS7 questionnaire. The LS7 is a simple scoring system to assess cardiovascular health with scores

ranging from 0 to 14, with the overall LS7 score categorised as inadequate (0–4), average (5–9), or optimum (10–14) cardiovascular health. These are; blood pressure, cholesterol, glucose, body mass index, smoking, physical activity, and diet.[37] The total LS7 score as well as individual LS7 items apart from blood pressure are secondary outcomes.

1. The Life's Simple 7 scale

Table 1. Definitions of the LS7 categories *

Life's Simple 7	Level of Cardiovascular Health		
	Poor	Intermediate	Ideal
Lifestyle Factors			
Body mass index. kg/m^2	≥ 30	25-29.99	<25
Physical activity. min/week	None	1-149 min/wk MPA or 1-74 min/wk V	≥ 150 min/wk MPA or ≥ 75 min/wk vV
Healthy diet score	0-1 components	2-3 components	4-5 components
Cigarette smoking	Current	Former ≤ 12 mo	Never or quit > 12 mo
Medical risk factors			
Blood pressure, mmHg	SBP ≥ 140 or DBP ≥ 90	I20 -139/80--89 or < 120/<80 with med	< 120/<80 no meds
Total cholesterol, m mol/L	>6.22	5.18 - 6.22 mmol/L or <5.18 with med	<5.18 mmol/L
Fasting blood glucose, mg/dL GlycosylatedHemoglobin, %	>6.99	5.55 – 6.99 or <5.55 with meds	<5.55

M, moderate; V, vigorous; **PA**, physical activity.

(i) Fruits and vegetables 4.5 cups/day; (ii) Fish 3.5-oz servings (preferably oily fish) 22 servings/week; (iii) Sodium <1500 mg/day;

(iv) Sweets/sugar-sweetened beverages 450 kcal (36 oz)/week; (v) Whole grains (I.I g of fiber in 10 g of carbohydrates), 1-oz--equivalent servings 23 servings/day.

*Note: Fasting blood glucose in mmol/l is ≥7.00 (poor), 5.55–6.99 (adequate) and <5.55 (optimum). Plasma total cholesterol, mmol/l≥ 6.22(poor), 5.18–6.21 (adequate) < 5.18(optimum).

2. Hospital Anxiety and Depression Scale (HADS)

The HADS is a commonly used scale to identify anxiety and depression disorders, including in stroke and TIA patients [65-67]. The scale has seven items for depression and seven items for anxiety, with a total possible score for 0-21 for each, with 0-7 being = normal, 8-10 – borderline abnormal and 11-21 = abnormal. As part of the screening for TIIPS, those who score ≥11 on either the depression or anxiety items will not be eligible to participate in the trial.

3. Stroke Awareness questionnaire

Stroke awareness is an important aspect of stroke prevention. Being aware of stroke risk factors allows individuals to make lifestyle changes. Being aware of stroke sign and symptoms allows individuals to recognise the signs if they or someone they know experience stroke, and action a call to emergency services/healthcare. The stroke awareness questionnaire is adapted an

Australian telephone community survey [68] to determine baseline knowledge regarding stroke risk factors, symptoms, treatment, and information resource.[64]

4. Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) [63] was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal. The TIIPS study considering ≥23 was deemed acceptable by the SC and team neuropsychology expert.

5. Modified Rankin Scale (mRS).

The modified Rankin Scale (mRS) is commonly used in the stroke setting as a scale for assessing the level of disability or dependence in daily activities.[69] It is widely used in stroke clinical trials as a way of assessing improvements in disability levels. The scale ranges from 0 to 6, with 0 denoting no symptoms at all, to 6 for death. The Figure below shows the individual items of the mRS. In this study, those who have an mRS score of 0-2, denoting independence in all personal activities without assistance, will be eligible for the trial.

6. Self-Efficacy For Appropriate Medication Use Scale (SEAMS)

SEAMS is a self-efficacy scale for medication adherence in chronic disease management that can be used in patients with a broad range of literacy skills.[70] It is a reliable and valid instrument for the assessment of medication self-efficacy in chronic disease management, Participants are asked to choose their level of confidence in taking medications correctly under different circumstances (1 = not confident, 2 = somewhat confident, and 3 = very confident). It was designed for patients with low literacy. The total score ranges from 13 to 39 where low scores indicate a low level of confidence and high scores indicate a high level of confidence. The SEAMs questionnaire has been used in a range of chronic condition settings such as secondary prevention of cardiovascular diseases. [71-73]

7. Participant Satisfaction with Life

(1) The Cantril's ladder[74] is a self-reported subjective measure of Satisfaction with life two item scale is a simple ladder scale asks respondents to think of a ladder, with their best possible life being a 10, and the worst possible life being a 0. They are then asked to rate their own current lives on that 0 to 10 scale. Participants are also asked to imagine their life in the best possible light and to describe their hopes and wishes for the future. Scoring: Low <6 points, Medium 6–7 points, and High 8 points. This is used in several studies including older populations as a measure of life satisfaction. [75, 76]

(2) The Satisfaction with Life Scale [77] [78]is a five item scale to measure general life satisfaction and subjective well-being, and is used in chronic conditions such as Parkinson's disease. [79]

8. Stroke Riskometer stroke risk assessment

The validated Stroke Riskometer is a mobile application that is free to download from App stores. The Stroke Riskometer App[80] is a novel, evidence-based app for the primary prevention of stroke. The App incorporates several evidence-based tools to promote behaviour change aligned with internationally recognised stroke prevention guidelines.[81] These include:

1) Provision of feedback on *absolute* risk of stroke within the next 5 to 10 years *and* compares a person's *relative* risk with those of a person of the same age and sex without risk factors). This approach has been demonstrated to motivate behaviour change when used in conjunction with other methods.[82]
2) Employs *tailored self-management* strategies including goal setting to engage the person in behaviour modification (see panel D).[83]
3) Includes *information on stroke risk factors and warning signs* aligned with the internationally relevant Face, Arm, Speech, Time (FAST) international mass media campaign.

Uses *reminders*, known as "push notifications", to prompt users to achieve their goals. Such reminders have been shown to increase adherence to programs.[84]

9. Health and Service Use and Productivity level

The net costs and benefits of the intervention compared to the control will be described and reported in accordance with the Consolidated Health Economic Evaluation Reporting Guidelines (CHEERS).[85] For each intervention arm, the probability of resource use and associated costs will be reported. Cost estimates will be presented in terms of direct costs (e.g. healthcare), indirect costs (e.g. lost productivity) and out-of-pocket costs. Unit prices for resources utilised will be sourced from the most appropriate and up-to-date source (PHARMAC). Costs will be measured in real prices for the reference year (e.g. 2023). Where prices in 2023 are unavailable, adjustment to the real price will be made using the published health sector specific deflator/inflators.

10. <u>Coaching compliance and coaching evaluation</u>

The compliance with health coaching will be assessed by completion of records on session attendance on REDCap. Sessions will be recorded as completed or missed and reasons for missed sessions will be recorded.

Coaching evaluation: At the completion of each session, health coaches will self-evaluate the session using the Coaching Evaluation questionnaire on REDCap. In addition, a random 10% of recordings will be evaluated by the coach trainer and supervisor to track the quality of coaching and identify any potential areas of improvement. This will be used to guide ongoing supervision of the coaches.

PROCESS FOR PHYSICAL MEASUREMENTS

<u>Study equipment:</u>

- Cardiocheck blood test kit
- Omron Blood pressure monitor
- Stadiometer
- Weight scales
- Gloves
- Medical Masks
- Hand sanitizers and wipes

- Biohazard waste bins

Participants will be requested to come in light clothing and will be asked to remove their shoes for height and weight measurement. Measures will include, in this order, BP measured after 10 minutes of rest using a Omron digital blood pressure monitor and European Society for Cardiology guidelines,[86] height with a stadiometer, weight with Omron digital scale, a capillary blood sample using a single use lancet and capillary tube will be used with a Cardiochek point of care monitor to obtain non-fasting glucose, total, HDL and LDL cholesterol and triglyceride levels. Assessments should take 30 minutes.

People identified as having high risk levels of BP will be encouraged to seek medical attention for further management. Please refer to the Blood Pressure Assessment section in Appendix A for further information (systolic BP reading over 220 mmHg or diastolic BP reading over 140 mmHg requires immediate medical attention: systolic reading over 180 or diastolic reading over 110 require the participant to seek medical advice in the next 48 hours).

3.6 RANDOMISATION

Randomisation will be conducted in REDCap. On completion of the baseline assessment, the study manager will randomise participants into HWC or UC. Stratified randomisation will be used to balance prognostic factors: age (<55, ≥55 years, sex (Male, Female), ethnicity; (European, Pacific, Māori, Asian and MELAA (Middle Eastern, Latin American and African), other.

Randomisation Procedure: The randomisation form in REDCap will be a hidden form, visible only to the study managers and data manager. The research assistants will not have access to the randomisation form. The randomisation parameters will be predefined, the stratified randomisation module will be selected, and the strata will be selected as: age (<55, ≥55 years), sex (M, F); and ethnicity (European, Pacific, Māori, Asian and MELAA (Middle Eastern, Latin American and African), other. The Dashboard display will show the allocation as HWC or Usual Care.

THE HEALTH AND WELLNESS COACHING INTERVENTION

1. TRAINING THE COACHES

Research staff will attend an intensive 4-week coaching course, at Momentum Coaching (www.coachmomentum.co.nz), with two sessions in the first two weeks and 4 which includes training in core coaching competencies and code of ethics, developed by the International Coach Federation (ICF) to support greater understanding of the skills and approaches used in the coaching profession. ICF coaching is an internationally recognized approach effectively used in various settings,[87] including our previously accomplished primary stroke prevention trial.[88] Coaches will receive regular group supervision, facilitated by a registered ICF coach, using a small group approach.[88] This model increases the capacity of the team to think from multiple perspectives, translating diverse experiences and issues to the group.

2. TRAINING MATERIALS

The coaches will be provided with relevant materials during training. The training is outlined as below:

Day 1:

1. Establish group rapport, practicalities e.g. Paperwork, safety procedures etc. Each person introduces themselves, share their interest in the project.

2. Develop the group contract

3. a. Define Life Coaching, increase understanding of differences between Coaching, Counselling, Psychotherapy, Mentoring and Consulting

4. Recognise coaching attributes

5. Explain and discuss the elements of the Co-Active, give group feedback.

6. a. Identify and be able understand the 3 levels of listening. Practice new listening skills.

7. a. Explain and demonstrate the Circle of Life tool, practise coaching in pairs, in whole group acknowledge each coach for the competencies done well in coaching practice, each person identify one competency that could be done better.

Day 2:

1. Demonstrate coaching by listening and responding in a coach-like manner in response to group members' sharing of breakthroughs and challenges of the week. Participate in group discussions, giving and receiving feedback. Engage in clearing personal issues that could otherwise prohibit full participation in session.

2. Discuss the importance of the Core Competencies and how we use them as the Foundation in coaching.

3. Recognise and identify various types of coaching questions, define specific types of questions and explain the effect of various questions types, differentiate effective and ineffective question types.

4. Explain, discuss and demonstrate Coaching Skills such as: paraphrasing, reframing, clarifying, analogy and metaphor, distinctions, bottom-lining, intruding, metaview, championing, challenging etc.

5. Practise coaching in pairs. In whole group acknowledge each coach for the competencies done well in coaching practice. Each person identify one competency that could be done better.

Day 3:

1. Define Personal Values. Understand the importance of Values in a coaching forum in order to facilitate learning and results from a deep understanding of self. Practise coaching in pairs using Personal Values Card Sort. Acknowledge each other for competencies demonstrated and name where improvement is possible.

2. Introduce a variety of Assessment tools and discuss the benefits of each. Discuss how to interpret the information attained and how to create a coaching plan most relevant to each specific clients' needs.

3. Name and demonstrate examples of the SMARTPP GOALS components. Establish a variety of goal-setting tools for use in coaching sessions. Become practiced at utilising a variety of methods/tools for goal- setting.

Day 4:

1. Experience the psycho-geometric profiling exercise (Susan Dellinger PhD). Identify and recognise own preferences in relation to psycho-geometric profiling, apply this tool in coaching session, gain awareness of uses of this tool in coaching sessions.

2. Demonstrate the use of the Focus Framework as a goal-setting Strategy, Remediation resource for under-achievement or Time-management resource.

3. Introduce the Decisional Balance framework as a resource for ambivalence or indecision. Practise coaching each other, give feedback on coaching.

Day 5:

1. Gain knowledge and understanding of the MOMENTUM Model of Coaching. Explain how it aligns with the Core Competencies.

2. Introduce the Coaching Evaluation Form. Discuss the use of it in conjunction to ongoing supervision.

3. Discuss the importance of identifying beliefs in coaching in the context of how they can help or hinder achievement. Introduce brainstorming as a useful resource in uncovering hidden beliefs.

4. Extend the topic of Beliefs into the concept of Self-Talk, The Inner Critic / Ally. Demonstrate the use of the resources. In pairs, practice coaching using the Self-Talk concept. Group feedback.

5. Understand the powerful impact of 'metaview' coaching by identifying and coaching PATTERNS (instead of separate scenarios). Demonstrate the process by using the Recurring Pattern Intervention concept, using one of the trainees' personal examples. Group feedback.

6. Coaching practice in 3's. Coach, coachee, observer.

Day 6:

1. Brainstorm all coaching knowledge covered on the course to-date. (Including the 8 Main Competencies)

2. Introduce the Relationship Overview resource. Recap Momentum Model.

3. Coaches practise coaching in 3's, feedback as a group. Practise filling out Coaching Evaluation Form

4. Introduce the Time Management resources: DDDS, Ideal Weekly Planner, Daily Prioritising, Weekly Prioritising, Weekly Planner with roll-over.

5. Discuss and agree upon Consistency of Coaching Structures and Toolkit for measurement, Supervision Structure.

Outline of sessions

Topic	Aims/Strategies for the first session (in-person)
Session opening	Introductions, setting expectations, discussing the study and confidentiality, setting agenda
Health risk assessment	Focus on positive and strengths, values and readiness to change for participant, make appropriate referrals

Wellness vision	Dreams and vision of self and wellbeing in 3-5 years, identify values and motivators
Three month goals	Mid-term goals for consistent behaviours to be doing in three months' time, consider barriers and supports
Weekly goal(s)	First experiment and short-term step forward in an area that the participant is motivated and ready to change
Session close	Affirm belief in the participant and their autonomy, review how the process can be improved, schedule next session
Topic	Aims/Strategies for the first session (over the telephone or in-person, if required)
Session opening	Check in, highlight of the week, set the agenda
Review weekly goals	Focus on positive, explore full experience, reflect participant's strengths and values. Review vision and three month goals. Confirm the vision and three month goals are still where the client is heading, only done once per month
General moment	Participant identifies a target behaviour to address, explore ideal situation, best past experience, values and strengths, and brainstorm ideas
Set weekly goals	Next step in behaviour change in an area the participant is motivated and ready to change, SMART (Specific, Measurable, Action-based, Realistic and Time-bound) goals
Session close	Affirm belief in the participant and their autonomy, review how the process can be improved, schedule next session (if relevant)

Coaching Tracking and compliance with session attendance

Addition Information to track study procedures on study completion
Feedback from health coaches on implementation of intervention
Number of participants who are (1) eligible, (2) recruited, (3) randomised, (4) withdrawn or lost to follow-up
Number of coaching sessions carried out in intervention group
Completion rate of case record forms; (1) number of forms completed; (2) average completion of individual forms

Data from the ARCOS V study on stroke risk factor prevalence and significance by age, sex and ethnicity, life satisfaction and other measures will guide the emphasis of the intervention on which particular health behaviours to focus on. As such, providing/referring to educational material is relevant to this model, including information booklets from the Heart and Stroke Foundation (https://www.heartfoundation.org.nz/resources) which include recommendations and guidelines on duration and frequency of exercise, weight loss, healthy eating, smoking cessation, and reducing alcohol intake,[89] and information about the free Stroke Riskometer mobile app (for stroke awareness and risk assessment, https://nisan.aut.ac.nz/Stroke-Riskometer). This is also in line with recent evidence recommending that RCT's for secondary disease prevention in TIA/minor stroke should include a combination of educational and behavioural interventions.[90-92]

3. ONGOING SUPERVISION

On completion of the initial 6 sessions, coaches will be asked to practice coaching with each other, and friends and family. Once coaching with study participants commences, the coaching trainer will

provide regular supervision and advice by way of a monthly coaching supervision meeting. Here coaches will share their experiences and receive feedback and advise on handling various scenarios. The meetings will be audio-recorded for training purposes (to be shared withing the coaching team only).

4. REPORTING AND COMPLIANCE OF INTERVENTION DELIVERY

At the end of each coaching session, coaches will complete the coaching compliance questionnaire on REDCap. This will record when the session took place, the length of the session, the coaches self-rating of how well they judged the session to have gone, and any relevant notes as free text. In addition, a random 10% of interviews will be reviewed by the health coach trainer and given a rating for compliance.

If a session was missed, the reasons for this and the plans to make up for this missed session will be recorded.

The intervention will combine educational material and intensive HWC coaching. Participants allocated to the HWC group will have up to 12 individual coaching sessions over 6 months with trained HWC coaches. The interval between sessions will be structured to be delivered initially a weekly sessions for the first month, followed by fortnightly, then monthly sessions. However, the intervals may be tailored based on individual participant needs and stroke recovery patterns. Participants with fatigue may require a longer recovery time and hence the sessions could be more frequent in the last 3 months of coaching. Sessions may take place closer together or further apart to ensure as many sessions as possible- sessions are conducted.

Coaching dose: Participants who attend six or more sessions will be deemed as having received the full HWC intervention, those who attended 3-5 sessions will be regarded has having received partial/moderate levels of coaching while those who attended less than 3 sessions will be regarding having received no coaching.

The initial session will be conducted face-to-face and remaining coaching sessions via telephone. However, the second session may be in person if the coach deems it appropriate (reasons to be recorded in REDCap). Between the final coaching session and the 12-month assessment, HWC participants will receive a short monthly telephone call from their coach to encourage maintenance of behaviour change. Coaching sessions will take up to 1 hour initially, with later sessions lasting about 30 minutes. IG participants will be provided with tools to assist with behaviour changes.

5. ASSESSMENT OF COACHING AGAINST ICF CORE COMPETENCIES

The coaching sessions will be evaluated by the coaching trainer against the following competencies (as listed in the case record forms):

Demonstrates Ethical Practice. Definition: Understands and consistently applies coaching ethics and standards of coaching

Embodies a Coaching Mindset. Definition: Develops and maintains a mindset that is open, curious, flexible and client-centered

Establishes and Maintains Agreements. Definition: Partners with the client and relevant stakeholders to create clear agreements about the coaching relationship, process, plans and

goals. Establishes agreements for the overall coaching engagement as well as those for each coaching session.

Cultivates Trust and Safety. Definition: Partners with the client to create a safe, supportive environment that allows the client to share freely. Maintains a relationship of mutual respect and trust.

Maintains Presence. Definition: Is fully conscious and present with the client, employing a style that is open, flexible, grounded and confident

USUAL CARE

Participants in the UC group will be informed of their group assignment post randomisation. UC participants will receive telephone assessments at 3, 9 and 12 months, and a face-to-face assessment at 6 months post randomisation. They will not be informed about the HWC intervention.

DATA COLLECTION AND FOLLOW-UP

Research assistants (RAs) will be provided training and ongoing supervision to conduct assessments. All assessments will be conducted in a standardised manner in accordance the Protocol. The Project Manager will conduct the randomisation and assign cases to the RAs. RAs will be blinded to the treatment group.

6. OUTCOME ASSESSMENTS (SEE TABLE 1 FOR THE FULL LIST OF OUTCOMES)

1. Baseline: The baseline assessment will be conducted prior to randomisation, and within 90 days of the index event. The Baseline assessment will be conducted in-person. The initial part of the assessment will be used to determine the full eligibility of the participant for the TIIPS trial. The full assessment will be completed for eligible participants only, and will include all measures required to analyse the primary and secondary outcomes
2. 3 months (plus or minus 2 weeks from date of randomisation): The assessment will be conducted by telephone only, and will assess secondary outcomes.
3. **6 months** (primary outcome) (plus or minus 4 weeks from date of randomisation): The 6- month assessment be conducted in-person and will re-assess the primary outcome as well as secondary outcomes.
4. 9 months (plus or minus 2 weeks from date of randomisation): The assessment will be conducted by telephone only, and will assess secondary outcomes.
5. 12 months (plus or minus 2 weeks from date of randomisation): The assessment will be conducted by telephone only, and will assess secondary outcomes.

7. PRIMARY END POINTS

The primary end-point will be measured at 6 months post randomisation. The primary end-point will be the difference in the mean change in systolic blood pressure at 6 months post-randomisation between UC and HWC.

8. SECONDARY END POINTS

Secondary outcomes include: (1) difference in the mean change in the LS7 scale score at 6 months post-randomisation between UC and HWC (2) the change in individual lifestyle components of the LS7 scale (BMI, smoking, physical activity, and diet) at 6 and 12 months; (2) diastolic BP (mmHg); (3) quality of life (EQ-5D-5L, (4) awareness of stroke risk factors and warning signs, (5) medication adherence (6) cognitive outcomes (7) adverse events including hospitalisations; and (6) health service use and costs.

The LS7 scale includes BP, cholesterol, blood glucose, BMI, smoking, physical activity, and diet. The score of LS7 will be calculated by providing 2 points for ideal, 1 point for intermediate, and 0 points for poor status of each of the 7 individual factors.[93, 94] Ideal levels of health factors were: non-smoker or quit >1 year ago; BMI <25 kg/m2; BP <120/80 mm Hg; total cholesterol <200 mg/dL; fasting blood glucose <100 mg/dL; ≥150 min/week of physical activity; and a healthy diet score (≥4 components). Study participants who were treated to target levels for hypercholesterolemia, hypertension, or diabetes mellitus were classified as intermediate for the respective health factor. Thus, the LS7 summary score will range from 0 to a maximum of 14 points, with a higher score indicating healthier status.

WITHDRAWAL

Participants will be able withdraw at any time during the trial without needing to provide a reason. Once a participant has withdrawn, there will be no further follow-up phone calls and data collection. The RA will record the withdrawal and the approximate date of withdrawal, and the reasons for withdrawal if provided. Participants in the HWC group may also withdraw from the intervention but continue to have follow-ups. This will be recorded as “withdrawn from the intervention”. Participants will be informed that any information about them has already been collected, analysed and/or included in a publication by the study, will not be able to be destroyed. This will be outlined in the Participant Information Sheet and Consent Form. A participant may be withdrawn from the TIIPS trial if:

1. The participant makes a voluntary decision to withdraw from the trial.

2. The trial is terminated.

STATISTICAL ANALYSES

9. POWER CALCULATION

The sample of 360 participants will provide a simulated 90% statistical power (two sided α=0.05 , β =0.10) to detect a clinically significant 6 mmHg (SD±20) difference in systolic blood pressure change at 6 months post-randomisation, assuming 20% non-compliance/loss to follow-up. Based on our RIBURST data (a observational stroke risk study)[95] data in NZ general population

(n=1265, with 0.07% incident stroke or TIA), the required sample size (n=360) will also provide 90% power (2-sided alpha) to detect 20% relative risk reduction in 5-year absolute risk of stroke. The estimated 5-year risk of stroke after TIA and minor stroke in NZ appeared to be greater than that in Europe,[4] likely due to greater risk of stroke in Māori and Pacific people constituting 20% of the NZ RIBURST Study population.

10. DESCRIPTIVE ANALYSES

These will be reported overall and compared between HWC and usual care groups using parametric and non-parametric techniques, depending on the distribution of the data. Means (95% CI), standard deviations, medians and quartiles will be reported for continuous risk factor variables while cross-tabulations will be reported for categorical risk factor variables.

11. INFERENTIAL ANALYSES

Intention to treat (ITT)[96] analyses and per protocol analysis will be used. To address the primary hypothesis ANCOVA will be used to compare the difference in systolic blood pressure at 6-months post randomisation between the HWC and usual care groups, accounting for baseline stratification factors: (age, gender and ethnicity), referral centres, geographical region and known influential clinical characteristics (e.g. comorbidities). To address the secondary hypotheses linear mixed effects (LME) repeated measures models will be used to investigate the differences in (1) adherence to medication (2) health-related quality of life (3) incidence of new vascular events including death (4) life satisfaction (5) cognition (6) mood) and (7) health service utilisation costs between the HWC and Usual care groups, and by ethnicity (sub-group analysis) at 6-months (plus life-style and adherence at 1-year post-randomisation. These LMEs will model effect of time (baseline, 3-, 6- 9- and 12-months (medication adherence, lifestyle and awareness at only 12 months), post-randomisation whilst accounting for key demographic stratification factors known to confound with outcomes. Any data not collected within 6-weeks of the follow-up points will be classified as missing data. Baseline covariates of age, sex, most recent blood pressure measure and any additional variables predictive of outcome data will be included in the imputation model.[46] The reasons for missingness and the reasons will be recorded and accounted for. Sensitivity analyses will be conducted to test the assumptions of the model (including a complete case analysis in which only subjects with complete data are included). Familywise error control will be used to account for the multiplicity of tests. Inferences will be based on a 5% significance level and two-sided alternatives.

For the analysis of - CVD adverse outcomes (fatal and nonfatal stroke, TIA, myocardial infarction and heart failure, death attributable to CVD and all-cause mortality), we will use Kaplan-Meier life-test and estimate the hazard ratios (HR) and adjusted HR using time-to-event Cox regression analysis. Time to event analysis will include recurrent events and time-dependant variables where appropriate.

Competing risk method will also be applied to compare the CVD adverse outcomes between the two interventional groups, accounting for mortality outcome.

INTERIM ANALYSES

The need for interim analysis will be the trial SC based on the recruitment rate or if advised by the independent DSMC using stopping guidelines for an effectiveness trial[97]

HOSPITALISATION – SERIOUS ADVERSE EVENTS

All hospitalisations (for any reason) are classified as Serious Adverse Events (SAEs), whether or not they are considered related to the heath coaching intervention and should be reported to TIIPS study Manager or PI by the Research Assistant as soon as possible by completing a serious adverse event form (Appendix C).This is further updated at 6 months & 12 months post-randomization and SAE form is to be completed as required If a participant is admitted to hospital, they should notify hospital staff that they are in the TIIPS trial. As this is an open label trial, clinical management should continue as usual.

All serious adverse events will be reported regularly to the Data Safety Monitoring Committee (see below). If at any time the DSMC considers there to be definite evidence of an excess of SAEs they will notify the TIIPS Trial Steering Committee of the findings. The Steering Committee will discuss the issues arising and determine the action to be taken. Copies of the reports issued by the DSMC will be available to Coordinating Centre staff.

DATA SAFETY MANAGEMENT COMMITTEE

An independent Data Safety Monitoring Committee (DSMC) will be established to oversee the overall conduct of the study and ensure the safety of the trial and review of all serious adverse events (SAEs). SAEs will include all hospitalisation, new stroke, heart attack, death, and significant mood issues. Given the low-risk (non-pharmacological, no medical procedures, low-level researcher contact) nature of the intervention, a DSMC will be established and will meet quarterly to ensure safety of the participants and integrity and efficacy of the trial. Members will include clinical experts in stroke and a i statistician, with an independent Chair appointed. Significant reporting of SAEs will be notified to the Trial Steering Committee of the findings who will discuss the issues arising and determine the action to be taken. A formal DSMC charter outlining the remit and role of the DSMC and the details of stopping rules for the trial will be drawn and signed off by the DSMC before the trial (Appendix B).

HEALTH ECONOMIC EVALUATION

The net costs and benefits of the intervention compared to the control will be described and reported in accordance with the Consolidated Health Economic Evaluation Reporting Guidelines (CHEERS). [98] For each intervention arm, the probability of resource use and associated costs will be reported. Cost estimates will be presented in terms of direct costs (e.g. healthcare), indirect costs (e.g. lost productivity) and out-of-pocket costs. Unit prices for resources utilised will be sourced from the most appropriate and up-to-date source (e.g. PHARMAC). Costs will be measured in real prices for the reference year (e.g. 2023). Where prices in 2023 are unavailable, adjustment to the real price will be made using the published health sector specific deflator/inflators. The overall ‘Program Costs’ (i.e. non-research related costs associated with providing the intervention) will be deducted from the potential cost-offsets from fewer readmissions or other resource savings. Sensitivity and uncertainty (probabilistic multivariable [Monte-Carlo simulated]) analyses to account for variability in point estimates will be performed to assess the robustness of results.

The analysis will include modelling the potential opportunity cost savings from future strokes averted based on changes in risk profile (e.g. change in blood pressure, absolute 5-year risk of stroke or clinically relevant change in LS7 score). An incremental cost/ quality-adjusted life year (QALY) gained will also be calculated. The EQ5D is the most commonly used in economic evaluations to estimate preference-based outcome measure and will be used to calculate QALYs for the cost utility analysis.[62, 99] Threshold and willingness-to-pay analyses, illustrated using cost effectiveness

acceptability curves, will be performed to assess uncertainty in the model parameters or a range of different scenarios, to explore under what conditions health coaching could be cost effective and yield potential cost offsets/savings. Potential savings will be calculated using a "case-adverted" approach, which estimates the direct and indirect costs savings if the use of HWC leads to annual reduction in stroke incidence. These estimates will be extrapolated to the overall New Zealand population.

TRIAL ORGANISATIONAL STRUCTURE

The TIIPS trial host centre is The National Institute for Stroke and Applied Neurosciences, Auckland University of Technology, Auckland, New Zealand.

12. TRIAL COMMITTEES

The Steering Committee of TIIPS, (a sub-committee of the ARCOS V Programme Steering committee), is responsible for the overall management of the trial including all aspects of trial design, conduct, analysis and publication, including:

- Trial design and recruitment
- Data management
- Committee coordination
- Ethics committee and Locality applications
- Initiation visits to participating centres
- Monitoring of data quality and adherence to applicable guidelines and regulations
- Statistical analysis
- Preparation of the final report and manuscript of main findings

The Operations Committee will be under the guidance of the Study Co-PI and study Project Manager, and will oversee the day-to-day management of the trial, including

- Participant consent and recruitment
- Protocol and procedures training
- Data entry and management
- Participant communication and queries
- Preparation of reports for the Steering Committee

STAFF TRAINING

Research assistants who will be conducting assessments will attend online and in-person training sessions on all aspects of their role, including,

- the design and aims of the TIIPS trial
- Informed consent processes, participant recruitment, and booking appointments
- Data entry on REDCap
- Assessment processes, including physical, cognitive and psychological measures, and completion of individual questionnaires, cultural considerations
- Reporting of adverse events
- Regular attendance of research assistant meetings

ETHICAL CONSIDERATIONS

The study will seek ethical approval for research in human participants through the Health and Disability Ethics Committees (HDECs) (https://ethics.health.govt.nz/). The processes of Informed consent and confidentiality will by informed by the National Ethical Standards for Health and Disability Research and Quality Improvement.

In addition, the study will seek institutional ethical approval from the AUT ethics committee (AUTEC) (https://www.aut.ac.nz/research/researchethics)

Locality Approvals will be sought for each of the District Health Boards, according to their guidelines.

Māori and Pacific cultural consultations will be conducted via the AUT Vision Mātauranga Committee and DHB Māori advisory teams.

DATA MANAGEMENT

The data will be managed by NISAN and stored at AUT University. Physical information (i.e. paper copies) will be kept in locked cabinets in secure offices at AUT. Computerised data will be kept on secure AUT servers. No identifiable data will be stored on cloud or shared via emails. AUT University follows a rigorous process where the data is stored, retained, and disposed in an ethical manner. The information is required to be protected under the NZ Health Information Privacy Code 1994 and NZ Privacy Act 1993. Information will not be shared with any third party.

The data will be kept for a period of 10 years. This is so that we can analyse this data and report it to the participants, agencies, and communities effectively. After 10 years all information will be destroyed by the study manager by deleting records on the REDCap database and shredding the paper copies. De-identified and aggregated data will be retained to conduct secondary analyses and for data pooling.

Although the participants will share some identifiable information, it will be stored on REDCap in an anonymised fashion and not shared outside the small research team. The participants will also be providing information about their estimated risk of having a stroke in the future. However, this information will not be linked to their identifiable information.

Data capture will be facilitated using REDCap (Research Electronic Data Capture) - a secure web-based application designed specifically for this purpose in a research study setting. REDCap provides 128-bit encryption from client to server, audit trails, easy-to-use forms with real-time field validation, ability to export to a variety of statistical packages, and security features (including user permissions). Two-factor authentication (2FA) is mandated system wide. AUT's ICT department manages and performs daily backups of the local REDCap installation, and appointed research data managers will develop, support and maintain the project's database structure and content.

Although data collection will be conducted via face-to-face manner at specified AUT clinics, data capture will be performed by Research Assistants (RA) using the web-based interface of REDCap. Each RA will have their own REDCap account and will be required to re-authenticate via Google Authenticator or email verification (presently the re-authentication window is 6.5 days). All direct identifiers will be marked accordingly in REDCap - only those users with appropriate training and permissions will be able to export these variables.

REDCap has a comprehensive user rights module that allows the ability to define user roles with specific rights to access forms and functionality and then assign users to each role. Once assigned user roles, the user can only interact with forms and records in a controlled environment. This feature protects unauthorised users from accessing identifiable participant information such as National Health Index (NHI) number, Date of birth (DoB), etc.

VISION MATAURANGA STATEMENT FOR PROJECT

Vision Mātauranga provisions for this project will ensure that Māori have access to their spiritual realm, their language and protocols throughout the consultation, implementation and reporting phases of this project.

AUT researchers have obligations under the Treaty of Waitangi and AUT's Vision Mātauranga policies to engage with iwi in a culturally safe manner. The values outlined in the AUT Vision Mātauranga policies require all staff to foster a culturally safe environment that promotes whānau support values. All whānau of Māori decent within this study will be able to opt into or out of the Vision Mātauranga provisions.

PUBLICATION POLICIES AND DISSEMINATION PROCESSES

This trial will be registered with www.actr.com, (ACTR Trial Registration Number: ACTRN12622000939796 (registered 01/07/2022)) an organisation that maintains a database of trials in progress to assist with the synthesis of controlled trials. The main results will be published as a journal article in a relevant journal as well as an internal report for NISAN.

In this context 'publication' refers to all work for intended for dissemination, as well as any poster or oral presentations of materials. The project lead refers to the person wishing to produce material for dissemination.

Steps to take:

1) As the Principal Investigator has ultimate responsibility for all aspects of the study performance and presentations, the Project Lead needs to discuss a preliminary idea about the proposed publication with the Principal Investigator.
2) The Project Lead will email their idea(s) to a person responsible for circulation of the Steering Committee agenda or PA of Prof. Valery Feigin (cc'd to the Principal Investigator and Co-Directors of the ARCOS V Programme TIIPS trial) to be added to the agenda for the next Steering Committee meeting. The email should include a brief title/description of the topic so that committee members unable to attend the meeting can comment.
3) For programme related works, The Project Lead will discuss the nominated publication(s) with Trial Steering Committee to agree the publication is in keeping with the key objectives of the programme, nominate junior researchers who they recommend be contributors to the publication and, ensure potential conflict with existing work are managed. The decision of the Programme Co-Directors will be entered in the minutes.
4) The proposed idea is to be discussed at the next Steering Committee meeting. At this stage the core individuals to contribute to the paper/presentation are to be identified (this is the *Writing Committee* for that particular work) and the most suitable forum for the work is to be discussed.
   Authorship will include those on the writing committee as well as any other members of the Steering committee who make a significant contribution. In the case of extensive multiple authorship being appropriate, the Writing Committee will be named authors and others will be represented in an agreed collective title
5) All decisions relating to proposed dissemination ideas are to be minuted. The minutes should include an invitation to any Steering Committee members who were unable to attend the

meeting to contact the primary author taking responsibility for the work before the next Steering Committee meeting if they also wish to contribute.

6) All project team members will be advised of the proposed publication, and can at this point indicate if they would like to contribute.
7) Once the publication is nearing completion, and has had input from all Writing Committee members, it is then to be circulated with the agenda for the next Steering Committee meeting before submission.
8) At this stage, discussion should pertain to ensure that the Authorship is appropriate and the targeted forum for the publication is the most appropriate (rather than manuscript content). At the end of this discussion, the decision of the Steering Committee should be minuted.
9) The Steering Committee should be informed of any editorial decisions made through presentation at the Steering Committee meeting. This includes acceptances as well as rejections, and in the case of rejections should contribute to any decisions about further submissions. All such developments should be minuted.
10) If the work is restricted by a tight timeframe (e.g. conference abstract submission deadline before the next steering committee meeting), the work may be approved for submission by the Principal Investigator and Co-Directors and the Steering Committee members informed of the decision.

STUDY ACKNOWLEGEMENT

By signing below, I confirm that I have received, read and understood the protocol, dated 12/5/2024, for the TIPPS randomised controlled trial study.

Name:_____

Signature: _____

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Appendices

APPENDIX A: PHYSICAL MEASURES AND EQUIPMENT

Requirements for face-to-face visit

- The Participant File with information and consent form.
- MoCA hardcopy for cognitive screening.
- Tablet or laptop within REDcap database open to 'baseline assessment – physical measurements' (can be used offline if no internet)
- Reminder sheet about blinding of the Research Assistants so that participants do not disclose if they are in the coaching group.

The following will occur at each visit:

- Any questions regarding the information sheet or consent form will be addressed, ensuring that the participant received an electronic copy of the consent form to keep and reassured that they can withdraw at any time.
- Before the baseline assessment the Research Assistant should review the completed online questionnaires. This will confirm eligibility in terms of medical history and behavioural items on the LS7 (blood pressure cut-off) using the in-built report, as well as the MoCA and HADs questionnaires.
- *Confirmation of non-medical inclusion & exclusion criteria:*

Participants that have proceeded to this stage will have met the cut-off for blood pressure score.

Following this, the Research Assistant will use a hard copy of the MoCA© and enter results directly into the REDCap form. This will calculate total score. If participant scores <23 they will need to be excluded. The Research Assistant performing the MoCA© should complete the online MoCA© Training and Certification Program at https://www.mocatest.org/.

The long versions of the questionnaire completed before assessment will confirm behavioural items. The clinical testing will confirm how many biomedical items are in the unhealthy range. It is highly unlikely that a person would be found to have <2 risk factors at this point.

If participants are ineligible at this stage they will be notified of not meeting the study requirements and thanked for their interest in the study. They should be offered reimbursement for their time, if requested, in line with local ethics approvals.

If the participant still meets the inclusion criteria, the physical assessments will continue (see below).

1.1 PHYSICAL MEASUREMENTS

All measurements are made according to International Standards for Anthropometric Assessment.

Measurement of Blood Pressure and Heart Rate

Three seated blood pressure (BP) measurements and heart rate will be taken using an OMRON model T9P automatic blood pressure monitor obtained at least 3 minutes apart, as required in Form B1.

If a participant is identified as having high risk blood pressure, they will be directed to seek further medical attention. A systolic blood pressure reading over 180mmHg or diastolic blood pressure

reading over 100 mmHg requires immediate medical attention. A systolic reading over 150 or diastolic reading over 100 requires the participant to seek medical advice in the next 48 hours. This advice will be given to participants during their study visit along with a copy of their results.

Instruction for Using the Omron T9P Automatic Blood Pressure Monitor

The Research Assistant is required to read the accompanying instruction manual carefully (a copy should be filed in the Trial Documentation File). The accuracy and reliability of BP measurements will be improved by following these standardised steps.

- Ensure that the participant has not eaten, consumed alcohol, smoked or exercised for at least 30 minutes before blood pressure measurement.
- The participant should rest for at least 5 minutes in the seated position.
- Remove tight-fitting clothing from the upper arm.
- The participant's feet should be flat on the floor with their arm supported on a table with the cuff at the same level as their heart.
- The arm goes through the cuff loop making sure that the bottom edge of the cuff is approximately 1-2 cm above the elbow and that the Green Marker on the cuff is above the brachial artery. (The tube should run down the centre of the arm approximately even with the middle finger)
- Pull the end of the cuff so that the entire cuff is evenly tightened around the arm and press the hook material firmly against the pile side of the cuff.
- Connect the printer to the monitor with the circle (●) symbol upper most.
- Press the ON / OFF button.
- Ask the participant to remain still and not talk until the measurement is completed.
- After the heart symbol (♥) appears on the digital panel, press the Start button.
- When the measurement is complete, the monitor displays the blood pressure and heart rate, and automatically deflates the cuff.
- Enter blood pressure readings into items in REDCap form 'baseline assessments – physical measurements'

Special Pitfalls and Problems

- The Auscultatory Gap

In some participants, particularly in those with hypertension, the sounds heard over the brachial artery when the cuff pressure is high disappear as the pressure is reduced and then reappear at some lower level. This early, temporary disappearance of sound is called the auscultatory gap. Because this gap may extend over a range as great as 40 mmHg, it is possible to seriously underestimate the systolic pressure or overestimate the diastolic pressure, unless its presence is excluded by first palpating for disappearance of the radial pulse as the cuff pressure is raised.

- Effect of Arm Position

The pressure in the arm increases as the arm is lowered from the level of the heart; conversely, raising the arm above this position lowers the pressure measurement. The effect is largely explained by hydrostatic pressure or by the effect of gravity on the column of blood. Therefore, when measuring indirect blood pressure, the participant's arm should be positioned so that the midpoint of the cuff is at the level of the heart. This location of the heart is arbitrarily taken to be at the junction of the fourth

intercostal space and the lower left sternal border.

- Participants with Large Arms

In participants with large upper arms, a longer and wider cuff is needed for adequate compression of the brachial artery. A cuff with a bladder width of 40-50% of the arm circumference should be used in all participants to assure adequate BP measurements. In participants with moderately large arms, a 15 cm wide cuff will generally be adequate. Determination of forearm blood pressure should not be used because of the falsely elevated diastolic readings, which occur with this technique.

Measurement of blood sugar and lipids

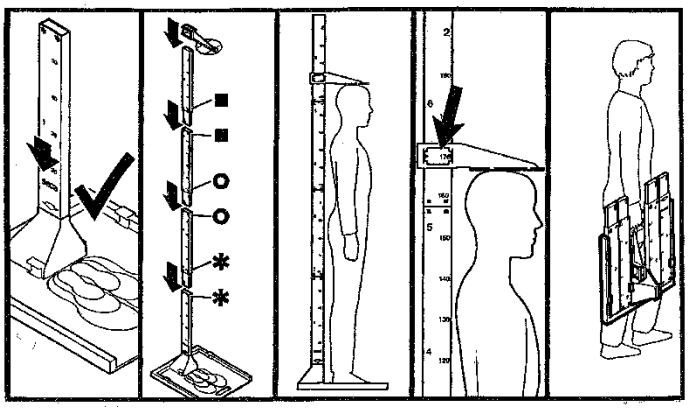
- Non-fasting blood test will be performed using certified Cardiochek PA Analyser (Figure). Cardiochek point of care system allows determination of the full lipid panel within 2 minutes.
- Medication should not be stopped

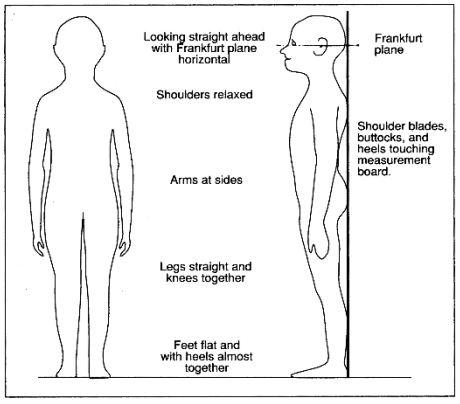
Measurement of Height

Seca model 214 stadiometer, with a maximum 2 metre range, will be supplied for height measurement.

- Assemble the stadiometer by placing the baseplate on the floor, selecting as firm a level as possible. Insert the measuring stick components into the baseplate.
- Ask the participant to remove their shoes and stand on the base plate with their back to the measuring stick. The participant should be told to stand as tall and straight as possible with feet on the “feet outline” of the baseplate and arms held loosely at the side and shoulders relaxed. Heels, buttocks and shoulders should be against the measuring stick.
- Ask the participant to breathe in and look straight ahead.
- Read the height to the nearest cm. Make one measurement of height. Record the value on the PRF.
- Record to nearest cm (round 0.1- 0.4 downwards and 0.5 - 0.9 upwards to the nearest whole number).

NB: If the participant is unable to stand, estimate the height by asking the participant.





Measurement of Weight

Salter bathroom scales model 9175

with a maximum 200kg range, will be supplied for weight measurement as required in relevant section of REDCap 'baseline assessments – physical measurements'. The scales have been calibrated and will be recalibrated annually.

All weight measurements are to be in kilograms. Ensure that the weight mode switch on the underside of the scales is set to KG.

- Weigh the participant without their shoes. The participant should ideally *wear light indoor clothing* only. Remove any heavy items of clothing, heavy items from pockets, and heavy jewellery.
- Place the scales on a flat level surface.
- Press the centre of the scale platform firmly with your foot to activate the scales.
- Remove foot and wait for the display to show a '0.0' reading.
- When zero is displayed ask the participant to step onto the scales and stand still.
- The participant should stand on the centre of the scales without support. Weight should be evenly distributed on both feet and the participant should look straight ahead.
- Make one measurement of weight – the weight display will appear after 2-3 seconds.
- Record weight to nearest 0.1kg.
- Warning indicators are: Err = overload (maximum load is 200kg) and picture of a battery = replace batteries.
- Batteries: when necessary replace with 4 new AA size batteries. Ensure +/- terminals are the correct way round.

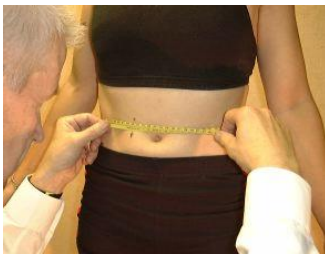
Measurement of Waist Circumference

A 2-meter tape measure will be supplied for the measurement of waist circumference as required in question 'baseline assessments – physical measures'.

- The waist circumference is to be measured with the participant wearing light indoor clothing. The participant should remove heavy outer garments and belts, loosen tight clothing and empty their pockets.
- Measure in a standing position with participant breathing normally. (Ask the participant a question as you are about to take the measurement).
- Participant should stand sideways to the Research Assistant in order to check that tape is horizontal.
- Measure waist half way between lower border of ribs and iliac crest.
- There should be no indentation of the skin due to the tape.
- Record waist measurement to nearest cm (round 0.1- 0.4 downwards and 0.5 - 0.9 upwards to the nearest whole number).

Waist measurement

- Use the circumference at the level of the noticeable waist narrowing located approximately half way between lower border of ribs and iliac crest.
- In participants where the waist is not apparent, an arbitrary waist measurement is made at this level.



APPENDIX B: DATA SAFETY MONITORING CHARTER

A DSMC charter will be developed according to the below guidelines at the commencement of the study.

Data Monitoring Committee Charter

TITLE OF PROTOCOL: TRIAL OF AN INDIVIDUALISED INTERVENTION FOR THE PREVENTION OF STROKE (TIIPS)

PROTOCOL NUMBER: Version 2

SPONSOR OF PROTOCOL: Health Research Council of NZ

DATE OF DOCUMENT: 04/05.2022 Updated 05/09/2022

1. Introduction

This Charter is for Data Safety Monitoring Committee (DSMC) for:

> ***Trial name: TRIAL OF AN INDIVIDUALISED INTERVENTION FOR THE PREVENTION OF STROKE (TIIPS)***
>
> ***Trial Registration Number:*** Australian New Zealand Clinical Trials Registry (ANZCTR). ACTRN: ACTRN12622000939796

Web address of trial: https://www.anzctr.org.au/ACTRN12622000939796.aspx

Date submitted: 9/06/2022 11:56:43 AM

Date registered: 1/07/2022 1:33:19 PM

Registered by: Rita Krishnamurthi

Principal Investigator: Rita Krishnamurthi

The purpose of this document is to define the primary roles and responsibilities of the DSMC, its relationship with other trial committees, its membership and the purpose, format and timing of its meetings. The Charter will also provide the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the DSMC, and an outline of the content of the Open and Closed Reports that will be provided to the DSMC.

2. Primary Responsibilities of the DMSC

The DSMC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DSMC will provide recommendations about stopping or continuing the trial. To contribute to enhancing the integrity of the trial, the DSMC may also formulate recommendations relating to the selection/recruitment of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedure for data management and quality control.

The DSMC will be advisory to the clinical trial leadership group, hereafter referred to as the Steering Committee (SC). The SC will be responsible for promptly reviewing the DSMC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in study conduct are required.

3. Organisational Diagram

The following diagram shows the relationships between DSMC and other committees and functional areas involved in the trial.

[***An Organisational Diagram should be inserted here***]

4. Membership of the DSMC

4.1 Members

The DSMC is an independent multidisciplinary group consisting of biostatisticians, clinicians and ethicists that, collectively, has experience in the management of patients with ***[fill in disease]*** and in the conduct and monitoring of randomised clinical trials.

DSMC Chair: Professor Alain Vandal - will chair the meeting and provide feedback on the open and closed reports.

DSMC Members:

1. *A/Professor Nada Signal – senior lecturer, physiotherapy, stroke expert, will be provided with adverse events and access to REDCap about patient information. Nada will consult external expertise such as a medical specialist if needed, but keep confidentiality.*
2. *Mr Don Scandrett – CEO, Stroke Foundation, community stroke advisor and advocate*
3. *Ms Jinghong Zeng*

-biostatistics student and in-training under the supervision of Prof Vandal, will take minutes of the DSMC meetings

4.2 Conflicts of Interest

The DSMC membership has been restricted to individuals free of apparent significant conflicts of interest. The source of these conflicts may be financial, scientific or regulatory in nature. Thus, neither study investigators nor individuals employed by the sponsor, nor individuals who might have regulatory responsibilities for the trial products, are members of the DSMC.

The DSMC members should be independent of the trial, and should not serve on DSMCs of similar concurrently active trials. They should not own stock in companies having products being evaluated by the clinical trial. Any competing interest, whether real or potential, should be declared. The DSMC will be responsible for deciding whether these competing interests materially impact their objectivity.

The DSMC members will be responsible for advising fellow members of any changes in competing interests that occur during the course of the trial. Any DSMC members who develop significant conflicts of interest during the course of the trial should resign from the DSMC.

DSMC membership is to be for the duration of the clinical trial. If any members leave the DSMC during the course of the trial, the SC will promptly appoint their replacements.

5. Terms of reference and specific roles of the DSMC

Terms of reference

The DSMC should receive and review the progress and accruing data of this trial and provide advice on the conduct of the trial to the SC.

Specific roles of the DSMC

To undertake to review the trial's progress by

- Assessing data quality, including completeness (thereby encouraging collection of high quality data
- Monitoring recruitment figures and losses to follow-up
- Monitoring compliance with the protocol by participants and investigators
- Monitoring evidence for treatment differences in the main efficacy and safety outcome measures – and thus recommending action when/whether the main trial question has been answered
- Monitoring evidence for treatment harm (eg toxicity, SAEs, deaths) in a timely way, receiving prompt reports of SUSARs and taking appropriate action to ensure patients' safety.
- Recommending whether the trial should continue to recruit or follow-up (see section on decision making)
- Assessing the impact and relevance of any external evidence provided
- Monitoring the compliance with previous DSMC recommendations
- Considering the ethical implications of any recommendations made by the DSMC

The DSMC will report its recommendations to the SC.

6. Timing and Purpose of the DSMC Meetings

6.1 Organisational Meeting

The initial meeting of the DSMC will be an Organisational Meeting. It will be held during the final stages of protocol development, to provide advisory review of scientific and ethical issues relating to study design and conduct, to discuss the standard operating procedures for the role and functioning of the DSMC, and to discuss the format and content of the Open and Closed Reports that will be used to present trial results at future DSMC meetings.

The Organisational Meeting will be attended by the DSMC, the lead trial investigators, the statistician, and the data manager. Representatives of the sponsors may also attend. Before the meeting, the DSMC will be provided with the drafts of the clinical trial protocol, the Statistical Analysis Plan, the DSMC Charter, and the current version of the case report forms. The DSMC will also receive the initial draft templates of the Open and Closed Reports. Agreement on the format and content of reports will ensure the DSMC is receiving the necessary data on the trial progress.

(Note that all DSMC members will have sight of the protocol/outline before agreeing to join the DSMC. DSMC members should be constructively critical of the ongoing trial, but supportive of the aims and methods of the trial.)

6.2 Monitoring meetings

Timing:

It is recommended that the DSMC meet at least every six months and will otherwise depend on the wishes of the DSMC. The needs of the trial office will be considered when planning each meeting.

The first meeting of the DSMC should take place during the early stage of recruitment, to review early safety information, to review factors relating to quality of trial conduct, and to review information provided to the DSMC.

Meetings will continue until the trial has six months left to completion.

Format:

The first meeting will be face-to-face. It is recommended that all subsequent meetings should be face-to-face too, with teleconference as a second option.

Attendance:

The Principal Investigator (PI) should attend open sessions of the DSMC meetings. It may also be useful for other members of the SC and the trial manager to attend the open sessions.
The trialDSMC liaison, Programme Manager, Mr Bala Nair will provide the link between the database and the DSMC, and they are the only person outside the DSMC to have access to unblinded data (data from closed reports, see below) during the trial. They are responsible for the production of the DSMC reports, will attend both the open and closed sessions of the DSMC meeting to talk the DSMC through the reports. They may also participate in some DSMC discussions.

Every effort should be made for all DSMC members, the trial PI and the trial liaison to attend meetings. The DSMC administrator will attempt to ensure a date is chosen to allow this. If, at short notice, any DSMC

member cannot attend, the meeting may still take place as long as at least three people are present, including one statistician, one clinician and the DSMC Chair. If the DSMC is considering recommending a major action after such a meeting the DSMC Chair should talk to the absent members as soon after the meeting as possible to check whether they agree. If they don't a further meeting by teleconference with the full DSMC should be held.

7. Procedures to Ensure Confidentiality and Proper Communication

To enhance the integrity and credibility of the trial, procedures will be implemented to ensure the DSMC has sole access to evolving information from the clinical trial regarding comparative efficacy and safety data, aggregated by treatment arm. An exception will be made to permit access for the trial liaison (ARCOS V Programme Manager, Mr Bala Nair) who will be responsible for serving as a liaison between the database and the DSMC. A nominated member of the DSMC will be provided immediate access on an ongoing basis to patient-specific information on SUSARs (Suspected Unexpected Serious Adverse Reactions).

At the same time, procedures will be implemented to ensure proper communication is achieved between the DSMC and the trial investigators and sponsor. To provide a forum for exchange of information among various parties who share responsibility for the successful conduct of the trial, a format for Open Sessions and Closed Sessions will be implemented. The intent of this format is to enable the DSMC to preserve confidentiality of the comparative efficacy results while at the same time providing opportunities for interaction between the DSMC and others who have valuable insights into trial-related issues.

7.1 Closed Sessions

Sessions involving only DSMC members and the statistician who generated the Closed Reports (called Closed Sessions) will be held to allow discussion of confidential data from the clinical trial, including information about the relative efficacy and safety of interventions. In order to ensure that the DSMC will be fully informed in its primary mission of safeguarding the interest of participating patients, the DSMC will be unblinded in its assessment of safety and efficacy data.

At a final Closed Session, the DSMC will develop a consensus on its list of recommendations, including that relating to whether the trial should continue.

7.2 Open Session

In order to allow the DSMC to have adequate access to information provided by study investigators, a joint session between these individuals and DSMC members (called an Open Session) will be held between the Closed Sessions. This session gives the DSMC an opportunity to query these individuals about issues that have arisen during their review in the initial Closed Session. With this format, important interactions are facilitated through which problems affecting trial integrity can be identified and resolved. These individuals will either be present in person at the DSMC meeting or be provided a telephone link.

Identification and circulation of external evidence (eg from other trials or systematic reviews) is not the responsibility of the DSMC. The PI will take responsibility to collate such information and provide it to the DSMC.

7.3 Open and Closed Reports

For each DSMC meeting, Open and Closed Reports will be provided (See Section 8 for outlines of the content of these reports). The trial statistician, ***[provide name of statistician]*** will prepare these reports.

Open Reports, available to all who attend the DSMC meeting, will include data on recruitment and baseline characteristics and pooled data on eligibility violations, completeness of follow-up and compliance.

Closed Reports, available only to those attending the Closed Sessions of the DSMC meeting, will include analyses of primary and secondary efficacy endpoints, subgroup and adjusted analyses, analyses of AEs and symptom severity, analyses of laboratory data, and Open Report analyses that are displayed by intervention group.

The Open and Closed Reports should provide information that is accurate, with follow-up that is complete to within two months of the date of the DSMC meeting. The Reports should be provided within *** working days before the date of the meeting.

7.4 Minutes of the DSMC Meeting

The DSMC will prepare minutes of their meetings. Two sets will be prepared: the Open Minutes and the Closed Minutes.

The Open Minutes will describe the proceedings in the Open Session of the DSMC meeting, and will summarise all recommendations by the DSMC. These minutes will be circulated immediately to the Principal Investigator and the Study Manager, therefore it is necessary that these minutes do not unblind the efficacy and safety data if the DSMC is not recommending early termination.

The Closed Minutes will describe the proceedings from all sessions of the DSMC meeting, including the listing of recommendations by the Committee. Because it is likely that these minutes will contain unblinded information, it is important that they are not made available to anyone outside the DSMC. The study statistican will receive minutes of the sections of the closed sessions they attend, and it is vital that these are kept confidential. Copies will be archived by the Chair and by the study Statistician, for distribution to the Principal Investigator, sponsor, and regulatory authorities at the time of study closure.

7.5 Recommendations to the Steering Committee (SC)

At each meeting of the DSMC during the conduct of the trial, the DSMC will make a recommendation to the Steering Committee to continue or to terminate the trial. This recommendation will be based primarily on safety and efficacy considerations and will be guided by statistical monitoring guidelines defined in the Charter.

The SC is jointly responsible with the DSMC for safeguarding the interests of participating patients and for the conduct of the trial. Recommendations to amend the protocol or conduct of the study made by the DSMC will be considered and accepted or rejected by the SC. The SC will be responsible for deciding whether to continue or to stop the trial based on the DSMC recommendations.

The DSMC will be notified of all changes to the protocol or to study conduct. The DSMC concurrence will be sought on all substantive changes to the protocol or study conduct prior to their implementation.

The SC may communicate information in the Open Report to senior management and may inform them of the DSMC recommended alterations to study conduct or early trial termination in instances in which the SC has reached a final decision agreeing with the recommendation. The SC will maintain confidentiality of all information it received other than that contain in the Open Reports until after the trial is completed or until a decision for early termination has been made.

8. Statistical Monitoring Guidelines

The Statistical monitoring will follow the CONSORT, New Zealand ethical guidelines for human interventional study and New Zealand Health Research Council (HRC) recommended guidelines for statistical monitoring.

The following guidelines include guidance on international best practice:

1.USA Food and Drug Administration Guidance document on the establishment and operation of clinical trial Data Monitoring Committees.

2. In UK, a report was commissioned by the Health Technology Assessment programme: Data Monitoring Committees: Lessons, Ethics and Statistics (DAMOCLES). Their report provides a systematic review of DMC practices and their recommendations for DMC processes.

The responsibilities of the DSMC are detailed in the following 8.1. It is modified from HRC DMC webpage- https://www.hrc.govt.nz/resources/data-monitoring-core-committee and https://www.niams.nih.gov/grants-funding/conducting-clinical-trials/clinical-trial-policies-guidelines-and-templates, according to the scope and perceived risk level of the study.

8.1 Responsibilities of the DSMC include:

- Reviewing the monitoring plan for the trial and provide advice to the study team on whether the plan meet the best practice.
- Review the research protocol, Data and Safety Monitoring Plan (DSMP), and informed consent documents, including all proposed revisions. The Standard Operating Procedures (SOP), which may contain the sections included above, is also reviewed.
- Evaluate the progress of the study on an ongoing basis, as needed, including periodic assessments of data quality, participant recruitment, accrual and retention, participant risk versus benefit, performance of study site(s), and other factors that can affect the outcome.
- Evaluate safety throughout the course of the study through the routine review of aggregated adverse event safety data, in addition to expedited review of unanticipated problems, serious adverse event reports, and protocol deviations impacting participant safety. The DSMB members review the documentation provided by the study team and makes recommendations to the regarding protection of the study participants.
- Evaluate proposals of new enrolment plan (for example, new sites that differ from the approved application) and make a recommendation as to whether the new enrolment plan is expected to enhance overall enrolment. Activities include evaluating the patient population pool, catchment area description, recruitment plan, and target enrolment.
- Consider the impact of factors external to the study when new information, such as scientific or therapeutic developments, becomes available and may affect safety of participants, their willingness to participate in the study or the ethics and conduct of the study.
- Assist the study group by commenting on any problems with study conduct or performance.
- Ensure that the plan for maintaining the confidentiality of the study data and the results by the investigative team are appropriate.
- Review and evaluate requests for protocol modifications.

- Review in advance of the study initiation the study specific stopping rules and plans for interim analyses as established by the PI and selected members of the study team. These plans outline the conditions under which a study may be stopped (e.g., difficulties in recruitment, retention, obtaining outcome measures, or other issues).

- Review the interim analyses and/or accumulating data at the specified interval(s), and as appropriate and make a recommendation to continue, terminate, or modify the study based on observed benefit or harm in accordance with the planned stopping rules.

8.2 Frequency of Data and Safety Monitoring and conditions for early study termination

This section describes the frequency of data and safety monitoring reviews. As the reviews of reportable events (AEs, SAEs, unanticipated problems, and protocol deviations) are included in main protocol section, this section focuses on the routine and ad hoc review of the full data and safety monitoring reports.

- Frequency and timing of interim analysis: one interim analysis will be conducted when 50% of targeted participants are recruited.
- Conditions for early study termination: there will not be any early termination rule based on primary outcome due to futility of efficacy in the trial. The potential study termination will be determined by safety outcome measures. (References: Item 7b. CONSORT checklist; page 40- NZ ethical guidelines of interventional study (NZEGI)).
  Condition 1: There is statistically significant difference in AE or SAE between treatment groups. The intervention group demonstrates higher % in protocol-related AE or SAE than the usual care group.
  Condition 2: There is no statistically significant difference in AE or SAE, but the intervention group had sever concerning AEs that relate to the intervention, the DSMC and study team make the judgment that the study should terminate early.
  Condition 3: There is major protocol deviation in the study. “There are some circumstances (e.g., a major deviation from study protocol) that may make it appropriate to terminate an intervention study early.”-NZEGI
- The review will be inclusive of simple uncertainty about safety aspects, and other trial related issues, but not including adapting sample size.

8.3 Content of Data and Safety Monitoring Report

This section describes the content of the data and safety monitoring reports. The specifics of the study and the requests of the DSMC will guide requirements for additional tables and listings. Tables for multi-site studies will present aggregated data as well as data by site.

For studies with more than one intervention group, this section should indicate the plans for providing data stratified by masked intervention group (i.e., Group A vs. Group B) as part of the closed report to the DSMC, while the open report should have data presented in aggregate without stratification by groups.

The complete data and safety monitoring report template should be included as an appendix.

8.4 Protection of Confidentiality

- This section describes how confidentiality of data presented to the Monitoring Body will be protected.
  Only unidentifiable data will be presented during the open sessions of the DSMC meetings. All data, whether in a report or discussed during a DSMC meeting, are confidential. Participant identities will be kept confidential unless safety concerns necessitate unmasking some or all data.

8.5 Data Management, Quality Control, and Quality Assurance

This section describes how the site will collect, document, and review the data. Who will be responsible for data entry and ensure they are accurate and complete? Which database will be used? Does it have audit tracking capabilities? What is the data query process and frequencies? Are there any planned mitigation strategies in the event of non-compliance? What is the process for locking the final study datasets? Are there any procedures on data access and sharing as appropriate? Is there a description of security measures in place? (If you have a separate Clinical Monitoring and Data Management Plan, please reference it and utilize that information to help populate this section).

Each study should have standard operating procedures (SOPs) and/or a quality management plan that describe the following (if this is a multi-site study, each site should have SOPs and a plan):

- Staff training methods and how such training will be tracked
- How data will be evaluated for compliance with the protocol and for accuracy in relation to source documents
- The documents to be reviewed (e.g., case report forms, clinic notes, product accountability records, specimen tracking logs, questionnaires), who is responsible, and the frequency for reviews
- Who will be responsible for addressing quality assurance (QA) issues (correcting procedures that are not in compliance with protocol) and quality control issues (correcting data entry errors). It is anticipated that QA review and data verification will be performed by someone other than the individual originally collecting the data, or by double-data entry. The frequency of internal QA review and measures to be taken for corrective action (e.g., for trends in errors) should be included
- QA measures for participant recruitment, enrollment, enrollment targets, and for the validity and integrity of the data. E6 Good Clinical Practice (R1): 1.46 defines quality assurance as “All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s)”

9 Content of DSMC’s Open and Closed Reports

9.1 Open Statistical Report: An Outline

- One-page outline of the study design, possibly with a schema
- Statistical commentary from the liaison (Mr Nair), explaining issues presented in Open Report figures and table
- DSMC monitoring plan and summary of Open Report data presented at prior DSMC meetings
- Major protocol changes
- Information on patient screening
- Study accrual by month and by institution
- Eligibility violations
- Baseline characteristics (pooled by treatment regimen)
  - Demographics
  - Laboratory values and other measurements
  - Previous treatment usage and other similar information
- Days between randomisation and initiation of treatment
- Adherence to medication schedule (pooled by treatment regimen)
- Attendance at scheduled visits (pooled by treatment regimen)
- Reporting delays for key events (pooled by treatment regimen)
- Length of follow-up data available (pooled by treatment regimen)
- Participant treatment and study status (pooled by treatment regimen)
- Completeness of data (pooled by treatment regimen)

9.2 Closed Statistical Report: An Outline

- Detailed statistical commentary explaining issues raised by Closed Report figures and tables (by coded treatment group, with codes sent to DSMC members by a separate mailing)
- DSMC monitoring plan and summary of Closed Report data presented at prior DSMC meetings
- Repeat of the Open Report information, in greater detail by treatment group
- Analyses of primary and secondary efficacy endpoints
- Subgroup analyses and analyses adjusted for baseline characteristics
- Analyses of adverse events and overall safety data
- Analyses of lab values, including basic summaries and longitudinal analyses
- Discontinuation of treatment (coaching)
- Information on crossover patients.

APPENDIX C CASE RECORD FORMS

List of TIIPS study case record forms

	Form Name	Purpose
1	Form A NHI number	Confidential record of NHI number
2	Form B Baseline and Screening	Screening for eligibility, and Baseline demographic and health related information
3	Form C Contact Details	Record of participant contact details, alternate contact and GP contact
4	Form E e-consent	Record of participant consent
5	Form F3 3-month Follow-up	Follow-up assessments at 3 months
6	Form F6 6-month Follow-up	Follow-up assessments at 6 months
7	Form F9 9-month Follow-up	Follow-up assessments at 9 months
8	Form F12 12-month Follow-up	Follow-up assessments at 12 months
9	MC Mental Health (Coach use only)	Mental health issue records for participants during coaching
10	MR Mental Health (RA use only)	Mental health issue records for participants during assessments
11	PH Physical Health form	Physical health issue records for participants during assessments
12	Participant Feedback Survey	Feedback from participants on their coaching experience
13	Participant Readiness of Coaching Survey	Readiness to start coaching
14	Form R Randomisation	Completion of data entry for randomisation, and record of group allocation
15	Form S Serious adverse events	Record of stroke/TIA/MI recurrent events, death and hospitalisation
16	Form Z Coaching assessment and compliance	Record of coaching sessions, compliance, and assessment of coaching quality